PROTOCOL

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Sponsor:

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Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

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2. LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>3TC</td>
<td>lamivudine</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>hepatitis B surface antibody</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>BV</td>
<td>bacterial vaginosis</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>CDC</td>
<td>U.S. Centers for Disease Control and Prevention</td>
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<tr>
<td>CHCT</td>
<td>couples HIV-1 counseling and testing</td>
</tr>
<tr>
<td>CLS</td>
<td>Contract Laboratory Services</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of Acquired Immunodeficiency Syndrome, National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>EAE</td>
<td>expedited adverse event</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediamine tetraacetic acid</td>
</tr>
<tr>
<td>EIA</td>
<td>enzyme-linked immunoassay</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
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<tr>
<td>FHI</td>
<td>Family Health International</td>
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<tr>
<td>FTC</td>
<td>emtricitabine</td>
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<tr>
<td>FTC/TDF</td>
<td>co-formulated emtricitabine/tenofovir disoproxil fumarate</td>
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<tr>
<td>GEE</td>
<td>generalized estimating equations</td>
</tr>
<tr>
<td>GUD</td>
<td>genital ulcer disease</td>
</tr>
<tr>
<td>HBsAg</td>
<td>hepatitis B virus surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HIV-1</td>
<td>human immunodeficiency virus type 1</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>HPTN</td>
<td>HIV Prevention Trials Network</td>
</tr>
<tr>
<td>HVTN</td>
<td>HIV Vaccine Trials Network</td>
</tr>
<tr>
<td>HSV-2</td>
<td>herpes simplex virus type 2</td>
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<tr>
<td>IAS</td>
<td>International AIDS Society</td>
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<tr>
<td>IAVI</td>
<td>International AIDS Vaccine Initiative</td>
</tr>
<tr>
<td>IDU</td>
<td>injection drug user</td>
</tr>
<tr>
<td>IL-2</td>
<td>interleukin-2</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>iPrEx</td>
<td>Iniciativa Profilaxis Pre-Exposición (South American PrEP trial)</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>LSHTM</td>
<td>London School of Hygiene and Tropical Medicine</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter</td>
</tr>
<tr>
<td>MSM</td>
<td>men who have sex with men</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health</td>
</tr>
<tr>
<td>NIH</td>
<td>U.S. National Institutes of Health</td>
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</tbody>
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**Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>NNRTI</td>
<td>non-nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>nucleoside/neuclotide reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PI</td>
<td>principal investigator</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PEP</td>
<td>post-exposure prophylaxis</td>
</tr>
<tr>
<td>PMTCT</td>
<td>prevention of mother-to-child HIV-1 transmission</td>
</tr>
<tr>
<td>PrEP</td>
<td>pre-exposure prophylaxis</td>
</tr>
<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>SHIV</td>
<td>chimeric simian-human immunodeficiency virus</td>
</tr>
<tr>
<td>SIV</td>
<td>simian immunodeficiency virus</td>
</tr>
<tr>
<td>STI</td>
<td>sexually transmitted infection</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TDF</td>
<td>tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>The Joint United Nations Programme on HIV/AIDS</td>
</tr>
<tr>
<td>UW</td>
<td>University of Washington</td>
</tr>
<tr>
<td>VCT</td>
<td>voluntary counseling and testing</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
3. STUDY SUMMARY

Protocol title: Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Rationale: HIV-1 uninfected individuals within HIV-1 discordant partnerships are at high-risk for HIV-acquisition. The majority of HIV-1 transmissions to adults in Africa occur within stable, HIV-1 discordant couples. Novel strategies to prevent HIV-1 transmission within discordant couples, especially interventions that might allow pregnancy to occur safely, are urgently needed. Pre-exposure chemoprophylaxis, in which an HIV-1 uninfected individual at high risk for contracting HIV-1 takes antiretroviral medications to maintain blood and genital drug levels sufficient to prevent HIV-1 acquisition, has been proposed as a potential HIV-1 prevention strategy. A randomized, blinded, placebo-controlled trial is required to demonstrate if PrEP decreases HIV-1 acquisition and has an acceptable safety profile when given to HIV-1 uninfected individuals within HIV-1 discordant partnerships.

Both tenofovir disoproxil fumarate (TDF) and co-formulated emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) have been proposed as possible safe and effective medications to serve as pre-exposure chemoprophylaxis. The potential for differential safety, cost, and efficacy for these two medications justifies evaluating both, against placebo, in a single clinical trial. This trial will directly answer whether PrEP decreases HIV-1 acquisition among HIV-1 uninfected individuals within HIV-1 discordant couples, a very high-risk heterosexual population who could benefit from this type of intervention, if found to be safe and efficacious.

Primary Objectives:

- To determine if once-daily, oral PrEP with TDF or FTC/TDF provides additional protective benefit in preventing HIV-1 acquisition among HIV-1 uninfected persons within heterosexual HIV-1 discordant couples who are also receiving standard prevention interventions.

- To assess the safety of daily PrEP using TDF or FTC/TDF by comparing rates of adverse events (AEs) among HIV-1 uninfected individuals randomized to TDF or FTC/TDF PrEP to those randomized to placebo.

Secondary Objectives:

1) Factors influencing efficacy

- To evaluate the efficacy of PrEP by the level of HIV-1 exposure for HIV-1 uninfected partners within HIV-1 discordant couples, defined by the frequency of sexual activity and the HIV-1 viral load in the HIV-1 infected partner.
• To assess efficacy of PrEP by gender of the HIV-1 uninfected partner.
• To measure the effect on efficacy of other factors, including CD4 count of the HIV-1 infected partner and, for both partners, herpes simplex virus type 2 (HSV-2) serostatus, sexually transmitted infections (STIs), and male circumcision.

2) Adherence:

• To assess adherence to once daily TDF or FTC/TDF PrEP among HIV-1 uninfected persons within HIV-1 discordant couples, and the effect of adherence on efficacy of PrEP to prevent HIV-1 acquisition.
• To evaluate the frequency of PrEP drug sharing between the HIV-1 uninfected and HIV-1 infected partners within HIV-1 discordant couples, as measured by drug assays in HIV-1 infected and uninfected partners.

3) Risk Compensation

• To characterize the association of once daily TDF or FTC/TDF PrEP with sexual behavior change of HIV-1 uninfected individuals within HIV-1 discordant partnerships.
• To compare risk behaviors among HIV-1 discordant couples previously enrolled in the Partners in Prevention trial (which evaluated the efficacy of HSV-2 suppressive therapy when given to the HIV-1 infected partner for preventing HIV-1 transmission), by examining changes in sexual behaviors when the HIV-1 infected versus HIV-1 uninfected partner is receiving a study drug.

4) Safety

• To assess the effect of TDF and FTC/TDF chemoprophylaxis on the rate of congenital abnormalities and growth among infants born to HIV-1 uninfected female participants who become pregnant during the study (and in whom study drug is stopped at the time pregnancy is detected, using monthly pregnancy testing).

5) Effect of PrEP on early HIV-1 disease

• Among those initially HIV-1 uninfected individuals in the trial who seroconvert to HIV-1, to assess the effect of PrEP on:
  • plasma HIV-1 viral load and CD4 cell counts during at least 12 months after HIV-1 seroconversion.
  • frequency of genotypic and phenotypic antiretroviral drug resistance.
  • other clinical, immunologic, and virologic parameters of HIV-1 disease.

Tertiary Objectives:

• To utilize stored samples for evaluation of immunogenetic and virologic determinants of HIV-1 transmission between transmitting and non-transmitting HIV-1 discordant couples, including viral phenotype and genotype, HIV-1 coreceptor usage, innate immune function polymorphisms, human leukocyte
antigen (HLA) match and other host genetic factors.

**Design:** Phase III, multi-site, randomized, double-blind, placebo-controlled trial

**Population:** Heterosexual HIV-1 discordant couples. The HIV-1 uninfected partners may be either male or female, and must not be chronically infected with hepatitis B. At the time of study screening, the HIV-1 infected partner must have a CD4 count $\geq 250$ cells/mm$^3$ and must not otherwise meet national guidelines for initiation of antiretroviral therapy.

**Study Size:** 3900 HIV-1 seronegative partners within HIV-1 discordant couples (1300 in each treatment arm) are estimated to be needed for this endpoint-driven trial.

**Study agents:** Tenofovir disoproxil fumarate (or TDF, 9-[(R)-2-[[bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate) and emtricitabine (or FTC, 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxatholan-5-yl]cytosine) are reverse transcriptase inhibitors that have been approved for the treatment of HIV-1 infection in humans by the U.S. Food and Drug Administration (FDA). TDF and a fixed-dose co-formulation of FTC/TDF will be used in this study.

**Treatment Regimen:** The HIV-1 uninfected partner will be assigned at random in a 1:1:1 ratio to one of three study arms: TDF, FTC/TDF, or placebo. Because similarly-appearing placebo tablets are not available for TDF and FTC/TDF, participants will take two tablets daily. Those randomized to the TDF arm will take active TDF 300 mg orally once daily + placebo FTC/TDF orally once daily. Those randomized to the FTC/TDF arm will take placebo TDF orally once daily + active FTC/TDF 200 mg / 300 mg orally once daily. Those randomized to the placebo arm will take placebo TDF orally once daily + placebo FTC/TDF orally once daily. Active and placebo TDF are indistinguishable, as are active and placebo FTC/TDF. Thus, participants and study staff will be blinded to each participant’s randomization group assignment throughout the study. All study medication will be taken orally once daily. The TDF and FTC/TDF dosages to be used in this study are in accordance with approved dosages of these medications.

**Justification for Placebo Arm:** Animal models of PrEP show promise as an HIV-1 prevention strategy but do not necessarily predict efficacy in humans. Moreover, evaluation of safety in HIV-1 uninfected persons is required. At this time, there is no evidence to favor any of the treatment groups in this randomized study of TDF or TDF/FTC.
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

versus placebo in HIV-1 uninfected persons who are receiving the highest quality prevention services, including risk reduction counseling, treatment of sexually transmitted infections (STIs), and condoms. Once prevention strategies are found to be efficacious and are incorporated into national guidelines (as is pending for adult male circumcision and may occur depending on the results of ongoing trials of acyclovir suppression), study participants will be counseled about these interventions, and either offered by the site or referred to local centers with appropriate expertise, in accordance with WHO and local guidelines.

Additional Study Services: All participants will receive regular individual and couples HIV-1 counseling, condoms, risk reduction counseling, and treatment for STIs. HIV-1 infected partners will not receive study drug but will receive services according to national guidelines and will be followed in an observational fashion, contributing information for secondary and tertiary study endpoints. HIV-1 infected participants who meet national criteria for initiation of antiretroviral therapy will be referred for such therapy. Counseling on the importance of not sharing study drug within the partnership will occur regularly.

Follow-up: HIV-1 uninfected participants will be followed monthly, and their HIV-1 infected partners will be followed quarterly.

As an endpoint-driven trial, we estimate that we will need a minimum of 24 months of follow-up per participant to accumulate sufficient study endpoints. Anticipating this, we will continue study follow-up for each participant up to a maximum of 36 months. The study Data and Safety Monitoring Board will review the study on a regular basis for assessment of efficacy, in addition to safety and study conduct.

After stopping study drug, HIV-1 uninfected partners will be followed for an additional 1 month to monitor for the possibility of delayed HIV-1 seroconversion as a result of study drug.

Participants who seroconvert to HIV-1 during follow-up will be followed for at least 12 months after HIV-1 seroconversion for assessment of viral resistance, plasma HIV-1 levels, and CD4 count.

HIV-1 uninfected women will undergo monthly pregnancy testing. If pregnancy is detected, women will stop study medication. Infants born to HIV-1 uninfected women will be followed quarterly for 1 year. Breastfeeding is a study exclusion criterion.

Study Duration: Accrual and follow-up will continue for a total of approximately 48 months, with approximately 12 additional months of follow-up to complete follow-up procedures for infants and seroconverters.
Primary Endpoints: HIV-1 seroconversion and AEs among HIV-1 uninfected partners

Secondary Endpoints: Reported risk behaviors, STI prevalence, pill counts and reported adherence. Among HIV-1 seroconverters, HIV-1 drug resistance, plasma HIV-1 RNA level, and CD4 T cell counts. Congenital abnormalities, growth and development among infants born to female participants taking study drug.

Study Sites: Estimated sites
Kenya: Eldoret, Kisumu, Nairobi, Thika
Uganda: Kabwohe, Kampala, Mbale, Tororo

Planned Start Date: January 2008
Planned End Date: June 2012
4. BACKGROUND

4.1 HIV-1 Prevention for HIV-1 Discordant Couples

The HIV-1 pandemic continues to have the greatest impact in sub-Saharan Africa, where 25 million of the estimated 40 million adults and children living with HIV/AIDS worldwide reside [1]. In Africa, the majority of HIV-1 transmissions are estimated to occur in stable HIV-1 discordant partnerships [2], and, in many settings, 50% of all couples in which one partner is HIV-1 infected are HIV-1 discordant (i.e. the other partner is HIV-1 uninfected) [1, 3]. Therefore, HIV-1 discordant couples are a key target for HIV-1 prevention initiatives.

HIV-1 discordant couples face unique challenges, including concerns over disclosure of HIV-1 status, social and cultural pressures to seek pregnancy, HIV-1 associated stigma, and fear of domestic violence. In particular, issues regarding conception are especially concerning to HIV-1 discordant couples. Pregnancy rates in Africa are high (commonly 15-20 per 100 person-years) [4] and HIV-1 incidence is high in pregnancy (ranging from 2-5% [5]), even in the context of reproductive health messages around HIV-1 infection [6]. Given the long development timelines, need for large clinical efficacy trials, and obstacles for distribution of new pharmaceutical products, availability of effective microbicides and vaccines to prevent HIV-1 acquisition is likely over a decade away. In the meantime, there is a critical public health need for a widely available, safe, non-contraceptive method to prevent HIV-1 seroconversions within heterosexual HIV-1 discordant relationships in Africa.

4.2 Overview of Interventions for Prevention of HIV-1 Transmission

In the absence of an HIV-1 cure and recognizing the long development timeline for microbicides and vaccines, prevention of new infections using existing drugs or behavioral changes is key to stemming the epidemic. Expansion of antiretroviral treatment alone will not significantly slow the HIV-1 epidemic – it is estimated that for each HIV-1 infected person initiated on antiretroviral therapy during 2006, six individuals were newly infected with HIV-1 [1]. Prevention efforts can be classified into two general groups: 1) antiretroviral or other drug treatment (e.g., HSV-2 suppression) or behavioral interventions with HIV-1 infected persons to reduce HIV-1 infectiousness and 2) use of antiretroviral or other biomedical or behavioral interventions for high-risk HIV-1 uninfected persons to reduce HIV-1 susceptibility. Table 1 summarizes relevant ongoing or recently concluded biomedical prevention studies.

Although recent studies have demonstrated significant efficacy of male circumcision in reducing HIV-1 acquisition [7-9], national policies are yet to be developed and widespread implementation of this intervention is yet to be achieved. It is unclear what its overall impact will be, as cultural acceptability and time to improve access to safe surgical procedures will be critical to realizing its potential benefits [10]. Herpes suppression offers hope for a widely applicable easily available treatment, but the proof-of-concept trials are still ongoing. Mathematical models suggest that antiretroviral therapy (ART) in HIV-1 infected persons could, over the long-run, reverse the epidemic from an expanding to retracting phase [11], and recent observational studies indicate that ART given to HIV-1 infected partners with clinical AIDS or CD4<200 can reduce
transmission among HIV-1 discordant couples significantly [12].

Table 1: Summary of Efficacy Trials of Biologic HIV-1 Prevention Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Target Population</th>
<th>Status of trials</th>
<th>Considerations for scale-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male circumcision</td>
<td>HIV-1 uninfected men</td>
<td>48-60% reduction in HIV-1 acquisition in 3 trials [7-9]</td>
<td>• Acceptability uncertain. • Scale up of surgical training, supplies for safe procedures and operational research needed.</td>
</tr>
<tr>
<td></td>
<td>HIV-1 infected men</td>
<td>Results in 2008-9</td>
<td>• Safety in HIV-1 infected men &amp; benefits to protect women is under evaluation.</td>
</tr>
<tr>
<td>Female diaphragm</td>
<td>HIV-1 uninfected women</td>
<td>No reduction in HIV-1 incidence among diaphragm users in context of condom promotion [13]</td>
<td>• Identified challenges in adherence with coitally-dependent barrier methods and efficacy trials in which condom use is high in the comparison group</td>
</tr>
<tr>
<td>HSV-2 suppression</td>
<td>HIV-1 infected/HIV-2 co-infected, CD4&gt;250</td>
<td>Partners in Prevention Trial; results due 2008-9</td>
<td>• If effective, could have wide utility in Africa, given 80% HSV-2 coinfection among those with HIV-1 • Would be one of the few interventions available to HIV-1 infected persons with CD4&gt;250 &amp; may also have clinical benefits • Need to reduce cost &amp; increase access of generic acyclovir for wide-scale implementation</td>
</tr>
<tr>
<td>Preventive HIV-1 vaccines</td>
<td>HIV-1 uninfected</td>
<td>HVTN/Merck phase IIb ongoing in Americas; PAVE 100 phase IIb to begin in Africa 2008</td>
<td>• Adenovirus vector-based vaccines anticipated to reduce viral set-point but not provide sterilizing immunity</td>
</tr>
<tr>
<td>Microbicides</td>
<td>HIV-1 uninfected women</td>
<td>NIH HPTN 035 (Buffergel and Pro2000), Pop Council (Carraguard), and MDP (Pro2000) ph IIb &amp; III trials, initial results 2007-8</td>
<td>• 1st generation products with broad specificity which target viral entry • Products with more HIV-1 specific activity (eg, NRTIs, tenofovir gel) in phase II testing or still in preclinical testing (NNRTI and CCR5 inhibitors) • Adherence issues with coitally-dependent methods</td>
</tr>
<tr>
<td>HIV-1 infected, CD4&lt;200 cells/ul and symptomatic</td>
<td>Up to 98% reduction of transmission in HIV-discordant couples with HAART for symptomatic HIV-1 infected partners [12]</td>
<td>• ART programs are constrained to meet treatment demand, given training, infrastructure, drug availability, costs • Resource-intensive weekly home-based adherence (plus ART) could have also decreased transmission</td>
<td></td>
</tr>
<tr>
<td>ART for treatment</td>
<td>HIV-1 infected, CD4 350-500</td>
<td>HPTN 052 (initiated 2007)</td>
<td>• Capacity of national ARV programs insufficient to adopt WHO recommendations to consider ART for CD4 200-350/ul • If ART reduces HIV-1 transmission when provided to persons with CD4 counts 350-500, need to weigh prevention benefits against longer exposure leading to greater cumulative costs, toxicity, and virologic failure</td>
</tr>
<tr>
<td>ART for post-exposure prevention (PEP)</td>
<td>HIV-1 uninfected after high risk exposure</td>
<td>No RCTs</td>
<td>• Not considered cost-effective, insufficient efficacy data • Toxicity and low completion rate for some combination regimens. • Difficulties in accurately recognizing high-risk exposures • Obstacles to accessing PEP early (ideally ≤24 hrs)</td>
</tr>
<tr>
<td>Antiretrovirals for pre-exposure prophylaxis (PrEP)</td>
<td>HIV-1 uninfected high-risk pre-exposure</td>
<td>Safe in West Africa tenofovir trial [14]; safety &amp; efficacy trials underway in Thailand (IDU), Botswana (heterosexuals), US &amp; So America (MSM)</td>
<td>• Biologic plausibility is high, based on macaque studies • Must be demonstrated to be very safe &amp; highly effective for public health applicability • Must target highest risk populations</td>
</tr>
</tbody>
</table>
However, multiple efforts are required to increase ART availability to treat HIV-1 infected persons in the developing world. Thus, ART is currently recommended only for HIV-1 infected persons with clinical AIDS or a CD4 <200 cells/mm³ and may be considered for persons with CD4 <350 cells/μL [15]. Most HIV-1 infected persons do not qualify for ART by these guidelines, and few national programs have infrastructure and resources to provide ART for CD4+ cell counts between 200-350, which limits the potential impact of ART on HIV-1 transmission. Thus, it is unlikely that efforts to expand ART to earlier initiation for HIV-1 infected individuals in order to reduce transmission will be implemented soon. For the HIV-1 discordant couples in particular, the majority of whom have asymptomatic HIV-1 infected partners with higher CD4+ cell counts, other prevention strategies are critically needed to reduce HIV-1 transmission.

4.3 Pre-exposure Chemoprophylaxis for HIV-1 Prevention

Antiretroviral medications for use by HIV-1 uninfected individuals offers a potential novel HIV-1 prevention strategy. The efficacy of use of ART by uninfected individuals to prevent HIV-1 acquisition has been best demonstrated for post-exposure prophylaxis (PEP) in the context of an occupational HIV-1 exposure [16]. Use of ART for post-exposure prophylaxis (PEP) for non-occupational (e.g., sexual) exposures has also been discussed widely. The efficacy of PEP after sexual exposures is unknown because randomized trials have not been conducted, but in a San Francisco open-label PEP study, the rate of seroconversions was 7/401 study participants (1.7%) [17]. Notably, however, sexual PEP has disadvantages in that efficacy is likely highly dependent on the time between exposure and PEP initiation [18, 19], with animal models suggesting that maximal efficacy may require PEP initiation within 12-24 hours [20, 21]. In humans, PEP initiation is compounded by difficulties in high-risk persons accurately recognizing what constitutes a high-risk sexual exposure, delay in seeking care for initiation of PEP, and variability in completing the 28 day course of combination ART which constitutes PEP [22]. For HIV-1 uninfected individuals with frequent high-risk exposures, like those in HIV-1 stable discordant partnerships [23], PEP may be costly and impractical, as it could lead to frequent episodic dosing of potentially toxic combination regimens.

Pre-exposure prophylaxis (PrEP) offers an alternative to PEP for individuals with frequent, high-risk HIV-1 exposures. With PrEP, an HIV-1 uninfected individual would take antiretroviral medications to maintain blood and genital drug levels sufficient to prevent HIV-1 transmission (e.g., by preventing the initial entry of HIV-1 into target cells in the genital tract and blood or by preventing viral replication early in the HIV-1 life cycle that would be necessary for the virus to establish infection). Safe, well-tolerated, highly potent, once-daily antiretroviral drugs in the nucleoside and nucleotide reverse transcriptase inhibitor (NRTI) class, specifically tenofovir disoproxil fumarate (TDF or Viread®) and co-formulated emtricitabine/tenofovir disoproxil fumarate (FTC/TDF or Truvada®), have been demonstrated in macaque SIV and SHIVSF162p3 challenge studies to be highly effective as PrEP using drug doses comparable to standard doses for humans.

4.3.1 Non-Human Primate and Human Data Regarding PrEP Efficacy

Initial non-human primate studies indicated high potency with pre-exposure administration of PMPA (the pro-drug of tenofovir) [18].
Consequently, most consideration for potential PrEP strategies has been based on the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) [24]. NRTIs target HIV-1 early in its life cycle and achieve high levels in genital secretions [25, 26], where HIV-1 exposure and transmission most often occurs. In comparison, other classes of HIV-1 medications have disadvantages for use as PrEP. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with high toxicity in HIV-1 negative persons (e.g., lactic acidosis and severe hepatotoxicity with nevirapine used as PEP) and high frequency of resistance and cross-class resistance. Protease inhibitors act late in the HIV-1 life cycle, have significant side effects, and are costly [27].

In the first non-human primate studies, high dose tenofovir given pre-exposure was shown to be completely protective against SIV challenge [18]. At TDF doses comparable to oral dosing in humans, five of 8 monkeys were protected against high dose oral SIV challenge [28]. With more physiologic doses of SHIVSF162p3, administered by low-dose weekly intra-rectal challenges to approximate sexual transmission, and oral TDF doses comparable to human doses, TDF delayed the time to breakthrough infection from 1.5 weeks in the control macaques to a median of 7 weeks in treated macaques [29]. The small number of macaques studied (e.g. 14), a high SHIV challenge dose (approximately 5 times the comparable levels of HIV-1 RNA in human semen in acute HIV-1 infection), and variable TDF levels with oral dosing limit definitive conclusions from this study. Nevertheless, these macaque studies demonstrated partial protection with TDF PrEP. Subsequent macaque studies using FTC/TDF have demonstrated higher efficacy and possible reductions in set-point viremia in breakthrough infections [30], suggesting that FTC/TDF could provide better PrEP protection than TDF alone. Given the small numbers of animals studied and the possibility of significant differences between experimental models and actual sexual HIV-1 transmission in humans, clinical trials are unarguably needed to determine the balance of efficacy, safety, resistance in seroconverters and costs of TDF versus FTC/TDF PrEP in different high-risk populations.

TDF and FTC/TDF are approved by the U.S. FDA for treatment of established HIV-1 infection. Multiple safety and efficacy studies of TDF and FTC/TDF for treatment of HIV-1 have been conducted (safety information detailed below). Pharmacokinetic properties, including half-life, phosphorylation, and drug penetration into genital tract secretions will likely be key to the potential efficacy of PrEP for preventing HIV acquisition. In studies of HIV-infected individuals taking TDF or FTC, concentrations of these drugs have been found to be several-fold higher in both seminal and cervicovaginal secretions than in plasma [25, 26], suggesting these medications are ideally suited for PrEP.

The initial human trials of PrEP were planned for populations of high-risk women in Cambodia and West Africa. The Cambodia TDF PrEP trial among female sex workers was not initiated due to a combination of political concerns and ethical debates. The TDF trial in Cameroon
encountered challenges in the study communities and was discontinued [31]. The first completed PrEP trial occurred in West Africa (Table 2), but was smaller than anticipated because of premature closures at 2 of the 3 study sites due to issues related to protocol compliance and to challenges in the communities related to care for HIV-1 seroconverters. Thus, the West Africa trial was ultimately underpowered to evaluate efficacy, but it did provide important confirmation of safety and acceptability of daily oral TDF among 936 women [32]. In that study, TDF showed excellent safety with an average of six months of drug exposures – none of the 22 serious adverse events were considered to be related to study product and there were no statistically significant differences in clinical or laboratory abnormalities between those randomized to TDF versus placebo. There were a total of 8 HIV-1 seroconversions on study drug, 2 on TDF and 6 on placebo (95% CI 0.03-1.93; p=0.24) [33]. Adherence to the daily PrEP study drug was ~70%, and there was no evidence of risk compensation among trial participants.

Prominent concerns raised during the first PrEP trials included questions regarding access to care for seroconverters after the trial ended and provision of standard prevention services. In the ongoing TDF PrEP trial among injection drug users in Thailand concerns have been raised about the lack of provision of clean needles and syringes [34]. Together, these controversies have identified critical issues regarding HIV-1 prevention trials among vulnerable populations and underscored the need for early and significant community and provider involvement, media engagement and health care for seroconverters [32, 35].

Subsequent trials have incorporated lessons from the initial PrEP trials into their design and preparation, and the PrEP research agenda has grown and attracted greater support [36].

Placebo-controlled trials of PrEP are now underway in several regions (Table 2). These include a phase II trial of PrEP safety in low-risk HIV-1 uninfected men who have sex with men (MSM, with TDF, in the US) and safety and efficacy trials among injection drug users (TDF, in Thailand), MSM (TDF/FTC, in Peru and Ecuador, started July 2007, and likely to be expanded to additional sites in North and South America and in Asia), and high-risk heterosexuals (TDF/FTC, in Botswana). However, these current trials will provide estimates of efficacy that have broad confidence intervals, given relatively limited sample sizes and estimated endpoint numbers. Moreover, these studies will include relatively small numbers of women, for whom new HIV prevention strategies are critically needed. Thus, additional large studies are needed, especially to define the efficacy and safety of PrEP among heterosexual, high-risk populations, prompting the initiation of this trial which is unique in evaluating safety and efficacy among HIV-1 discordant couples.
### Table 2. Completed, Ongoing, and Planned PrEP Studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Sponsor</th>
<th>Population</th>
<th>PrEP strategy</th>
<th>Status</th>
<th>Approach to pregnancy and breastfeeding</th>
<th>Approach to hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Africa (Ghana, Nigeria, Cameroon)</td>
<td>Family Health International</td>
<td>936 high-risk women</td>
<td>TDF</td>
<td>Completed (results published)</td>
<td>No requirement for contraception.</td>
<td>No exclusion for HBV infection.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stopped study drug when pregnancy detected.</td>
<td>No hepatitis flares after TDF discontinuation among 22 participants positive for HBsAg</td>
</tr>
<tr>
<td>United States</td>
<td>CDC</td>
<td>400 men who have sex with men</td>
<td>TDF</td>
<td>Ongoing (results 2008)</td>
<td>Not applicable (men only)</td>
<td>Active HBV infection excluded.</td>
</tr>
<tr>
<td><strong>Phase III</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>CDC</td>
<td>2000 injection drug users (~20% women)</td>
<td>TDF</td>
<td>Ongoing (results late 2009)</td>
<td>Non-barrier contraception required for female participants.</td>
<td>Active HBV infection excluded.</td>
</tr>
<tr>
<td>Botswana</td>
<td>CDC</td>
<td>1200 men and women</td>
<td>FTC/TDF</td>
<td>Ongoing (results late 2009)</td>
<td>Non-barrier contraception required for female participants.</td>
<td>Active HBV infection excluded.</td>
</tr>
<tr>
<td>Peru, Ecuador (will like expand to sites in the United States, South America, Thailand)</td>
<td>NIH</td>
<td>1400 men who have sex with men (potential expanded sample size of 2300)</td>
<td>FTC/TDF</td>
<td>Ongoing (results ~2010)</td>
<td>Not applicable (men only)</td>
<td>No exclusion for HBV infection. HBV infected participants monitored for 24 weeks after drug discontinuation</td>
</tr>
<tr>
<td>Kenya, South Africa, Malawi, Zimbabwe, Tanzania</td>
<td>Family Health International</td>
<td>3800 high-risk women</td>
<td>FTC/TDF</td>
<td>Planning (protocol not finalized)</td>
<td>Non-barrier contraception required.</td>
<td>No exclusion for HBV infection.</td>
</tr>
<tr>
<td>Africa and India (sites to be determined)</td>
<td>Microbicide Trials Network, NIH</td>
<td>4200 high-risk women</td>
<td>Oral and vaginal TDF, oral FTC/TDF</td>
<td>Planning (protocol development beginning)</td>
<td>To be determined</td>
<td>To be determined</td>
</tr>
</tbody>
</table>

**Partners PrEP Protocol**

**Version 3.0, 12 October 2007**
4.3.2 PrEP Safety

TDF and FTC have important characteristics that make them suitable for consideration as chemoprophylaxis, including prolonged intracellular half-lives, once-daily dosing, potent antiviral effects, and high tolerability. TDF is a nucleotide reverse transcriptase inhibitor approved by the U.S. FDA in 2001 for treatment of established HIV-1 infection. In the initial placebo-controlled studies among antiretroviral-experienced HIV-1 infected participants (Gilead 902 and Gilead 907), rates of serious adverse events and laboratory abnormalities for TDF were similar to placebo during 48 weeks of follow-up [37-39]. The most common adverse events were mild to moderate gastrointestinal events, such as nausea, diarrhea, and flatulence. In the Gilead 903 study, which compared TDF versus stavudine, both in combination with lamivudine and efavirenz, for initial treatment of antiretroviral-naïve HIV-infected individuals, the overall incidence of clinical adverse events and grade 3 and 4 laboratory abnormalities during 3 years of follow-up was similar between the two study arms [40]. Lipid abnormalities and events attributable to mitochondrial toxicity (e.g., peripheral neuropathy, lipoatrophy) were significantly less common among those randomized to TDF. Notably, in vitro and clinical trial data suggest that TDF rarely causes lactic acidosis, which can be a serious side effect from other antiretroviral medications.

A greater percentage decrease in bone mineral density was seen in the TDF arm, compared with the stavudine arm, in the 903 study; however, there was no increase in fractures observed [40]. Five-year follow-up of 86 participants assigned TDF in the 903 study found a total of 5 fractures, all traumatic and none of which were felt to be attributable to TDF [41]. Among 85 participants in the 903 study originally randomized to stavudine, and later switched to TDF, there was one traumatic fracture observed over 2 years of follow-up [42]. In other studies, no clinically significant bone abnormalities have been observed in long-term follow-up on TDF, including 4 year follow-up from the TDF expanded access program and post-marketing safety database, in which the frequency of fractures was <0.1% [43]. The effect of TDF on bone density among HIV-1 uninfected individuals is currently unknown, although data will be forthcoming from the CDC phase II and DAIDS phase III trials among MSM as well as among a subset of women and men in the Botswana phase III trial and among a subset of African high-risk women in the FHI multi-site trial to be initiated in 2008.

While a number of case reports have linked TDF to acute renal failure and Fanconi’s syndrome (renal tubular damage with hypophosphatemia) [44], the incidence of renal dysfunction with TDF was low in the large controlled studies. In the 903 study, only 2 of 299 patients on TDF developed grade 2 nephrotoxicity, a rate similar to that in the stavudine arm [40]. Five-year follow-up of 903 participants found no statistically significant change in estimated glomerular filtration rate and no discontinuations due to renal toxicity [41]. The four-year expanded
access program data showed an incidence of serious renal adverse events of 0.5%, with lower CD4 count, older age, lower baseline weight, higher baseline serum creatinine, and concomitant nephrotoxic medications as risk factors for an increase in serum creatinine [43]. In the case studies, tubular dysfunction has generally been reversible with withdrawal of the drug. A recent review concluded that TDF is felt to have low potential for nephrotoxicity [44]. However, TDF does require adjusted dosing for patients with severely compromised renal function (i.e., creatinine clearance <50 ml/min).

FTC is a nucleoside reverse transcriptase inhibitor approved for treatment of HIV-1 infection by the U.S. FDA in 2003. The fixed-dose combination of FTC 200 mg plus TDF 300 mg was approved for HIV-1 treatment in 2004. In clinical trials, the most common adverse events in patients receiving FTC (or TDF/FTC) have been gastrointestinal events, headache, and skin rashes; these have generally been mild to moderate in severity and have occurred at similar rates to the comparison groups [45]. Rarely, skin and nail discoloration can occur among those taking FTC. The skin discoloration is usually mild and resolves with discontinuation of the drug.

4.3.3 TDF and FTC Experience in Pregnant Women and Infants

4.3.3.1 Animal and Human Data

Both TDF and FTC are pregnancy category B medications. No controlled human studies of these medications among pregnant or breastfeeding women have been conducted.

Animal studies, using doses several-fold higher than standard human doses, did not demonstrate adverse effects on fertility or on the incidence of fetal malformations from administration of TDF or FTC [46-48]. Specifically, studies of TDF among rats and rabbits at doses up to 14 and 19 times standard human doses and of FTC among mice and rabbits at doses up to 60 and 120 times standard human doses did not demonstrate increased rates of fetal malformations.

Limited non-human primate data have found some suggestion that chronic, high-dose (30 mg/kg) exposure to TDF during gestation and the post-partum period may result in growth and bone abnormalities. In one study, among rhesus monkeys exposed in utero and until 9 months post-partum, significant growth restriction was observed in 25% (2 of 8) of animals [49]. Bone studies of these animals found TDF inhibited mineralization of newly formed bone [50]. However, a follow-up study, using 4 gravid rhesus macaques administered the same dose during gestation, found normal fetal development at term [51]. Fetuses had lower body weights and a small reduction in fetal bone porosity that the investigators described as of uncertain physiologic significance. Limited data among HIV-1 infected children have demonstrated that TDF use
results in loss of bone mineral density, which recovers with discontinuation of the drug [52, 53].

Pharmacokinetic data are available for single maternal dosing of 600 mg TDF, which show maternal and cord blood concentrations similar to values expected to provide antiretroviral therapy [54]. A study of paired maternal blood plasma and genital tract aspirates during pregnancy and the post-partum period in women given TDF or other antiretrovirals was conducted, in which amniotic fluid and cord blood specimens were also obtained. This study demonstrated that cord blood and amniotic fluid levels relative to blood plasma were highest for TDF followed by lamivudine (3TC) and zidovudine [55].

A retrospective registry of teratogenic events associated with use of antiretroviral therapy by HIV-1 infected pregnant women noted a 2.6% (6/231, 95% CI 1.0%-5.6%) rate of birth defects associated with exposure to TDF during the first trimester [56]. This rate is similar to the 2-3% rate of birth defects generally observed in the United States. The registry had sufficient numbers of first trimester exposures to detect 2-fold increased risks of birth defects as a result of exposure to lamivudine (3TC), a compound closely related to FTC, as well as several other antiretroviral medications (including zidovudine, abacavir, efavirenz, nevirapine, ritonavir, and stavudine). No such increase has been reported across all these antiretroviral drugs, with the exception of stavudine, for which no specific pattern of defects has been found. Extensive experience with 3TC in pregnant women has made it one of the drugs of choice for treatment HIV-1 infection during pregnancy [57]. A recent study, conducted prospectively among 200 African HIV-1 infected pregnant women, 70% of whom took TDF, in addition to other antiretroviral medications, found that the rate of congenital deformities was low (2%) [58].

No data on excretion of TDF or FTC/TDF in human breast milk have been reported. One pharmacokinetics study in a non-human primate model, which used 2 macaques, found that peak concentrations and area under the curve values for tenofovir (the active derivative of TDF) in breast milk were approximately 3 and 20% of those detected in serum, respectively [59].

3TC (again, closely related to FTC) has been found in concentrations in breast milk ~3-fold higher than in serum among HIV-1 infected women taking 3TC (median 1828 ng/mL versus 678 ng/mL, respectively) [60]. In that study, 3TC levels were measurable in serum obtained from breastfeeding infants (median 28 ng/mL). However, it was estimated that infants exposed to 3TC in breastmilk receive <5% of the recommended infant therapeutic dosing of 3TC (i.e., the dosing of 3TC used for treatment of HIV-1 in infants) [61].

Thus, limited experience suggests safety of TDF and TDF/FTC with regard to pregnancy and lactation. There are no prospective safety data
regarding use of TDF or FTC/TDF PrEP in HIV-1 uninfected women who become pregnant or who are lactating.

4.3.3.2 HIV-1 Risk during Pregnancy and Breastfeeding

Pregnancy and the early post-partum period have been shown to be periods of increased risk for HIV-1 acquisition by African women [5, 62, 63]. In one study, among the Rakai community-based cohort in Uganda, risk ratios for incident HIV-1 were 2.16 (95% CI 1.39-3.37) for pregnant women and 1.16 (95% CI 0.82-1.63) for breastfeeding women, compared with non-pregnant, non-lactating women. In that study, a trend was observed in which women in HIV-1 discordant relationships were also at increased risk during pregnancy (RR 1.73, 95% CI 0.62-4.03). The investigators suggested that biologic factors, rather than differences in sexual behavior of the women or their male partners, likely explained the elevated risks. HIV-1 acquisition by pregnant or lactating women likely poses a significant risk of HIV-1 to their infants, as high plasma, genital, and breast milk HIV-1 viral loads, which are increased during primary HIV-1 infection, are strong predictors of mother-to-child HIV-1 transmission [64].

4.3.4 Safety among Persons with Hepatitis B Infection

Both TDF and FTC have potent activity against hepatitis B virus (HBV) and are used as treatment for HBV among HIV/HBV co-infected individuals [65]. In HIV-1/ HBV coinfected patients who had failed lamivudine therapy, TDF was as effective as FTC/TDF (~80%) in achieving HBV suppression [66]. HBV exacerbations (e.g., defined as >10-fold increase in liver transaminases) have been observed after stopping adefovir (a nucleotide similar to TDF) or lamivudine (closely related to FTC) in ~20% of persons with chronic active hepatitis B [67, 68]. Flares were typically self-limited but case reports of more serious liver decompensation have been reported [69]. The risk is thought to be greater among persons with clinically apparent liver disease [70]. The risk of hepatitis flares when TDF is used (for PrEP or other purposes) in persons with HBV and without evidence of advanced liver disease may be low, but this has not been studied in detail. In the West African TDF safety study, none of 22 women with hepatitis B infection had hepatitis flares after stopping TDF [32].

4.3.5 Resistance

Drug resistance to TDF is well-defined, primarily involving the K65R mutation in reverse transcriptase. This mutation confers reduced antiviral activity to abacavir, didanosine, and lamivudine as well, but not to thymidine analogues (e.g., zidovudine and stavudine). In TDF dose-ranging studies, using monotherapy for up to 28 days, no accumulation of the K65R mutation was observed [71]. In the 903 study, 8 (of 299) participants developed a K65R mutation. Notably, the K65R mutation has been associated with a 50% decreased replicative capacity [72].
Recently, the K70E mutation has also been associated with TDF resistance, although this mutation is rare.

In large viral resistance survey studies, the K65R mutation has been found to be rare (<1%) among HIV-1 infected populations in the Canada, U.S., and Britain [73-75]. Even among the treatment-experienced individuals enrolled in the TDF clinical trials, the prevalence was 3% or less [40, 76].

Two recent, small observational studies from southern Africa suggest that HIV-1 subtype C infected individuals may have an increased propensity to develop the K65R mutation during antiretroviral treatment, especially treatment with didanosine [77, 78]. However, this has not been found in limited evaluations in studies in which patients were treated with TDF [79]. In fact, clinical data from Zimbabwe and Uganda have demonstrated that TDF-containing regimens have good virologic efficacy and little development of TDF resistance [80]. HIV-1 subtype C is responsible for most infections in southern Africa; however, in East Africa (e.g., Kenya and Uganda, the countries in which this trial will be conducted), subtype C is responsible only for a minority of infections.

Mutations at M184V confer resistance to FTC and to the related drug lamivudine (3TC). This mutation decreased replication capacity significantly (to 25%) and restores susceptibility to TDF. Taken together, this suggests that the combination of TDF/FTC may have an even higher barrier for resistance than TDF alone. In one report, among 2 macaques who developed break-through infection in spite of pre-exposure FTC/TDF chemoprophylaxis, 1 developed the M184V mutation but neither developed K65R [81]. In considering PrEP for high-risk HIV-1 negative persons, selection of resistant strains and safety are as paramount as efficacy, given that resistant variants can be archived [82, 83], thus potentially impacting future response to some medications for those who become HIV-1 infected in spite of PrEP. Several medications continue to be fully active against HIV-1 strains resistant to either TDF, FTC, or both, including zidovudine, non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and all protease inhibitors.

4.4 PrEP in HIV-1 Discordant Couples: Need for a Clinical Trial

If found to be safe and effective, HIV-1 discordant couples will be a priority target group for PrEP since the majority of HIV-1 transmissions in Africa occur within stable HIV-1 discordant relationships [2]. Prevention options for such couples are currently limited. The majority of HIV-1 infected partners in discordant couples do not qualify for ART initiation, based on no AIDS-defining illness or CD4 criteria, limiting this potential strategy to prevent HIV-1 transmission. Additionally, HIV-1 discordant couples have often been together for years with low condom use, before learning of their HIV-1 discordant serostatus. Thus, HIV-1 discordant couples who stay together desire prevention strategies in addition to condoms. Finally, in Africa, pregnancy is often an important objective, particularly for HIV-1 uninfected women in a stable, HIV-1
discordant relationship. If HIV-1 prevention alternatives and pregnancy opportunities are presented as an "either/or" situation, such as with condoms, the desire for pregnancy will often supersede that for HIV-1 prevention, resulting in continued high-risk exposures.

There is a need for an array of effective prevention strategies, since none will be 100% effective or be acceptable and suitable for all risk groups and cultural contexts. With microbicide, vaccine and other novel pharmacological interventions years away, it is a public health priority to test the safety and efficacy of PrEP among HIV-1 discordant couples. Implementation of a PrEP trial among HIV-1 discordant couples has additional benefits:

- Since both partners in the HIV-1 discordant relationship are followed, further insight on biologic and behavioral factors modulating efficacy can be gained by characterizing whether there is a ‘threshold’ of PrEP efficacy based on frequency and quantity of HIV-1 exposure as assessed through sexual behavior, CD4, and viral load in the HIV-1 infected partner. As demonstrated by analysis of HIV-1 discordant couples in Rakai [23, 84, 85], biologic and behavioral data on both partners are useful in identifying potential interventions to reduce HIV-1 transmission and susceptibility, and inform evaluation of those interventions in clinical trials (e.g. effect of male circumcision and HIV-1 level on HIV-1 infectiousness). This efficacy analysis will enable modeling and development of guidelines about the relative benefit: risk ratio with respect to HIV-1 transmission by treating the HIV-1 infected partner with combination ART to reduce viral load versus providing PrEP to the susceptible partner, based on sexual behavior and the HIV-1 infected partner’s CD4 and viral load.

- PrEP adherence by HIV-1 uninfected partners and their frequency of drug sharing with their HIV-1 infected partners – two related issues that have significant potential to impact PrEP efficacy among HIV-1 discordant couples – can be simultaneously assessed by testing drug levels.

- Finally, current, smaller PrEP trials may demonstrate efficacy, but with wide confidence intervals, which could span very low efficacy estimates. It is critical that sufficiently-powered clinical trials of PrEP be conducted that will rule out <30% efficacy, since if PrEP is to be implemented if found to be effective, the potential for low efficacy must be excluded, given the drug costs and potential safety monitoring costs for PrEP. Moreover, if found to be efficacious, tight estimates of PrEP efficacy would be needed for planning subsequent non-inferiority studies of PrEP. While these final goals need not be achieved solely by a PrEP study among HIV-1 discordant couples, this clinical trial will have sufficient statistical power to achieve these objectives.

Within the context of HIV-1 discordant couples, PrEP offers a potential promising, safe, non-contraceptive method to prevent HIV-1 acquisition that may be applicable regardless of the stage of disease for the HIV-1 infected partner. However, public health concerns must be evaluated regarding safety, risk compensation, and selection of resistant viruses, thus justifying the objectives of this clinical trial of PrEP.

### 4.4.1 Potential Benefits of the Study to Participants
Participants in this study will benefit from HIV-1 education and prevention messages. In particular, couples enrolled in this study will receive regular and ongoing couples HIV-1 prevention counseling, conducted by counselors trained in issues specifically relevant to HIV-1 discordant couples. Participants will receive free HIV-1, STI, and HBV serologic testing and free medical treatment for diagnosed curable STIs. Those found to be susceptible to HBV will be offered standard HBV vaccinations. HIV-1 infected partners and participants who acquire HIV-1 infection during the study will be provided with HIV-1 services, including CD4 T cell counts and access to ART and opportunistic infection prophylaxis that will be used in accordance with national policies.

4.4.2 Potential Benefits Should the Intervention Prove Effective and Safe

HIV-1 discordant couples are particularly likely to benefit if TDF and/or FTC/TDF prophylaxis is found to be effective in preventing HIV-1 acquisition and has limited toxicity. The cost of chemoprophylaxis is lower than the cost of treating HIV-1 infected individuals with multiple antiretroviral regimens, coupled with costs of lost productivity. HIV-1 incidence remains high in many parts of sub-Saharan Africa, in spite of widespread behavioral change education policies. Thus, the identification of novel approaches to decreasing HIV-1 transmission using simplified antiretroviral regimens in high-risk populations is timely and of critical importance.

4.4.3 Risk/Benefit Analysis

Animal studies and an extensive safety record in humans, including among pregnant women, suggest that TDF and FTC/TDF chemoprophylaxis may prove to be highly effective for HIV-1 prevention while having little toxicity. Clinical trials are essential because animal models are not yet known to be predictive of efficacy in humans, and confirmation of safety in HIV-1 uninfected people is required. At this time, there is no evidence to favor either TDF or FTC/TDF for PrEP, nor is there sufficient evidence that either TDF or FTC/TDF PrEP is superior to placebo among HIV-1 discordant couples receiving standard prevention measures. Chemoprophylaxis may prove to be ineffective in people because of poor adherence or because HIV-1 transmission is facilitated by disruption of mucosal barriers during sexual intercourse. The toxicity and tolerability of daily oral TDF and FTC/TDF in HIV-1 uninfected humans has not been established in large numbers of people. Low level TDF and FTC/TDF toxicity may have been obscured in studies of HIV-1 infected persons because of symptoms due to HIV-1 infection or toxicity due to concomitant medication. The study described in this protocol is optimized to evaluate the risks and benefits of daily oral TDF and FTC/TDF with respect to laboratory and clinical AEs and prevention of HIV-1 infection.
4.4.4 **Justification for Placebo**

While animal studies indicate potential high efficacy of TDF and FTC/TDF PrEP and human studies of TDF and FTC/TDF have shown very favorable safety and pharmokinetics, the relevance of the macaque SIV and SHIV challenge models for human HIV-1 acquisition is not known. Until a placebo-controlled PrEP trial demonstrates safety and efficacy in humans, a state of equipoise will exist for whether use of PrEP is justified for preventing HIV-1 acquisition. Given this state of equipoise, placebo-controlled PrEP trials are ethical, since the efficacy of PrEP is not known and use of a placebo allows the investigators and study participants to remain blinded, ensuring an objective and accurate assessment of safety and efficacy. Placebos also are a safeguard to remind study participants that they may not be receiving an active product, and thus should practice known effective risk reduction strategies such as condom use.

4.4.5 **Comparison to Other Trials of PrEP**

The concept of pre-exposure chemoprophylaxis against HIV-1 acquisition is a topic of considerable global public health interest. At the time of this protocol, seven studies of PrEP, using TDF or FTC/TDF, are completed, ongoing, or planned. These studies are being conducted on four continents, among heterosexual men and women, men who have sex with men, and injection drug users. A comparison of the study populations is presented in Table 2.

The diversity in study populations – in terms of gender, region of the world, circulating HIV-1 subtypes, route of HIV-1 exposure, and prevalence of cofactors for HIV-1 acquisition and transmission – is necessary, given the potential for PrEP to have different safety and efficacy in different populations, which will influence policy decisions about implementation of PrEP for different target groups. Thus, it will be valuable that PrEP trials will be conducted in populations representing both men and women, with different routes of HIV-1 acquisition, and with different comorbidities. Ongoing studies will provide important information on the safety and efficacy of PrEP, but their sample sizes and number of endpoints will not generate definitive results. Importantly, none of these trials will test PrEP among HIV-1 discordant couples.

4.4.6 **Justification for Parallel Comparison of TDF and FTC/TDF as PrEP**

To date, no human trials evaluating the efficacy of PrEP using either TDF or FTC/TDF have been completed. There is evidence from non-human primate studies that both TDF and FTC/TDF PrEP may have high efficacy in preventing HIV-1 acquisition. Some animal model studies suggest that FTC/TDF may have higher efficacy for prevention of HIV-1 than TDF alone, and there is biologic plausibility that combination therapy could more effective than single-drug therapy. However, the significance and validation of the primate model to sexual HIV-1 transmission among humans is unknown, and thus it is yet to be determined whether TDF and
FTC/TDF would have substantive differences in efficacy among human populations when used as PrEP.

Several considerations support the need to evaluate TDF and FTC/TDF in parallel for use as PrEP against HIV-1 acquisition. First, cost differences between TDF and FTC/TDF as PrEP may argue for use of TDF alone if found to be similar in efficacy to FTC/TDF, or even if found to be slightly less efficacious. Both TDF and FTC/TDF will be made in generic form within the next few years, and thus their total price will undoubtedly decrease substantially. However, it is likely that generic FTC/TDF will continue to be priced higher than generic TDF, if solely for differences in cost of manufacturing. Evaluating the cost-benefit differences for consideration of TDF and FTC/TDF will ultimately be facilitated through a study evaluating the efficacy of these medications in parallel in a population with a similar route of HIV-1 exposure.

Second, there is the potential that FTC/TDF will carry additional toxicity risks beyond TDF alone. Although FTC is widely felt to be an extremely safe and well-tolerated medication when used for treatment of persons with HIV-1 infection, the occurrence of side effects among HIV-1 uninfected persons has yet to be evaluated in a large clinical trial.

Third, the relative rates of resistance among persons who become infected with HIV-1 in spite of TDF and FTC/TDF PrEP are unknown. The barrier to resistance for TDF is considerably higher than that for FTC. Importantly, FTC resistance confers cross-resistance to lamivudine (3TC), an important component of first-line HIV-1 treatment regimens, as well as regimens for the prevention to mother-to-child HIV-1 transmission (PMTCT). It is possible that the combination of FTC/TDF will slow the development of FTC resistance in individuals exposed for brief periods after seroconversion, although this is unknown. A parallel comparison trial will allow concurrent evaluation of both study drug efficacy and resistance rates, as, from a public health standpoint, it is both efficacy and resistance that will contribute to consideration of whether and how to implement PrEP, if found to prevent HIV-1 acquisition. For example, FTC/TDF may be found to be extremely efficacious (e.g., 90%) in preventing HIV-1 acquisition, in which case even modestly high rates of FTC or TDF resistance among seroconverters might be tolerated from a public health standpoint. On the other hand, if TDF and FTC/TDF are found to have similar efficacy, with similar low rates of TDF resistance, and some low rate of FTC resistance among those using FTC/TDF, TDF might be chosen for implementation. Modeling studies have estimated that resistance rates among seroconverters in the ongoing and planned PrEP studies will be very low, and it will be important to compare both TDF and FTC resistance rates across studies and in analyses pooling data from all trials.

Thus, there are compelling reasons to consider a comparison of TDF and FTC/TDF for PrEP for prevention of HIV-1 acquisition. This trial will be a parallel comparison, which will allow concurrent measurement of rates of
HIV-1 acquisition, resistance among seroconverters, and adverse events among individuals randomized to TDF, FTC/TDF, and placebo. Although this trial will not be sufficiently powered to statistically assess equivalence in efficacy for TDF versus FTC/TDF (such a trial would require >12,000 individuals to be randomized to TDF vs. FTC/TDF), the parallel presentation of efficacy, adverse events, and resistance will be useful to policy makers considering guidelines for PrEP implementation, if found to be successful. Lastly, this parallel comparison of TDF and FTC/TDF among HIV-1 discordant couples will be augmented by pooled analyses with other ongoing trials of either TDF or FTC/TDF compared to placebo, which will increase the power to evaluate efficacy, resistance in seroconverters, and safety of TDF compared to FTC/TDF as PrEP.

4.4.7 Assessment of PrEP Use in Pregnancy

As detailed in Section 4.3.3., limited data suggest safety of TDF and FTC/TDF during pregnancy, although controlled studies have not been conducted among HIV-1 infected or uninfected women. For the current PrEP trial, women will be counseled monthly on the available safety information related to use of TDF and FTC/TDF in early pregnancy and on contraception options, with contraception available at no cost at the research sites. Women will be monitored monthly for pregnancy and will stop study drug if pregnancy is detected.

Less than 20% of women in sub-Saharan Africa use a modern, non-barrier method of contraception, such as hormonal methods, an intrauterine device, or tubal ligation [86]. Among stable HIV-1 discordant couples, use of contraception is even more infrequent; we have found that <10% of HIV-1 discordant couples in the ongoing Partners in Prevention Trial use non-barrier contraceptives (i.e., other than condoms – notably, however, participants in that study reported 75% condom use after being counseled about their HIV-1 discordant status). Moreover, the desire for safe options to allow conception is great among HIV-1 discordant couples. If PrEP is to be a viable public health option, its safety in women who may become pregnant requires careful, controlled assessment. With frequent pregnancy testing, discontinuation of study drug early in pregnancy (at a maximum of ~6 weeks of gestation, given monthly testing), and follow-up of infants exposed in utero, the current trial aims to provide a rigorous evaluation of the safety of this potential HIV-1 prevention intervention within this high-risk population.

4.4.8 Assessment for PrEP Use During Lactation

Limited animal data suggest that tenofovir levels in breast milk may be significantly reduced compared with serum concentrations. Moreover, while the oral bioavailability of tenofovir disoproxil fumarate (the pro-drug formulation that is the component of TDF tablets) is high, this compound undergoes esterase hydrolysis during absorption and is converted to tenofovir in the bloodstream. It is tenofovir that is excreted in breastmilk.
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

[59]. Tenofovir, when not in the DF form, has poor oral bioavailability [87] and thus it is expected that infant absorption of tenofovir will be low [59].

No data are available concerning excretion of FTC into breast milk or absorption by breastfed infants. However, data from studies of 3TC suggest FTC may be present in breast milk. Importantly, lamivudine or emtricitabine are components of first-line therapy for treatment of HIV-1 infection in infants [88].

For the present study, HIV-1 uninfected women who are breastfeeding will be excluded from study participation. Given the high prevalence of breastfeeding in sub-Saharan Africa, where women may serially breastfeed several infants, additional studies will be essential to demonstrate the safety of PrEP for infants potentially exposed to PrEP medications through breast milk, if PrEP is shown to be efficacious in preventing HIV-1 acquisition.

4.4.9 PrEP and HBV Infection

TDF and FTC/TDF have activity as treatments against HBV infection. Ongoing large clinical studies are assessing the safety and efficacy of these medications for treatment of HBV. Some data suggest the potential for hepatitis flares among individuals treated with TDF or FTC/TDF, especially after withdrawal of these medications. There are only limited data on the safety of withdrawal of these medications when used as PrEP among HIV-1 uninfected, HBV infected persons.

For the present study, we have excluded HIV-1 uninfected individuals with chronic HBV infection. We anticipate that <10% of individuals screened for this study will be chronically infected with hepatitis B. As detailed in Table 2, some of the other ongoing or planned PrEP studies will evaluate the safety of TDF and FTC among individuals infected with HBV. If these, or other studies demonstrate safety of treatment and withdrawal of TDF and/or FTC/TDF for HIV-1 uninfected, HBV infected persons while our study is ongoing, a protocol revision may be initiated to permit inclusion of HBV infected partner participants.

4.5 Summary and Rationale

Proposed criteria for PrEP regimens have been recently reviewed [27], and NRTIs have the best combination of potency, long half-life for once daily dosing, high genital concentrations, safety, tolerability, and high resistance thresholds. Accordingly, non-human primate and human PrEP research have focused on potent and well-tolerated NRTIs, which meet these criteria, particularly tenofovir disoproxil fumarate (TDF) and emtricitabine/tenofovir (FTC/TDF). TDF and FTC/TDF have long half-lives, permitting once daily dosing, and excellent safety and tolerability profiles, including lack of significant drug interactions with hormonal contraceptives and tuberculosis drugs, which may be commonly used in target populations for PrEP.
For stable, heterosexual, HIV-1 discordant partners in particular, there is a critical public health need to identify non-contraceptive based interventions that can prevent HIV-1 acquisition. There are two main reasons for initiating a trial among heterosexual HIV-1 discordant couples to evaluate the efficacy of PrEP in reducing HIV-1 transmission:

1. The majority of new HIV-1 infections in Africa, the region hardest hit by the pandemic, occur among HIV-1 discordant couples. This estimate was validated by the 2005 Ugandan population-based serosurvey which indicated that up to 65% of incident infections occur among married couples [2].

2. Only a trial among HIV-1 discordant couples can examine the impact of biological and behavioral characteristics of both HIV-1 susceptible and infected partners on the efficacy of PrEP. In particular, the effect of the HIV-1 plasma viral load of the infected partner may be important in determining the efficacy and utility of PrEP. This critical exposure cannot be measured in other PrEP studies. Indeed, only a study that enrolls couples can assess HIV-1 infected partners' perceptions of PrEP, changes in sexual behavior as a result of PrEP use, and the extent to which PrEP modifies the risk of transmission based on differences in HIV-1 viral load and CD4 count of the HIV-1 infected partner.

The current protocol details a 3-arm, placebo-controlled, proof-of-concept, phase III safety and efficacy trial of once-daily TDF, FTC/TDF, or placebo taken by HIV-1 uninfected partners within heterosexual HIV-1 discordant couples for prevention of HIV-1 transmission, with follow-up of HIV-1 uninfected participants (on study drug, unless held/discontinued for pregnancy/breastfeeding or for toxicity) for a minimum of 24 and up to a maximum of 36 months, with follow-up of HIV-1 seroconverters (with study drug stopped at the time of detection of HIV-1 seroconversion) for at least 12 months after seroconversion.

5. STUDY OBJECTIVES

5.1 Primary Aims

5.1.1 Primary Aim 1a

- To measure the efficacy of once daily pre-exposure prophylaxis (PrEP) with TDF or FTC/TDF in preventing HIV-1 acquisition among HIV-1 uninfected persons within heterosexual HIV-1 discordant couples.

5.1.2 Primary Aim 1b

- To assess the safety of daily PrEP using TDF or FTC/TDF by comparing rates of adverse events (AEs) among HIV-1 uninfected individuals randomized to TDF or FTC/TDF PrEP to those randomized to placebo.

5.2 Secondary Objectives
5.2.1 Factors Influencing Efficacy

- To evaluate the efficacy of PrEP by the level of HIV-1 exposure for HIV-1 uninfected partners within HIV-1 discordant couples, defined both by the frequency of sexual activity and the HIV-1 viral load in the HIV-1 infected partner.

- To assess efficacy of PrEP by gender of the HIV-1 uninfected partner.

- To measure the effect on efficacy of other factors, including CD4 count of the HIV-1 infected partner and, for both partners, herpes simplex virus type 2 (HSV-2) serostatus, sexually transmitted infections (STIs), and male circumcision.

5.2.2 Adherence

- To assess adherence to once daily TDF and FTC/TDF PrEP among HIV-1 uninfected persons within HIV-1 discordant couples, and the effect of adherence on efficacy of PrEP to prevent HIV-1 acquisition.

- To evaluate the frequency of PrEP drug sharing between the HIV-1 uninfected and HIV-1 infected partners within HIV-1 discordant couples, as measured by drug assays in HIV-1 infected partners.

5.2.3 Risk Compensation

- To characterize the effects of once daily TDF or FTC/TDF PrEP on the sexual behaviors of HIV-1 uninfected individuals within HIV-1 discordant partnerships.

- To compare risk behaviors among HIV-1 discordant couples previously enrolled in the Partners in Prevention trial (which evaluated the efficacy of HSV-2 suppressive therapy when given to the HIV-1 infected partner in preventing HIV-1 transmission), by examining changes in sexual behaviors when the HIV-1 infected versus HIV-1 uninfected partner is receiving study drug.

5.2.4 Safety

- To assess the effect of TDF and FTC/TDF chemoprophylaxis on the rate of congenital abnormalities and growth among infants born to HIV-1 uninfected female participants who become pregnant during the study (and in whom study drug is stopped at the time pregnancy is detected, using monthly pregnancy testing).

5.2.5 Effect of PrEP on early HIV-1 disease
Among those initially HIV-1 uninfected individuals in the trial who seroconvert to HIV-1, to assess the effect of PrEP on:
- plasma HIV-1 viral load and CD4 cell counts during the first 12 months after HIV-1 seroconversion.
- frequency of genotypic and phenotypic antiretroviral drug resistance
- other clinical, immunologic, and virologic parameters of HIV-1 disease.

5.3 Tertiary Objectives

- To utilize stored samples for evaluation of immunogenetic and virologic determinants of HIV-1 transmission between transmitting and non-transmitting HIV-1 discordant couples, including viral phenotype and genotype, HIV-1 co-receptor usage, innate immune function polymorphisms, human leukocyte antigen (HLA) match and other host genetic factors.

6. STUDY DESIGN

6.1 Overall Design

This study is a Phase III, multi-site, randomized, double-blind, placebo-controlled, three-arm trial evaluating the safety and efficacy of pre-exposure chemoprophylaxis with either TDF or FTC/TDF, administered orally once daily, for prevention of HIV-1 acquisition among HIV-1 uninfected individuals within an HIV-1 discordant partnership.

Within the HIV-1 discordant partnerships, the HIV-1 infected partner must have a CD4 count ≥250 cells/mm$^3$ and must not otherwise qualify for initiation of ART at the time of study screening, and may not be on ART at the time of enrollment. However, HIV-1 infected partners who enroll in the study will be referred for ART initiation, and other HIV-1 care, according to national guidelines, and may begin ART at any point after enrollment the study.

The HIV-1 uninfected partner in the couple must report an average of 6 coital acts in the past 3 months. Eligibility determination of the HIV-1 uninfected partner will include normal renal, liver, and hematologic function based on clinical and laboratory screening. HIV-1 uninfected partners must be uninfected with hepatitis B, as determined by a negative test for hepatitis B surface antigen. Hepatitis B seronegative participants will be offered hepatitis B vaccination at no cost.

We will randomize 3900 eligible and consenting HIV-1 negative participants to receive once daily study drug in a 1:1:1 ratio to either 300 mg TDF (Viread®) or FTC 200 mg/TDF 300 mg (Truvada®) or placebo (thus, 1300 in each study arm). Because similarly-appearing tablets are not available for TDF and FTC/TDF, participants will take two tablets daily. Those randomized to the TDF arm will take active TDF + placebo FTC/TDF. Those randomized to the FTC/TDF arm will take placebo TDF + active FTC/TDF. Those randomized to the placebo arm will take placebo TDF + placebo.
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

FTC/TDF. Active and placebo TDF are indistinguishable, as are active and placebo FTC/TDF. All study medication will be taken orally once daily.

Participants will be followed on study drug for a minimum of 24 months and up to a maximum of 36 months. This follow-up schedule is designed to result in accumulation of sufficient person-years of follow-up and study endpoints, for this endpoint-driven trial. Importantly, follow-up of up to 36 months for some study participants will provide important long-term adherence and safety data regarding use of PrEP in HIV-1 uninfected individuals.

Participants will be followed for 1 month after study drug is discontinued in order to identify if PrEP delays seroconversion and to avoid misclassification of HIV-1 status at the exit visit.

Rapid HIV-1 tests will be performed at monthly visits to minimize the time participants could be on mono or dual NRTI therapy after HIV-1 acquisition. HIV-1 seroconverters will be followed for at least 12 months after their first HIV-1 seropositive visit.

HIV-1 uninfected women will be tested for pregnancy monthly; women who become pregnant will stop study medication at the time of pregnancy detection. Infants born to these women will be followed soon after birth and then quarterly for 1 year for clinical evaluation for teratogenicity, parameters of growth, and early renal function. Breastfeeding women will be excluded from study participation.

6.2 Study Participants

6.2.1 Description of Population

The study will enroll 3900 heterosexual HIV-discordant couples, with approximately 500-800 couples from each participating study site. The final sample size will be determined by the rate of accrual of confirmed endpoints in this endpoint-driven trial. For purposes of this study, heterosexual couples are defined as sexual partners of the opposite gender who are married, have been living together, or otherwise consider each other a primary partner. In order to be considered eligible, both partners must expect to maintain their relationship for the study period. One partner in the couple must be infected with HIV-1 and will be referred to throughout this protocol as the index participant. The index (HIV-1 infected) participant may be either male or female. The other partner must be HIV-1 uninfected partner and will be referred to throughout this protocol as the partner participant. Couples will not be excluded from study participation if either the index (HIV-1 infected) participant or the partner (HIV-1 uninfected) participant within the couple has other sexual partners, including other primary sexual partners (e.g., a male participant with multiple wives). However, in situations where multiple primary relationships exist (e.g., a male participant with multiple wives), only one index-partner pair will be enrolled – this will be done to maintain independence of HIV-1 transmission risk within the study.

Participants will be recruited from a variety of sources, including HIV-1 voluntary counseling and testing (VCT) centers, antenatal clinics and programs for prevention of mother-to-child HIV-1 transmission, referral from HIV-1 care providers, and community
promotion activities for couples’ VCT and other HIV-1 related prevention and care activities. Participants may also be referred to the study from other local research projects and health and social service providers serving the target study population.

HIV-1 discordant couples previously enrolled in the Partners in Prevention HSV/HIV Transmission Trial will be allowed to enroll in this PrEP trial if they meet study eligibility criteria. For such couples, only those who had no more than 2 missed visits and no more than 2 visits outside the visit window during the course of the Partners in Prevention HSV/HIV Transmission Trial will be permitted to be screened for the PrEP trial. Those who do not meet these criteria will generally be excluded from screening participation, although individual exceptions may be considered after discussion between site staff and the Protocol Chair and Medical Director. A three month break between termination of the Partners in Prevention HSV/HIV Transmission Trial and screening for the Partners PrEP Trial will be required.

### 6.2.2 Partner (HIV-1 Uninfected) Participants

#### 6.2.2.1 Inclusion Criteria

Potential partner (HIV-1 uninfected) participants must meet the following criteria (by self-report, unless otherwise indicated) in order to be eligible for inclusion in the study:

- Of legal age to provide independent informed consent for research per local regulations and guidelines
- Age \( \geq 18 \) and \( \leq 65 \)
  
  *This specific additional age restriction reflects that pharmacokinetic data for TDF and FTC/TDF are unavailable or are limited for individuals less than 18 years of age or greater than 65 years of age.*
- Able and willing to provide written informed consent to be screened for and to take part in the study
- Part of a heterosexual couple in which one partner meets the study eligibility criteria for index (HIV-1 infected) participants and the other partner meets the study eligibility criteria for partner (HIV-1 uninfected) participants, including the following criteria for the couple:
  
  - are partners who are sexually active (defined as having had vaginal intercourse with the partner [HIV-1 uninfected] participant at least 6 times in the last three months)
  
  - plan to remain in the relationship for the duration of the study period.
Each study site will develop appropriate criteria for determining whether a couple is likely to remain in the relationship (i.e., married, duration of partnership, cohabitation, children in the home).

- HIV-1 uninfected based on parallel negative HIV-1 rapid tests, both at study screening and at the enrollment visit

- Able and willing to provide adequate locator information for study retention purposes, as defined by local standard operating procedures

- Adequate renal function, defined by creatinine clearance ≥ 60 ml/min estimated by the Cockcroft Creatinine Clearance Formula AND serum creatinine level of ≤ 1.3 mg/dL for men / ≤1.1 mg/dL for women, measured within 56 days of enrollment

- Adequate hepatic function, defined by total bilirubin ≤1.5x upper limit of normal AND hepatic transaminases (ALT and AST) <2x upper limit of normal, measured within 56 days of enrollment

- Adequate hematologic function, defined by absolute neutrophil count >1,300/mm³, platelets >125,000/mm³, and hemoglobin >11 g/dL, measured within 56 days of enrollment

- Not infected with HBV, as determined by a negative hepatitis B surface antigen test, further defined in Appendix VI

**Note:** Potential partner (HIV-1 uninfected) participants who do not meet the renal, hepatic, and/or hematologic inclusion criteria at screening will be allowed to repeat the screening process one additional time. The rescreening process can occur any time >28 days after the initial screening labs were obtained. All other eligibility criteria for these potential participants (as well as all eligibility criteria for the corresponding index participant) must be met for these individuals to be eligible to enroll.

### 6.2.2.2 Exclusion Criteria

Potential partner (HIV-1 uninfected) participants who meet any of the following criteria (by self-report, unless otherwise indicated) will be excluded from the study:

- Current pregnancy, or planning to become pregnant during the study period

- Current breastfeeding
• Must not be currently enrolled in another HIV-1 vaccine or prevention trial.

• Known plans to re-locate or travel away from the study site for more than two consecutive months during the study period.

• Repeated positive (≥1+) urine dipstick tests for glycosuria or proteinuria. Participants with definite evidence of glucose and/or protein in their urine will not be eligible. If a urine dipstick is positive for either glucose and/or protein at the first screening visit, a second urine sample will be tested.

• Active and serious infections, including active tuberculosis infection or osteomyelitis and all infections requiring parenteral antibiotic therapy; active clinically significant medical problems including cardiac disease (e.g., symptoms of ischemia, congestive heart failure or arrhythmia), pulmonary disease (steroid dependent chronic obstructive pulmonary disease), diabetes requiring hypoglycemic medication; and previously diagnosed malignancy expected to require further treatment.

  Note: Enrollment procedures should be delayed in the case of a febrile illness (e.g., malaria) until the potential participant has been treated and recovered.

• History of pathological bone fractures not related to trauma

• Receiving ongoing therapy with any of the following: antiretroviral therapy (ART), including nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, protease inhibitors or investigational antiretroviral agents, interferon (alpha, beta, or gamma) or interleukin (e.g., IL-2) therapy, metformin, aminoglycoside antibiotics, amphotericin B, cidofovir, systemic chemotherapeutic agents, other agents with significant nephrotoxic potential, other agents that may inhibit or compete for elimination via active renal tubular secretion (e.g., probenecid), and/or other investigational agents

• At enrollment, has any other condition that, based on the opinion of the investigator or designee, 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 (including, for couples previously enrolled in the Partners in Prevention HSV/HIV Transmission Trial, having more than 2 missed visits or more than 2 visits outside the visit window)

6.2.3 Index (HIV-1 Infected) Participants
6.2.3.1 Inclusion Criteria

Potential index (HIV-1 infected) participants must meet the following criteria (by self-report, unless otherwise indicated) in order to be eligible for inclusion in the study:

- Of legal age to provide independent informed consent for research per local regulations and guidelines.

- Able and willing to provide written informed consent to be screened for and to take part in the study.

  Note: Index participants who are not willing to provide genital tract specimens for HIV-1 viral load quantification but who are willing to undergo all other study procedures will be considered eligible for inclusion in the study.

- Part of a heterosexual couple in which one partner meets the study eligibility criteria for index (HIV-1 infected) participants and the other partner meets the study eligibility criteria for partner (HIV-1 uninfected) participants, including the following criteria for the couple:
  
  - are partners who are sexually active (defined as having had vaginal intercourse with the partner [HIV-1 uninfected] participant at least 6 times in the last three months)
  
  - plan to remain in the relationship for the study period

Each study site will develop appropriate criteria for determining whether a couple is likely to remain in the relationship (i.e., married, duration of partnership, cohabitation, have children).

- HIV-1 infected based on positive EIA.

- CD4 cell count \(\geq 250 \text{ cells/mm}^3\) and not otherwise meeting national guidelines for initiation of antiretroviral therapy.

- No history of any clinical AIDS-defining diagnoses.

- Able and willing to provide adequate locator information for study retention purposes, as defined by local standard operating procedures.

6.2.3.2 Exclusion Criteria

Potential index (HIV-1 infected) participants who meet any of the
following criteria (by self-report, unless otherwise indicated) will be excluded from the study:

- Current use of antiretroviral therapy
- Currently enrolled in another HIV-1 treatment trial
- At enrollment, has any other condition that, based on the opinion of the investigator or designee, 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 (including, for couples previously enrolled in the Partners in Prevention HSV/HIV Transmission Trial, having more than 2 missed visits or more than 2 visits outside the visit window)

Note: Current pregnancy in the potential index (HIV-1 infected) participant is not an exclusion criterion for this study. Pregnant index partners will be referred to services for antenatal care and prevention of mother-to-child transmission of HIV-1, or treated at the study site, depending on the referral structure for the site.

Note: Current breastfeeding in the potential index (HIV-1 infected) participant is not an exclusion criterion for this study. HIV-1 infected women who are breastfeeding will be counseled on site or referred to prevention of mother-to-child transmission programs to receive information on HIV-1 transmission risks associated with breastfeeding, in accordance with WHO and national recommendations concerning breastfeeding by HIV-1 infected women in developing country settings.

6.3 Recruitment

The process of identifying HIV-1 discordant heterosexual couples in which both partners meet the study eligibility criteria will be time- and labor-intensive. Each site will therefore establish local recruitment and screening methods that operationalize protocol-specified requirements for eligibility determination in a manner that is tailored to and most efficient for the local study setting and target study population.

Recruitment strategies will include partnering with existing voluntary counseling and testing (VCT) centers and outreach workers, public promotion of couples VCT by well-known figures and community organizations such as churches, and community mobilization around couples VCT promotion (e.g., around Valentine’s Day). Recruitment materials will educate couples about the probability of being HIV-1 discordant based on available data, and risks of unknown HIV-1 discordancy in terms of transmission to the HIV-1 uninfected partner, and will emphasize the benefits of couples VCT with
specialized counseling services. Couples may be recruited for possible inclusion in the study through referrals from VCT centers and other community-based organizations, direct outreach, or other activities conducted at the study sites.

Regardless of recruitment source, each partner in each couple will provide independent informed consent for screening. The screening process will proceed in a step-wise manner for both partners until either all screening procedures are completed or one or both of the partners is determined to be ineligible.

Although all required screening procedures may be completed in as few as two visits for each partner, additional visits may be conducted as needed (for example, if one or both partners want more time to consider whether to enroll in the study). At least one screening visit and the enrollment visit must be attended by both partners of a couple together, and at least one couples counseling session must take place during the screening process. The screening process must be completed over, at most, 56 days; in addition the partner (HIV-1 uninfected) participant must test HIV-1 negative and female partner (HIV-1 uninfected) participants must have a negative urine pregnancy test within 56 days prior to enrollment in the study as well as on the day of enrollment. In order to meet these requirements, partner (HIV-1 uninfected) participants will likely required to undergo HIV-1 and pregnancy testing more than once during the screening process. If the couple has not enrolled within 56 days of signing the screening consent form, all screening procedures will need to be completed again before the couple is eligible to enroll, with the exception of HIV-1 testing for index (HIV-1 infected) participants who had been laboratory confirmed during study screening to have HIV-1.

For those couples found to be eligible for the study, informed consent for study participation and enrollment in the study may proceed on the same day when eligibility is determined. Each partner will be asked to provide independent informed consent for study participation. For couples in which both partners are willing and able to provide informed consent, partner (HIV-1 uninfected) participants will be assigned at random to one of the three study treatment groups and provided with:

- supplies of the assigned study drug
- instructions for study drug storage and administration
- adherence counseling
- instructions to contact study staff with questions about the study and reports of side effects or other problems
- risk reduction counseling, condoms, and HIV-1 prevention information

Index (HIV-1 infected) participants of randomized partner (HIV-1 uninfected) participants will be provided with instructions to contact study staff with questions about the study, reports of genital symptoms and requests for STI-related services, as well as reports of other clinical symptoms.

Individuals who enroll in the study also may be offered participation in support groups for HIV-1 infected and HIV-1 uninfected persons (e.g., “post-test clubs”) and clinical services available through the study staff, according to local standards of care and prevalence of endemic infections, which may include contraceptives, Pap smear screening, malaria screening, Bactrim prophylaxis, chest x-rays for tuberculosis (TB) case detection, and — when consistent with TB prevalence and local TB program...
objectives — isoniazid for TB prophylaxis. STI treatment will be provided for treatable STIs based on either etiologic laboratory testing or syndromic management guidelines, according to local standards of care.

6.4 Co-enrollment Guidelines

Participants in this study may not take part in other concurrent randomized trials of experimental products or HIV-1 prevention strategies.

6.5 Participant Retention

Once a participant has enrolled in the study, the study site will make every reasonable effort to retain him or her for the duration of follow-up, in order to minimize bias associated with loss-to-follow-up. Both index (HIV-1 infected) and partner (HIV-1 uninfected) participants will be maintained in follow-up if their partner withdraws from the study and/or if their relationship ends prior to completion of follow-up.

Partner (HIV-1 uninfected) participants who seroconvert will continue with follow-up (off study drug), as detailed in the procedures for follow-up of seroconverters. Index (HIV-1 infected) partners of partner (HIV-1 uninfected) participants who seroconvert will continue for 3 months of formal follow-up as described in the seroconverter follow-up procedures.

An annual participant retention rate of at least 85 percent in the first year is targeted, with a retention rate of 80 percent at the end of 2 years. Study staff are responsible for developing and implementing local standard operating procedures to achieve this goal. Components of such procedures may 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 both study treatment groups to the overall success of the study.
- Collection of extensive locator information at the study screening visits and active review and updating of this information at each subsequent visit.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up of 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-1/AIDS and explain the purpose of HIV-1 prevention research and the importance of completing research study visits.

The data management center will generate twice monthly reports on the number and percentage of participants completing the follow-up visits throughout the course of the study. The Protocol Team will track retention rates closely and work with study sites as needed to take any required action to address below-target retention rates.

6.6 Participant Withdrawal

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 and Biostatistician. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, or local Institutional Review Boards (IRBs) or Ethics Committees (ECs) terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff will record the reason(s) for all withdrawals from the study in participants’ study records.

7. STUDY DRUG

7.1 Formulation

This study will randomize HIV-1 uninfected individuals (partner participants) in HIV-1 discordant couples to TDF 300 mg, co-formulated FTC/TDF at 200 mg / 300 mg respectively, or placebo. The doses of TDF and FTC/TDF are standard doses approved by the U.S. Food and Drug Administration. As defined in Sections 6.2.2 and 12.9.2, partner (HIV-1 uninfected) participants must have normal renal function in order to be eligible for the study, and study drug will be permanently discontinued if evidence of renal dysfunction develops during the study. For these reasons, renal dosing adjustments of TDF and FTC/TDF will not be needed in this study.

Because similarly-appearing tablets are not available for TDF and FTC/TDF, participants will take two tablets daily. Those randomized to the TDF arm will take active TDF + placebo FTC/TDF. Those randomized to the FTC/TDF arm will take placebo TDF + active FTC/TDF. Those randomized to the placebo arm will take placebo TDF + placebo FTC/TDF. Active and placebo TDF are indistinguishable, as are active and placebo FTC/TDF. All study medication will be taken orally once daily.

Tablets are stable in bottles for up to 4 years (stability information detailed in this section provided by Gilead Sciences). It has been demonstrated that FTC/TDF tablets are stable at 25°C and 60% relative humidity for up to 48 months, at 30°C and 65% relative
humidity for up to 24 months, and at 40°C and 75% relative humidity for up to 6 months. Additionally, tablets have been shown to be stable at 50°C for up to 1 month.

It has been demonstrated that TDF tablets are stable at 25°C and 60% relative humidity for up to 48 months, at 30°C and 65% relative humidity for up to 36 months, and at 40°C and 75% relative humidity for up to 6 months.

Although FTC/TDF tablets, tenofovir tablets, and placebo tablets to match each will be stored at the clinical site(s) under controlled temperature and humidity conditions (25°C, excursions not exceeding 15-30°C) to ensure stability of the product, the aforementioned data does support dispensing a 30 day supply to study participants who may keep their study agent in conditions that exceed these recommended storage conditions.

Additional information on drug information, side effects, and storage conditions can be found in the Viread® (tenofovir disoproxil fumarate) and Truvada® (emtricitabine/tenofovir disoproxil fumarate) package inserts (Appendices XIII and XIV).

7.2 Supply

TDF, FTC/TDF, and placebo tablets will be supplied by Gilead. Tablets will be packaged as a one-month supply (30 tablets of TDF or placebo TDF + 30 tablets of FTC/TDF or placebo FTC/TDF, according to the randomization groups defined in Section 7.1) in bottles with child-resistant screw caps. In addition to the tablets, each bottle contains a silica gel desiccant to protect the product from humidity and the polyester packing material that cushions it during handling and shipping. Gilead will prepare bottles of study agent that are each labeled with expiry date, storage conditions, and a study ID number, which will be assigned to participants at the time of randomization during the enrollment visit. Bottles will be packaged in 2-bottle kits – with one bottle containing TDF or placebo TDF and the second bottle containing FTC/TDF or placebo FTC/TDF. This will ensure that participants receive the correct pairing of active/placebo study medication.

7.3 Pharmacy Facilities

The pharmacy facilities will be located at the study sites and staffed by credentialed pharmacists or pharmacy technicians. The pharmacy will have adequate space to store sufficient quantities of study agent to assure continuous access to all study participants. The study drug will be stored in accordance with the drug manufacturer’s recommendations. Both pharmacy storage and the study pharmacy will be locked by a secure door. The pharmacy and storage facility will have climate-controlled environments, with controlled humidity and temperature to remain within limits allowed by the manufacturer for drug storage.

7.4 Drug Inventory

The pharmacist at each study site will receive the study agent and store it in the pharmacy. Access will be restricted to pharmacy personnel authorized by the pharmacist.
of record. The pharmacist will be responsible for keeping accurate records of the material received. At monitoring visits, the study drug inventory logs will be reviewed by the study monitors. At the end of the study, the pharmacist will perform the final drug accounting of unused study material on the proper log documents. Unused study agent will be disposed of as instructed by the Protocol Team.

7.5 Drug Dispensing

A pharmacist or pharmacy technician will be responsible for dispensing the drug to partner (HIV-1 uninfected) participants. Once such a participant is enrolled and assigned a study ID number at the enrollment visit, the pharmacist will receive a prescription which includes the study ID number. At enrollment, the pharmacist will dispense a set of two bottles labeled with the corresponding study ID numbers. At each monthly follow-up visit, a new set of two bottles will be dispensed. The number of unused tablets from the previous month’s bottles will be recorded. Returned tablets will not be re-dispensed. For each bottle dispensed, the pharmacist will enter the bottle label information and date in a Drug Dispensation Log. Participants who anticipate being away from the study site area for a 2 month period will be dispensed a 2 month supply of study drug on a limited basis.

Counseling on the medications being used, their side effect profiles, how to take the study medication, what to do if side effects are experienced, and the importance of not sharing study medication to optimize potential efficacy and to reduce the chances of developing resistance through suboptimal HIV-1 suppression if study medication is shared with the index (HIV-1 infected) partner or with others (including other spouses – e.g., a 2nd wife – if applicable) will occur at each study visit.

7.6 Adherence Counseling and Assessment

High adherence to study drug will be important for determining the efficacy of PrEP in preventing HIV-1 acquisition in this study. At each monthly visit, study staff will assess participant adherence with the assigned treatment regimen through a structured interview and tablet count. Study staff also will provide adherence counseling at each monthly visit, including instructions for what to do in the event of a missed dose – specifically to not double the next dose, to avoid toxicity. Adherence messaging will be reinforced by counselors, clinicians, and pharmacy staff. Weekly pill boxes will be provided to study participants to aid adherence; we have previously found, in the Partners in Prevention HSV/HIV Trial, that study participants taking daily medication feel that such an aid substantially helps their ability to remember to take study medication. Both the partner (HIV-1 uninfected) and index (HIV-1 infected) participants will be counseled at each visit about the risk of study drug sharing in terms of reducing efficacy in preventing HIV-1 acquisition in the partner participant and of increasing the possibility of development of viral resistance (and, consequently, later decrease in response to antiretroviral therapy) in the index participant.

7.7 Treatment Interruption

Use of study drug may be interrupted by the site Investigator, after consultation with the
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Protocol Chair, due to safety concerns for the participant or if the participant is unable or unwilling to comply with study procedures. All treatment interruptions will be documented on applicable case report forms. Participants who interrupt treatment will continue in follow-up for endpoint determination as originally scheduled (i.e., up to a maximum of 36 months).

7.8 Concomitant Medications

At enrollment or any time during follow-up, partner (HIV-1 uninfected) participants may not be receiving ongoing therapy with any of the following: ART, including nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, protease inhibitors or investigational antiretroviral agents, interferon (alpha, beta, or gamma) or interleukin (e.g., IL-2) therapy, metformin, aminoglycoside antibiotics, amphotericin B, cidofovir, systemic chemotherapeutic agents, other agents with significant nephrotoxic potential, other agents that may inhibit or compete for elimination via active renal tubular secretion (e.g., probenecid), and/or other investigational agents. Information on concomitant medications taken in response to adverse events (AEs) will be recorded on applicable study case report forms.

If an HIV-1 uninfected partner is prescribed post-exposure prophylaxis (PEP) against HIV-1 at any time during the study, regardless of the agents used, study drug will be held during the PEP period. PEP for sexual exposures is used rarely in the study areas, predominantly after sexual assault.

8. STUDY PROCEDURES FOR PARTNER (HIV-1 UNINFECTED) PARTICIPANTS

Partner (HIV-1 uninfected) participants will be randomized to receive study drug and will be monitored for HIV-1 seroconversion and adverse events, and thus they will be the focus of the primary endpoints for this study.

In general, enrollment criteria will be evaluated through study screening procedures. Eligible participants will be enrolled within 56 days of screening and followed at 4 week intervals for evidence of HIV-1 seroconversion, adherence to study agent, and clinical toxicity. If enrollment fails to occur within 56 days of the screening, and the couple wishes to participate in the study, they will need to repeat the screening visit procedures. Laboratory measures of safety will be performed quarterly. Participants who no longer wish to continue on randomized study medication will be encouraged to remain under follow-up, including for HIV-1 testing and counseling. A table detailing the study procedures for index participants is detailed in Appendix I. Unless otherwise specified, the laboratory procedures listed in this section are performed at the local study site laboratories.

8.1 Screening

Listed in this section are all required study screening procedures for partner (HIV-1 uninfected) participants. Each study site will establish the most optimal sequencing of
required screening procedures for the local study setting and target population. A minimum of two screening visits will be conducted to complete all required screening procedures with each potential participant; the second screening visit may occur on the same day as study enrollment, for those wishing to proceed with enrollment and for whom eligibility is confirmed during the screening process. Additional visits may be conducted as needed. For each couple, independent written informed consent will be obtained from both the index (HIV-1 infected) and partner (HIV-1 uninfected) participants prior to conducting other screening procedures. Both partners must attend at least one screening visit together. For potential participants who do not meet the study eligibility criteria, the screening process for both partners will be discontinued when ineligibility of either is determined. For potential participants who do meet the study eligibility criteria, the enrollment procedures may proceed immediately after completing the screening process (assuming that informed consent is obtained for study enrollment).

8.1.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for screening
-Locator information
- Behavioral eligibility information
- Demographic information
- HIV pre- and post-test counseling
- Couples counseling about HIV-1, including the significance of HIV-1 discordance
- Provision of condoms, other HIV-1 prevention supplies
- Contraception counseling and provision/referral
- Risk reduction counseling

8.1.2 Clinical Procedures

- Medical history
- Blood collection
- Urine collection
- Test results disclosure

8.1.3 Laboratory Procedures

- HIV-1 serology established by EIA
- HBV serology
  - This will include tests for HBV surface antibody (anti-HBs), and HBV surface antigen (HBsAg), detailed in Appendix VI.
- Serum chemistries
  - Total CO2 or bicarbonate, phosphate, creatinine, total bilirubin, AST, and ALT
- CBC
  - Total leukocyte count, automated three-part differential, total hemoglobin or hematocrit, and platelet count
8.2 Enrollment

The procedures listed in this section are conducted after all screening procedures are completed and, in particular, after eligibility has been confirmed and the participant and his/her partner have provided written informed consent to take part in the study. Enrollment must take place within 56 days of screening, or screening procedures will need to be repeated.

8.2.1 Administrative, Behavioral, and Regulatory Procedures

- Obtain informed consent
- Locator information
- Couples HIV-1 counseling
- Provision of condoms, other HIV-1 prevention supplies
- Risk reduction counseling
- Contraception counseling and provision/referral
- Comprehension questionnaire (Appendix XI)
  - Participants must complete this successfully, demonstrating clear understanding of each point. Counselors at the Enrollment Visit will provide additional counseling to potential participants about initially-incorrect answers.
- Randomization

8.2.2 Clinical Procedures

- Medical history questionnaire
- HBV vaccination, if indicated
- Blood collection
- Physical examination
- Genital exam for STI assessment
- STI treatment (based on local standard of care using WHO Syndromic STI Management guidelines for STI treatment of urethritis, vaginitis, cervicitis, and genital ulcer disease)
- Endocervical Pap smear (for sites where Pap smears are the standard of care for women, and where cytopathology and referral services for dysplasia are available)
- Vaginal swabs collection
- Urine collection
- Study drug supplies, instructions for use, and adherence counseling (after eligibility is confirmed and informed consent is provided)
8.2.3 Laboratory Procedures

- HIV-1 serology
- HSV-2 serology (will be done at the study site if results of ongoing studies of HSV-2 suppressive therapy to prevent HIV-1 acquisition demonstrate efficacy. Prior to those results becoming available, or if those results do not demonstrate efficacy, testing will be done in a batched fashion at the Central Laboratory)
- Syphilis serology
- Serum for local site archive and central archive
- Plasma for local site archive and central archive
- DNA archive (blood spots and whole blood) for HLA typing and host genetic polymorphisms of innate/adaptive immunity, including HIV-1 coreceptor polymorphisms at the University of Washington (UW)
- Urine archive
- Endocervical Pap smear (for sites where Pap smears are the standard of care for women, and where cytopathology and referral services for dysplasia are available)
- Endocervical swab archive for gonorrhea, chlamydia, trichomonas PCR (women only) on batched samples to assess prevalence of STIs across sites, to be performed at the UW
- Vaginal swab and slide for evaluation of bacterial vaginosis (women only)
- Urine pregnancy test (women only)
- Urine for gonorrhea, chlamydia, trichomonas PCR (men only) on batched samples to assess prevalence of urethral STIs across sites, to be performed at the UW

8.3 Follow-up

Partner (HIV-1 uninfected) participants will have monthly follow-up, with target dates scheduled every 28 days. Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, visits may be completed within a window around the target date. For partner (HIV-1 uninfected) participants, the window is 5 days before the target date and 5 days after. For those who return more than 5 days after the target date, the visit will be recorded as missed, an interim visit will be conducted, and study medication (sufficient to last until the next scheduled visit, plus 2 extra doses) will be dispensed.

At monthly follow-up visits, HIV-1 rapid testing will be performed, in the context of pre-test, risk reduction, and post-test counseling.
Participants will be assessed with respect to clinical symptoms; laboratory measurements of chemistry and hematology parameters will be done on a quarterly basis. Laboratory markers will also be checked at Month 1. In addition, if symptoms warrant, laboratory monitoring may be ordered at any time at the discretion of the clinical staff.

After Month 1, monthly visits can be conducted at home, by trained study staff, using standard operating protocols adapted from the Uganda Home-Based Voluntary Counseling and Testing Programme and the Uganda Home-Based AIDS Care. Monthly visits will focus on HIV-1 rapid testing, study drug dispensation, and adherence counseling.

Adherence will be measured by survey and pill count. Adherence counseling will be provided to all participants at each visit. Counseling will include reminders to contact study staff with questions about product use, as well as counseling to not share the study agent (including with the index [HIV-1 infected] participant). For participants who have adherence problems, efforts will be made to identify adherence strategies to increase their rates of product use throughout the course of the study.

For participants who do not complete scheduled visits within the allowable window, the visit will be considered “missed” and relevant case report forms will be completed to document the missed visit.

Participants who become infected with HIV-1 during follow-up will continue follow-up, according to seroconverter procedures.

Partner (HIV-1 uninfected) participants who become pregnant during follow-up will stop study drug, as detailed in Section 11. Pregnant women will be referred for prenatal care. Pregnancy testing will occur on a monthly basis for all female partner (HIV-1 uninfected) participants.

8.3.1 Administrative, Behavioral, and Regulatory Procedures

- Ongoing informed consent (as needed at all visits)
- Locator information
  - At all visits.
- HIV-1 risk behavior interview
  - At all visits
- Couples HIV-1 counseling (and/or individual counseling if more convenient)
  - At all visits.
- Provision of condoms, other HIV-1 prevention supplies
  - At all visits
- Risk reduction counseling
  - At all visits
- Contraception counseling and provision/referral
  - At all visits
- HIV-1 pre- and post-test counseling
  - At all visits
8.3.2 Clinical Procedures

- Medical history questionnaire
  - At monthly follow-up
- STI symptom questionnaire
  - At quarterly follow-up and at study exit.
  - At monthly visits in response to intercurrent symptoms/illnesses.
- Physical exam
  - Month 1 and every 3 months
  - At monthly visits in response to intercurrent symptoms/illness
- Genital exam for STI assessment:
  - At 12-monthly follow-up and at study exit.
  - At monthly visits in response to intercurrent symptoms/illnesses.
- Blood collection:
  - At monthly follow-up and at study exit.
- Urine collection
  - Monthly (women only, for pregnancy testing)
  - At Month 3 and at 12-monthly follow-up and at study exit
- Endocervical swab collection (women only):
  - At 12-monthly follow-up and at study exit.
- Vaginal swabs for evaluation of bacterial vaginosis
  - At 12-monthly follow-up and at study exit.
- STI treatment, if clinically indicated based on local standard of care, using either WHO Syndromic STI Management guidelines for treatment of urethritis, vaginitis, cervicitis and genital ulcer disease, or based on STI diagnostic tests
- Test results disclosure
  - As needed at all visits
- Collection of prior drug supplies, adherence assessment (structured interview and tablet count):
  - At all scheduled visits.
- Provision of study drug supplies, instructions for use, and adherence counseling:
  - At all scheduled visits, except at study exit
  - Additionally if needed/requested.

8.3.3 Laboratory Procedures

- HIV-1 serology
  - Monthly
- Syphilis serology:
  - Every 12 months, and when clinically indicated by the presence of an ulcer or rash suggestive of syphilis.
- Serum chemistries
  - Month 1 and every 3 months
• CBC
  - Month 1 and every 3 months
• Serum for local site archive and central archive
  - Month 1 and every 3 months
• Plasma for local site archive and central archive
  - Month 1 and every 3 months
• Blood spots for central archive
  - Every 6 months, which will permit back-up samples
• Whole blood archive for DNA archive HLA typing and host
genetic polymorphisms of innate/adaptive immunity, including
HIV-1 coreceptor polymorphisms at the UW
  - Every 6 months, which will permit back-up samples
• Urine archive
  - Month 3 then Month 12 and every 12 months thereafter
• Vaginal swab and slide for evaluation of bacterial vaginosis
  - Every 12 months
• Endocervical swab archive for gonorrhea, chlamydia,
trichomonas PCR (women only) on batched samples to
assess prevalence of STIs across sites, to be performed at the UW
  - Every 12 months
• Urine for gonorrhea, chlamydia, trichomonas PCR (men only)
on batched samples to assess prevalence of urethral STIs
across sites, to be performed at the UW
  - Every 12 months
• Urine pregnancy test (women only)
  - Monthly

8.4 Stop Visit

The final visit for each participant while on study medication will be designated the Stop
Visit. Some participants will complete the maximum of 36 months of follow-up, in which
case the Month 36 visit will be the Stop Visit. There is the potential for the trial to be
stopped earlier at any time by the Data and Safety Monitoring Board, in that case, Stop
Visits may occur at any point in an individual participant’s follow-up. All participants,
regardless of where in study follow-up they may be, will complete Stop Visit procedures.
These Stop Visits will include all procedures as defined for a 12-month visit.

8.5 Post-Study Drug Completion Visits

After completing follow-up on study drug, participants will have two post-study drug
follow-up visits, one and two months after completing the Stop Visit, to observe for
delayed endpoints. Of note, other PrEP studies (e.g., the South American iPrEx study
among MSM), will also have post-study drug visits (in that specific case, 2 months, plus
additional follow-up for those infected with hepatitis B).
8.5.1 Administrative, Behavioral, and Regulatory Procedures

- Locator information
- HIV-1 risk behavior interview
- Couples HIV-1 counseling (and/or individual counseling if more convenient)
- Provision of condoms, other HIV-1 prevention supplies
- Risk reduction counseling
- HIV-1 pre- and post-test counseling

8.5.2 Clinical Procedures

- Medical symptom questionnaire
- Physical exam
- Genital exam for STI assessment (if indicated based on symptoms)
- Blood collection
- Urine collection for pregnancy testing (women only)
- STI treatment, if clinically indicated, based on local standards of care, using either WHO Syndromic STI Management guidelines for treatment of urethritis, vaginitis, cervicitis and genital ulcer disease, or based on STI diagnostic tests
- Test results disclosure

8.5.3 Laboratory Procedures

- HIV-1 serology
- Serum chemistries
- Serum for local site archive and central archive
- Plasma for local site archive and central archive
- Urine pregnancy test (women only)

8.6 Interim Visits

Interim visits may occur at any time during the study. Interim visits may occur for the following reasons: (1) for operational reasons, e.g., a participant may request to reschedule, or to ask questions; (2) for product-related reasons, e.g., a participant may need additional study product or want to discuss problems with adherence to product use; (3) for AE-related reasons. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide appropriate medical care or make appropriate referrals; (4) for interim STI counseling and testing in response to STI symptoms; or (5) for other reasons at participant request. All interim contacts and visits will be documented in participants' study records and on applicable CRFs. If a study participant presents to an interim visit with symptoms suggestive of acute HIV-1 infection syndrome, rapid HIV-1 testing will be performed, as at a usual monthly visit, and study medication will be held if a positive rapid test is documented.
8.7 Adherence

Data on adherence to the product use regimen will be collected monthly via standardized interviewer-administered questions to ascertain product use. Additionally, staff will count pills remaining in bottles returned to the study site and record the number of pills returned. Based on study drug adherence in the HPTN 039 and Partners in Prevention HSV/HIV Transmission trials, we will target 90% adherence of pills dispensed. Members of the Protocol Team will monitor adherence rates over time, and counseling methods will be updated if needed to address lower-than-expected rates. Results will be used to provide feedback and recommendations to members of the Protocol Team and relevant study site staff to optimize adherence.

Adherence will also be assessed through batched drug levels in the partner (HIV-1 uninfected) participants from a selected time point (e.g., the month 12 visit). In addition, drug levels will be measured at the visit closest to seroconversion among index (HIV-1 infected) partners of HIV-1 seroconverters in order to determine whether evidence of drug sharing in the index participant was associated with early viral resistance in the seroconverting partner participant. To characterize the overall proportion of drug sharing among enrolled couples, drug levels will be measured in all index participants at a single time point (e.g., the month 12 visit). These assays will be batch-tested at the end of the study to avoid unblinding, unless requested earlier by the DSMB.

8.8 Discontinuation of Study Treatment

Study treatment will be discontinued under any of the following circumstances:

1. Completion of scheduled follow-up on study drug
2. Acquisition of HIV-1 infection. Study drug will be temporarily discontinued for any reactive HIV-1 test, and permanently discontinued if HIV-1 infection is confirmed.
3. The participant expresses intent to leave the region, or be otherwise unavailable for follow-up.
4. A study drug-related toxicity is found, requiring that the participant permanently discontinue treatment.
5. Pregnancy detection among a female partner (HIV-1 uninfected) participant taking study medication.
6. The study participant voluntarily chooses to leave the study for disclosed or undisclosed personal reasons.
7. The administration of study drug is terminated by the Protocol Chair, as may occur upon recommendation from the DSMB.
8. The participant initiates medications that were excluded at the time of enrollment in this study, or that the on-site principal investigator deems to affect the safety of the participant.
9. Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
10. Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or
seriously interfere with the validity of the study results.

In each case, a product interruption form will be completed. This evaluation will include a structured interview in which clinical symptoms and risk factors will be assessed. Blood will be obtained for HIV-1 serological testing and laboratory toxicity studies. Reasons for discontinuing study medication will also be assessed and recorded. Non-adherence to study medication will not lead to discontinuation of study participation. Participants who no longer wish to continue on randomized study medication will be encouraged to remain under follow-up, including for scheduled testing of HIV-1 status. Participants who discontinue study agent because of an AE will be followed every 4 weeks until resolution, or more frequently at the discretion of the site clinician, in communication with the Safety Monitor and Medical Director.

8.9 Final Contact

Since participants' last study follow-up visits will include a number of laboratory tests, a final contact is required to provide participants with their final study test results, post-test counseling, and treatment, if needed. These contacts may be completed 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. In the case of seroconversion additional visits may be necessary (see section on seroconverter procedures).

9. STUDY PROCEDURES FOR INDEX (HIV-1 INFECTED) PARTICIPANTS

Both index (HIV-1 infected) and partner (HIV-1 uninfected) individuals within an HIV-1 discordant couple will be enrolled in this study. The partner (HIV-1 uninfected) participants will be randomized to receive study drug and will be monitored for HIV-1 seroconversion and adverse events, and thus they will be the focus of the primary endpoints for this study. Index (HIV-1 infected) participants will be followed observationally for issues relevant to the secondary and tertiary study endpoints.

A table detailing the study procedures for index (HIV-1 infected) participants is detailed in Appendix II. Unless otherwise specified, the laboratory procedures listed in this section are performed at the local study site laboratories.

9.1 Screening

Listed in this section are all required study screening procedures for index (HIV-1 infected) partners. Each study site will establish the most optimal sequencing of required screening procedures for the local study setting and target population. A minimum of two screening visits will be conducted to complete all required screening procedures with each potential participant; the second screening visit may occur on the same day as study enrollment, for those wishing to proceed with enrollment and for whom eligibility is confirmed during the screening process. Additional visits may be
conducted as needed. For each couple, independent written informed consent will be obtained from both the index (HIV-1 infected) and partner (HIV-1 uninfected) participants prior to conducting any other screening procedures. Both partners must attend at least one screening visit together. For potential participants who do not meet the study eligibility criteria, the screening process for both partners will be discontinued when ineligibility of either is determined. For potential participants who do meet the study eligibility criteria, the enrollment procedures may proceed immediately after completing the screening process (assuming that informed consent is obtained for study enrollment).

9.1.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for screening
- Locator information
- Behavioral eligibility information
- Demographic information
- HIV-1 pre- and post-test counseling
- Couples counseling about HIV-1, including the significance of HIV-1 discordance
- Provision of condoms, other HIV-1 prevention supplies
- Contraception counseling and provision/referral
- Risk reduction counseling

9.1.2 Clinical Procedures

- Blood collection
- Test results disclosure
- Medical history (including past history of ART use)

9.1.3 Laboratory Procedures

- HIV-1 serology by EIA
- HBV serology
- CD4 cell count

9.2 Enrollment

The procedures listed in this section are conducted after all screening procedures are completed and, in particular, after eligibility has been confirmed and the participant and his/her partner have provided written informed consent to take part in the study.

9.2.1 Administrative, Behavioral, and Regulatory Procedures

- Obtain informed consent
- Locator information
- Couples HIV-1 counseling
• Provision of condoms, other HIV-1 prevention supplies
• Contraception counseling and provision/referral
• Risk reduction counseling

9.2.2 Clinical Procedures

• HBV vaccination, if indicated
• Blood collection
• Physical exam
• Genital exam for STI assessment
• STI treatment (based on local standard of care using WHO Syndromic STI Management guidelines for STI treatment of urethritis, vaginitis, cervicitis, and genital ulcer disease)
• Endocervical Pap smear (for sites where Pap smears are the standard of care for women, and where cytopathology and referral services for dysplasia are available)
• Endocervical swab collection
• Vaginal swabs collection
• Urine collection

9.2.3 Laboratory Procedures

• HSV-2 serology (will be done at the study site if results of ongoing studies of HSV-2 suppressive therapy to prevent HIV-1 transmission demonstrate efficacy. Prior to those results becoming available, or if those results do not demonstrate efficacy, testing will be done in a batched fashion at the Central Laboratory)
• Syphilis serology
• Serum for local site archive and central archive
• Plasma for local site archive and central archive (including for HIV-1 RNA PCR testing and, for a subset of participants, genotypic and phenotypic resistance at the UW)
• DNA archive (blood spots and whole blood) for HLA typing and host genetic polymorphisms of innate/adaptive immunity, including HIV-1 coreceptor polymorphisms at the UW
• Urine archive
• Endocervical Pap smear (for sites where Pap smears are the standard of care for women, and where cytopathology and referral services for dysplasia are available)
• Endocervical swab archive for gonorrhea, chlamydia, trichomonas PCR (women only) on batched samples to assess prevalence of STIs across sites, to be performed at the UW
• Endocervical swab archive for HIV-1 RNA PCR at the UW (women only)
• Vaginal swab and slide for evaluation of bacterial vaginosis
• Urine pregnancy test, if indicated (women only)
• Urine for gonorrhea, chlamydia, trichomonas PCR (men only)
on batched samples to assess prevalence of urethral STIs
across sites, to be performed at the UW

9.3 Follow-up

Formal follow-up of index (HIV-1 infected) participants will occur quarterly, although
index participants will be encouraged to attend the monthly follow-up visits that will be
scheduled for partner (HIV-1 uninfected) participants. Acknowledging that it will not
always be possible to complete follow-up visits on the targeted dates, visits may be
completed within a window around the target date. For index (HIV-1 infected)
participants, the window is 27 days before the target date and 56 days after.

For participants who do not complete scheduled visits within the allowable window, the
visit will be considered “missed” and relevant case report forms will be completed to
document the missed visit.

Note: Index (HIV-1 infected) participants who become pregnant during follow-up may be
maintained in follow-up as originally planned based on their study enrollment date. Follow-up
procedures may be modified. For example, after 24 weeks of pregnancy, pelvic exams and
endocervical specimen collection may be discontinued. Pregnant HIV-1 infected women will be
referred to programs for the prevention of mother-to-child transmission and antenatal care.

9.3.1 Administrative, Behavioral, and Regulatory Procedures

• Ongoing informed consent
  - As needed at all visits
• Locator information
  - At all visits.
• HIV-1 risk behavior interview
  - At all visits
• Couples HIV-1 counseling (and/or individual counseling if
  more convenient)
  - At all visits.
• Provision of condoms, other HIV-1 prevention supplies
  - At all visits
• Contraception counseling and provision/referral
  - At all visits
• Risk reduction counseling
  - At all visits

9.3.2 Clinical Procedures

• Medical history, including HIV-1 staging, use of opportunistic
  infection prophylaxis, and use of antiretroviral therapy
  - At quarterly follow-up and at study exit.
- Additionally in response to intercurrent symptoms/illnesses.

- Physical exam
  - At quarterly follow-up and at study exit.

- STI symptom questionnaire
  - At quarterly follow-up and at study exit.
  - Additionally in response to intercurrent symptoms/illnesses.

- Genital exam for STI assessment:
  - At 12-monthly follow-up and at study exit.
  - Additionally in response to intercurrent symptoms/illnesses.

- Blood collection:
  - At 6-monthly follow-up and at study exit.

- Urine collection
  - At any visit, for pregnancy testing, when clinically indicated (women only)
  - At 12-monthly follow-up and at study exit

- Endocervical swab collection (women only):
  - At 12-monthly follow-up and at study exit.

- Vaginal swabs for evaluation of bacterial vaginosis
  - At 12-monthly follow-up and at study exit.

- Semen collection (men only):
  - At Month 6 and Month 12

- STI treatment, if clinically indicated based on local standard of care, using either WHO Syndromic STI Management guidelines for treatment of urethritis, vaginitis, cervicitis and genital ulcer disease, or based on STI diagnostic tests

- Test results disclosure:
  - As needed at all visits

### 9.3.3 Laboratory Procedures

- Syphilis serology:
  - Every 12 months, or when clinically indicated by the presence of an ulcer or rash suggestive of syphilis.

- CD4 cell count:
  - At 6-monthly follow-up and at study exit

- Serum for local site archive and central archive

- Plasma for local site archive and central archive (including for HIV-1 RNA PCR testing at the UW)

- DNA archive (blood spots and whole blood) for HLA typing and host genetic polymorphisms of innate/adaptive immunity, including HIV-1 coreceptor polymorphisms at the UW
  - At 6-monthly follow-up and at study exit

- Urine archive
  - At 12-monthly follow-up and at study exit

- Vaginal swab and slide for evaluation of bacterial vaginosis
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- At 12-monthly follow-up and at study exit
  - Endocervical swab archive for gonorrhea, chlamydia, trichomonas PCR (women only) on batched samples to assess prevalence of STIs across sites, to be performed at the UW
  - Urine archive for gonorrhea, chlamydia, trichomonas PCR (men only) on batched samples to assess prevalence of urethral STIs across sites, to be performed at the UW
  - Urine pregnancy test (women only), if missed menses, if symptoms/signs suggesting pregnancy, or if requested by the participant
  - Endocervical swab archive for HIV-1 RNA PCR at the UW
  - Seminal cells and plasma archive for HIV-1 RNA PCR at the UW
    - At 12-monthly follow-up and at study exit
      - At Month 6 and Month 12.

9.4 Stop Visit

The final visit for each participant will be designated the Stop Visit. Given the variable maximum follow-up for this trial (i.e., participants followed up to a maximum of 36 months, with the potential for the trial to be stopped earlier at any time by the DSMB), Stop Visits could occur at any point in an individual participant’s follow-up. All participants, regardless of where in study follow-up they may be, will complete Stop Visit procedures. These will include all procedures scheduled for a 12-month visit.

9.5 Post-Study Drug Follow-up Visit

No follow-up visits equivalent to the post-study drug follow-up visits for partner (HIV-1 uninfected) participants are scheduled for index (HIV-1 infected) participants. Once partner (HIV-1 uninfected) participants complete study medication, index participants will have no scheduled follow-up procedures. However, as at all visits, index (HIV-1 infected) participants will be encouraged to attend post-follow-up visits with their HIV-1 uninfected partners.

9.6 Interim Visits

Interim visits may occur at any time during the study. For index (HIV-1 infected) participants, interim visits will likely occur for scheduling reasons (e.g., to reschedule an upcoming visit) or for symptoms, at the participant’s request. All interim contacts and visits will be documented in participants’ study records and on applicable CRFs.

Female partner (HIV-1 uninfected) participants who are diagnosed with an STI at an interim visit or who present for an interim visit complaining of gynecologic symptoms will
undergo pregnancy testing.

Partner (HIV-1 uninfected) participants diagnosed with an STI at an interim visit will have HIV-1 serologic testing completed.

9.7 Final Contact

Since participants' last study follow-up visits will include a number of laboratory tests, a final contact is required to provide participants with their final study test results, post-test counseling, and treatment, if needed. These contacts may be completed 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. In the case of partner seroconversion additional visits may be necessary (see section on seroconverter procedures).

10. HIV-1 SEROCONVERTERS

Partner (who must be HIV-1 seronegative at Screening and Enrollment) participants who are found to have a reactive HIV-1 rapid antibody test during the study will be instructed to stop the study drug. They will be counseled that additional HIV-1 testing is required, and blood will be drawn for confirmatory HIV-1 serology and additional testing, as detailed in Appendix III. Participants will be asked to return after 2 weeks to receive the results of confirmatory testing. Additional samples will be collected at that time.

Specimens will be collected at several time points post-seroconversion:

1) at the visit when seroconversion is first identified by HIV-1 rapid assay (identified as the “acute seroconversion visit”)

2) 2-4 weeks after seroconversion is first identified at a point when HIV seroconversion has been confirmed by HIV EIA, (identified as the “<1 month post-seroconversion” visit) and

3) at subsequent quarterly visits (identified based on the time since the acute seroconversion visit, i.e. the “3-month post seroconversion visit”, “6-month post seroconversion visit” etc...), until the study is completed, or to at least 12 months post-seroconversion for those who seroconvert late in the study.

Specimens will include serum chemistries and CBC (these only at the seroconversion visit), as well as blood and genital specimens for assessment of HIV-1 viral levels and CD4 counts. Samples will be archived for drug resistance testing (genotypic and phenotypic) at the Central Laboratory or at a designated laboratory for resistance assays.

Resistance testing will be done in a batched fashion, using both genotypic and phenotypic testing. Samples from the first two post-seroconversion visits will be tested. If standard genotypic resistance testing is negative, ultrasensitive resistance testing will
be performed. Of note, phenotypic resistance will also provide some indication of viral fitness, which is relevant among those with genotypic viral resistance. Results will be made available to the study sites and to study participants, so that the findings are considered in ART regimen selection when seroconverters meet national guidelines for ART initiation. HIV-1 seroconverters will be provided or referred for HIV-1 clinical care, including primary care, screening and treatment for a variety of disease manifestations, and antiretroviral therapy, according to national guidelines. This clinical care will be provided under the best clinical judgment of the study clinicians, and will be either provided at the study site during the trial or through well-established referral to clinical care programs. During the course of the study, it is possible that guidelines will change regarding clinical care of persons with HIV-1 (including timing of initiation of ART, optimal therapy, prophylaxis, etc.). At all times during the study, treatment and referral practices for HIV-1 infected persons in the study will adhere to national guidelines for HIV-1 infected persons.

The index (HIV-1 infected) participant corresponding to a seroconverting partner participant will also be asked to provide one set of samples at a visit as close as possible to the date that partner seroconverter specimens are collected. Genotypic and phenotypic resistance testing will be performed; results will be made available to participants and the study sites. Index participants will then continue on in their follow-up (i.e., to a maximum of 36 months). Index participants whose partner seroconverts to HIV-1 at the Stop Visit or at the Post-Study Drug Completion Visits will be asked to provide one set of samples only.

All specimens to be collected related to HIV-1 seroconversion are detailed in Appendix III.

11. PREGNANCY AMONG PARTNER (HIV-1 UNINFECTED) PARTICIPANTS

Limited animal and human data, detailed in Section 4.3.3, suggest safety of TDF and FTC/TDF when used by HIV-1 infected women during pregnancy and breastfeeding. However, no controlled studies have been conducted, and no data are available concerning the risks associated with use of TDF or FTC/TDF by HIV-1 uninfected women who are pregnant or breastfeeding.

For the purposes of this trial, study medication will be discontinued when pregnancy is detected. Infants exposed to study medication in utero (i.e., during early pregnancy, prior to discontinuation of study medication) will be followed. Breastfeeding will be a study exclusion criterion, and study medication will not be dispensed to women who initiate breastfeeding during the study.

Female partner (HIV-1 uninfected) participants will be counseled about the limited available data on pregnancy risk at study enrollment and at each study follow-up visit. As new data become available related to safety of TDF and FTC/TDF for pregnant women, summaries of this information will be compiled by the Coordinating Center and circulated to the study sites, so that women have up-to-date information on risk/benefit decisions related to these study medications. The Coordinating Center will provide updates on a 6-monthly basis, with additional updates more frequently in the case more timely data become available.
11.1 Procedures

Based on previous experience with the Partners in Prevention Trial, a pregnancy rate of ~15 per 100 woman-years is expected among female partner (HIV-1 uninfected) participants in this study, which will mean that ~600 total pregnancies are anticipated to be detected (assuming equal male:female ratio among partner participants enrolled in the study). Given the frequency of pregnancy testing, the majority of pregnancies detected will likely end in spontaneous miscarriages – these have been called “subclinical” or “chemical” pregnancies. Overall, ~200 pregnancies in this study are expected to go to term.

Pregnancy testing for female partner (HIV-1 uninfected) participants will be scheduled for monthly visits. In the event of a positive urine pregnancy test, female partner participants will stop study medication. Thus, the maximum time from conception to discontinuation of study medication will be approximately 6 weeks. Women who become pregnant will be counseled by study staff. They continue with follow-up as otherwise scheduled, with the exception that they will not receive study medication and related services (e.g., adherence counseling). HIV-1 testing and other study procedures will continue to occur monthly as scheduled. Data on time off of study medication will be recorded at each study visit.

Pregnant women will receive antenatal care at the study site or be referred for such care.

For pregnancies that do not go to term, female partner (HIV-1 uninfected) participants will be allowed to resume study medication, according to their follow-up schedule, after confirmation by a negative urine pregnancy test. For example, if a pregnancy is detected at the Month 7 visit for a female partner participant, she will stop study drug that day. She will continue in follow-up, with her next scheduled visit being for Month 8 visit, at which time HIV-1 testing and other scheduled procedures (with the exception of those related to study medication) will be completed. If her pregnancy ends between her Month 8 and Month 9 visits, she may resume study medication at the Month 9 visit, after a negative pregnancy test. Women whose pregnancies end after their scheduled study time will not resume study medication.

For women whose pregnancies do not go to term, or whose pregnancies end in stillbirth, data on timing of pregnancy loss and nature of pregnancy loss (i.e., spontaneous or elective termination) will be recorded. Research study staff will have no part in any decisions related to the timing, method, or procedures related to potential pregnancy termination. Study staff will have no part in determining fetal viability. No inducements, monetary or otherwise, will be offered relating to pregnancy termination. Female partner (HIV-1 uninfected) participants who become pregnant, regardless of the outcome of the pregnancy or resumption/non-resumption of study drug, will continue follow-up and HIV-1 testing on schedule until the end of their follow-up duration.

For pregnancies that go to term, follow-up of infants exposed to study medication will be conducted over the first year of life. The first visit will occur soon after birth (within 1 month, but ideally within 1 week). Women will be asked to bring their newborn to the
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study clinic or a home visit will be conducted. Evaluation will include assessment for congenital abnormalities, measures of weight and length, and blood measurements of renal function. Additional visits for the infant will occur quarterly for 12 months, when measurements of weight and length will be recorded. Blood will be obtained at the 3 month visit for measurement of renal function.

Study medication will be held after pregnancy while women breastfeed. HIV-1 uninfected women who successfully complete a pregnancy during the study will be encouraged to breastfeed, according to WHO policies. Study medication can resume once women are no longer breastfeeding (and are not pregnant).

Female partner (HIV-1 uninfected) participants who become pregnant and are found to have seroconverted to HIV-1 – either at the same follow-up visit, at a prior visit (i.e., who first seroconvert to HIV-1 and later become pregnant), or at a subsequent visit (i.e., who are found to be pregnant and, while pregnant, seroconvert to HIV-1) will have expedited HIV-1 resistance testing performed in order to provide information about possible resistance that might impact the efficacy of antiretroviral therapy regimens to reduce mother-to-child HIV-1 transmission. Importantly, resistance mutations against TDF or FTC should not adversely influence the efficacy of short-course antiretroviral therapy using either nevirapine and/or zidovudine, which are the standard agents used for prevention of mother-to-child HIV-1 transmission in Kenya and Uganda. Antenatal care for pregnant study participants will be provided by the study clinics or by referral.

Infants born to female partner participants who have seroconverted to HIV-1 either prior to or during pregnancy will be tested for HIV-1 by PCR and/or ELISA, according to local guidelines. Those found to be HIV-1 seropositive will be managed according to national recommendations for care of HIV-1 infected children.

12. SAFETY AND ENDPOINT MONITORING AND ADVERSE EVENT REPORTING

The study site Investigators are responsible for continuous safety monitoring of all study participants, and for alerting the Safety Monitor, Medical Director, and Protocol Chair if unexpected concerns arise. The Safety Monitor, Medical Director, and Protocol Chair will monitor participant safety throughout the course of the study. To support this monitoring, study statisticians will work to prepare study progress reports and tabulations of reportable adverse events (AEs, defined below) experienced by partner (HIV-1 uninfected) participants (blinded to treatment assignment) for review by the Protocol Team at least monthly. Protocol Team members will routinely review these reports and discuss potential participant safety issues via conference call throughout the period of study implementation.

Safety monitoring will focus on partner (HIV-1 uninfected) participants, as they will be administered study drug, and on infants born to female partner (HIV-1 uninfected) participants.

Index (HIV-1 infected) participants in this study will be followed in an observational fashion only, as they will not receive study drug. Only adverse event data on death and
harm directly related to study participation will be collected for index participants.

The severity of clinical and laboratory AEs occurring among partner (HIV-1 uninfected) participants and infants exposed to study medication will be scored according to criteria established by the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. National Institutes of Health (NIH) [89] (see Appendix XV).

This study also is subject to oversight by an independent DSMB that will complete interim analyses of study safety and efficacy data. The DSMB also may complete additional reviews at their discretion. The DSMB may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Reports from all DSMB meetings will be provided to study sites for their information and for submission to their IRBs/ECs.

### 12.1 Laboratory Monitoring

Partner (HIV-1 uninfected) participants will be assessed at screening, enrollment, and throughout follow-up by laboratory monitoring for adverse events as a result of study drug, as well as for HIV-1 seroconversion.

Laboratory results will be flagged by the laboratory as abnormal or critical using pre-determined criteria for each laboratory. The International AIDS Vaccine Initiative (IAVI) has recently developed tables of normal laboratory values specific to sub-Saharan African populations; these will be used to define normal ranges. Site-specific tables will reflect the criteria as defined by the DAIDS toxicity tables. Abnormal values will be confirmed by repeat testing of the same specimen. All critical values will be reported to the study site clinician on-call by phone. All results will be documented in laboratory records. All laboratory test results will be reported by the laboratories to the site clinicians according to a written SOP. Participants who are not present at the study site at the time an abnormal value is detected will be contacted in person by a recruiter and brought back to the study site for further evaluation, referral, and counseling.

#### 12.1.1 Urine Dipstick Testing

Urine dipstick tests for glycosuria and proteinuria will be performed at the screening visit. A repeat urine sample will be collected if initial testing is 1+ or higher. Urine dipstick tests that are repeatedly 1+ or higher for these parameters will be exclusion criteria at baseline.

#### 12.1.2 Serum Chemistries

Blood for serum chemistries will be drawn at screening to determine eligibility and intermittently during follow-up. The chemistry tests will be phosphate, total CO2 or bicarbonate, creatinine, total bilirubin, AST, and ALT.

Renal insufficiency is an exclusion criterion for the study. Study medication will be permanently discontinued if estimated
creatinine clearance is less than 50 mL/min at any time during the study.

TDF and FTC/TDF have not been evaluated in patients with hepatic impairment. Normal hepatic function at screening is an inclusion criterion for this study. FTC/TDF is not metabolized by liver enzymes, so the impact of liver impairment should be limited. There are no known interactions between TDF or FTC/TDF and hormonal contraception, anti-tuberculosis drugs, or ethanol ingestion.

12.1.3 Complete Blood Counts

Blood for complete blood counts will be obtained at screening and intermittently during treatment with the study agent. The complete blood counts will include total leukocyte count, automated three-part differential, total hemoglobin or hematocrit, and platelet count. Normal hematologic function is an inclusion criterion for this study.

12.1.4 Hepatitis Testing

All participants (both partner and index) will undergo testing for HBV at the screening visit. This will include tests for HBV surface antibody (anti-HBs) and HBV surface antigen (HBsAg). Partner (HIV-1 uninfected) participants found to be infected with hepatitis B, as defined by a positive HBsAg, will not be eligible for the study. Participants (both index and partner) found to be HBV susceptible at screening will be given information and offered the HBV vaccine series starting at their enrollment visit. They may elect to start the HBV vaccine series at any time.

Partner (HIV-1 uninfected) participants who are HBV susceptible at screening but who decline vaccination will be tested annually for HBV (at Month 12, 24, and 36, as well as at the Stop visit – whether that occurs at Month 36 or sooner). In addition, HBV testing will also be performed for partner (HIV-1 uninfected) participants who are HBV susceptible at screening, who either decline vaccination or who have not completed the vaccine series, and who stop study drug during the study (e.g., for pregnancy, for adverse events). If HBV susceptible individuals are found to become HBV infected during follow-up, serum chemistries will be monitored monthly for 2 months after they stop study drug to assess for hepatitis flares.

12.1.5 HIV-1 Serologic Testing

HIV-1 testing for partner (HIV-1 uninfected) participants will be performed monthly, according to the algorithm detailed in Appendix VII. Two rapid tests will be performed in parallel at the visit site at monthly visits by laboratory personnel trained in
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

accordance with the manufacturer’s instructions. The brand of rapid tests use will be determined by test availability within each participating country, as long as tests pass proficiency testing and meet national HIV-1 testing approval. If one or both rapid tests are positive, blood will be drawn for EIA confirmation testing, again using tests meeting national policies, and the participant will be taken off study drug, as described in the procedures for HIV-1 seroconversion. Discordant rapid tests will be retested with one well in each of two different EIA kits. All HIV-1 testing will be supported with regular proficiency testing coordinated through the study coordinating center and the Africa-based laboratory contractor.

HIV-1 testing will be accompanied by couples and/or individual counseling, depending on attendance of the index (HIV-1 infected) participant at a study visit. All counseling and testing approaches will be in accordance with national HIV-1 counseling and testing guidelines.

12.2 Symptom Monitoring

Clinical symptoms will be systematically assessed in a structured medical history administered to partner (HIV-1 uninfected) participants monthly for the length of the trial. Clinical side effects of TDF and FTC/TDF that have been reported are primarily gastrointestinal, including nausea, vomiting, and flatulence. The severity of clinical symptoms will be scored using the DAIDS Table for Grading the Severity of Adult and Pediatric AEs [89].

Clinicians licensed to practice medicine and assigned to the project will evaluate clinical AEs and determine the grade of AE and probability that it was related to the study drug. All clinical symptoms and signs will be recorded on clinic forms and study CRFs. Grade 2, 3, and 4 clinical findings will be referred to the on-site physician investigator at the time of the visit.

12.3 Overdose

If an overdose of greater than 3 tablets occurs in one day, the study agent will be stopped and the participant will be monitored for evidence of renal and hepatic toxicity every week, or more frequently at the discretion of the site lead clinician, until the toxicity resolves. TDF and FTC/TDF are cleared renally. In the event of renal failure, TDF and FTC/TDF can be removed by hemodialysis, and participants requiring advanced clinical care after overdose, including hemodialysis, will be referred emergently for such care.

12.4 AE Definition

An AE is defined as any untoward medical occurrence in a clinical research participant who has been administered an investigational product, and that does not necessarily
have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition will be applied to all three study treatment groups, even though one group is not assigned to receive an investigational product, and will be applied to these groups beginning from the time of randomization.

For the purposes of this trial, AEs will be monitored among partner (HIV-1 uninfected) participants starting at randomization and continuing through the final study visit (including the post-follow-up visit). Index (HIV-1 infected) participants, who will not receive study drug, will not be monitored for routine AEs, but deaths and adverse events that occur as a result of study procedures will be recorded.

Partner (HIV-1 uninfected) participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation at the study site. With permission of the participant, and whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study CRFs.

12.5 Discontinuation of Study Drug Due to an AE

The on-site clinician on call, in concert with the site PI, has authority to stop study agent for any partner (HIV-1 uninfected) participant due to clinical or laboratory AEs. The decision to discontinue study drug will be immediately communicated to the Protocol Team.

The on-site principal investigator, or a designated lead clinician, will assess whether an AE is related to the study agent (unrelated, probably not related, possibly related, probably related, definitely related) using the available information about TDF and FTC/TDF and his/her clinical judgment.

12.6 Social Harm

Participation in the study could lead to social harms that may include loss of privacy, stigmatization, relationship difficulties, physical or verbal abuse, interference with gainful employment, and coercion. Information regarding social harms will be solicited at quarterly follow-up and will be recorded on CRFs. In addition, social harms may be identified by other study staff, including recruiters, receptionists, nurses, physicians, pharmacist, and others. All social harms will be brought to the attention of the on-site lead clinician. Participants who report social harms will be referred to speak with a study counselor.

12.7 Follow-up of AEs
Laboratory AEs will be managed according to established protocols. Laboratory results that require action will be documented and the outreach coordinator will be contacted to schedule a repeat visit. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Summaries of AE reports will be reviewed with clinic medical staff and the site investigators. Reports of all AEs will be reviewed by the Protocol Chair, Medical Director, and Safety Monitor. The reports will be discussed during teleconference calls with protocol chair, Protocol Team, and site investigators.

12.8 Expedited Adverse Events

All AEs will be reported to the study Coordinating Center using AE CRFs. The following AEs will be protocol-defined as Expedited AEs (EAEs) and will have additional reporting requirements:

Among partner (HIV-1 uninfected participants)
- Death
- Life-threatening, or otherwise Grade 4
- Hospitalization or prolongation of hospitalization
- Persistent, significant disability or incapacity
- All Grade 3 AEs
- Fetal loss
- Congenital anomaly / birth defect
- Any medical event requiring treatment to prevent any of the above
- Grade 2 creatinine elevation
- Bone fracture

Among index (HIV-1 infected participants)
- Death
- Related to study procedures or participation

Among infants born to partner (HIV-1 uninfected) participants
- Death
- Related to study procedures or participation
- Grade 2 or greater creatinine toxicity

Expedited AEs will be reported to the study Safety Monitor within 48 hours using an EAE reporting form. The Safety Monitor will confer with the Protocol Chair, Medical Director, and Regional Medical Director. In addition to AE CRF recording, EAEs will be summarized in greater detail on EAE reporting forms.

12.8.1 Grading Severity of Events

All AEs will be graded using the DAIDS AE Grading Table (see Appendix XV) except that Grade 1 creatinine toxicity will be
defined as ≥ 1.5 x the participant’s baseline serum creatinine even if serum creatinine is in the normal or Grade 0 range. A creatinine clearance <50 mL/min will be defined as a Grade 2 creatinine toxicity if the creatinine value is in the normal or Grade 1 range.

When not specified in Appendix XV, AEs will be graded using the following scale:

- **Grade 1 Mild**: Transient to mild discomfort; no limitation in activity; no medical intervention/therapy required.
- **Grade 2 Moderate**: Mild to moderate limitation in activity, some assistance may be needed; no medical/psychiatric intervention required.
- **Grade 3 Severe**: Marked limitation in activity, some assistance usually required; medical/psychiatric intervention required; hospitalization possible.
- **Grade 4 Life-Threatening**: Extreme limitation in activity, significant assistance required; significant medical/psychiatric intervention required, hospitalization or hospice care probable, or death.

### 12.8.2 Expedited Adverse Event (EAE) Reporting Periods

EAEs will be reported within 48 hours during the protocol-defined EAE Reporting Period, which is: the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason). After the end of the protocol-defined EAE reporting period stated above, sites must report serious, unexpected, clinically suspected AE drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

### 12.9 Toxicity Management

All clinical and laboratory toxicities (apart from creatinine and phosphorus) will be managed according to uniform guidelines and graded according to the DAIDS AE Grading Table (Appendix XV). Separate guidelines for toxicity related to renal dysfunction (including creatinine and phosphorus) are discussed below. All Grade 2, 3 and 4 abnormal laboratory values should be confirmed by repeat testing of an additional specimen, preferably within seven calendar days, unless such a delay is not consistent with good medical practice. All abnormal values (Grade 1-4) involving creatinine should be confirmed by repeat testing of an additional specimen, preferably within seven calendar days. Participants with clinical or laboratory toxicity that requires
discontinuation of study agent will be followed at weekly intervals, with additional testing when deemed clinically appropriate, until the toxicity resolves or stabilizes.

12.9.1  Clinical and Laboratory Toxicity Not Associated with Renal Function

The study agent will be continued at the discretion of the on-site investigator. Study drug may be continued if a Grade 2 or 3 toxicity is considered to be unrelated to study medication based on an evaluation by the site investigator. Study medication should be withheld if grade 2 or 3 toxicity is considered to be related to the study medication. After the toxicity returns to grade 1, the participant can be restarted on study drug. If any of these toxicities recur and are considered to be related to study medication, then study medication will be permanently discontinued. If any of these toxicities recur and are considered to be unrelated to study medication, study medication may be continued based on the judgment of the on-site investigator after discussion with the protocol chair.

For all Grade 4 laboratory-identified or clinical toxicities, the study agent will be withheld. Laboratory toxicity will be promptly confirmed by repeating the test on an additional specimen, preferably within seven days. If grade 4 toxicity persists on repeat testing and is considered to be related to study medication, the study medication will be permanently discontinued. Study medication may be resumed after resolution to Grade 1 of any Grade 4 laboratory toxicity or clinical event considered to be unrelated to study medication based on the judgment of the on-site investigator, in discussion with the Protocol Chair, Medical Director, and Safety Monitor.

12.9.2  Serum Creatinine Management

Renal toxicity management will be based on changes in serum creatinine relative to the baseline value, which is expected to vary between 0.5 and 1.4 mg/dL for healthy men and women based on laboratory normal ranges. Those with serum creatinine >1.3 for men / >1.1 for women or with a creatinine clearance <60 ml/min estimated by the Cockcroft-Gault equation at the screening visit will be excluded from the trial. The Cockcroft-Gault equation has been shown to reflect true creatinine clearance with high accuracy among African individuals [90]. If at any time serum creatinine is increased >1.5-fold above baseline, the serum creatinine should be repeated as soon as possible, preferably within 7 days. Participants with confirmed serum creatinine increases >1.5-fold above baseline will be determined to have grade 1 creatinine toxicity and will temporarily discontinue study drug. Participants with a confirmed increase in serum creatinine >1.5-fold above baseline will have serum creatinine monitored monthly until serum
creatinine decreases to \( \leq 1.3 \)-fold above baseline or until stabilization, or more frequently at the discretion of the site investigator. Study drug may be restarted if serum creatinine returns to within 1.3-fold above baseline. All creatinine toxicity will be reported to the Medical Director according to the protocol specific reporting for elevated creatinine.

In the case of Grade 2, 3, or 4 creatinine toxicity, or calculated creatinine clearance <50 mL/min (defined as Grade 2 creatinine toxicity if the creatinine is within the normal or Grade 1 range), creatinine testing will be repeated on an additional specimen, preferably within 7 days. Creatinine clearance will be calculated using the Cockroft-Gault equation using standard tables. Study medication will be permanently discontinued. Study participants will be followed at weekly intervals until the toxicity resolves or creatinine stabilizes.

12.9.3 Phosphorus Management

The DAIDS AE Grading Table defined Grade 1 phosphorus abnormalities as from 2.5 mg/dl (lower value) to the lower limit of normal (upper value). For the purposes of this study, the lower limit of normal for phosphorus will be defined as 2.5 mg/dl. Thus, there will be no Grade 1 phosphorus abnormalities defined for this study.

For participants with Grade 2 phosphorus abnormalities, phosphorus level testing should be repeated using an additional specimen, preferably within 7 days. Study drug may be continued if there are not other signs of renal toxicity. Assessment for additional signs of tubular dysfunction will include a serum bicarbonate (or CO\(_2\)) \( \leq 17 \) mEq/L, new glycosuria \( \geq +1 \), or new proteinuria \( \geq +2 \).

For Grade 3 or 4 hypophosphatemia, phosphate will be repeated using an additional specimen, preferably within 1 week. For asymptomatic Grade 3 decreases in phosphorus, subjects may remain on study drug with the following caveats: there should be no other signs of renal tubular acidosis; subjects should be treated with oral phosphate supplements; and phosphorus levels should be re-tested weekly until phosphorus returns to the normal range. Serum phosphorus levels should be followed weekly until resolution to Grade 2 or less, or until stabilization. If study drug is stopped, it can be resumed at the discretion of the site investigator upon resolution of hypophosphatemia. If Grade 3 or 4 hypophosphatemia recurs after resuming study drug, study drug will be discontinued permanently.

12.9.4 Management of Intercurrent Medications
Certain medications that may be taken during the study may exacerbate possible TDF or FTC/TDF toxicity. We will ask participants at 4 week interval visits if they have begun taking any other medications including over-the-counter medications, such as non-steroidal anti-inflammatory drugs (NSAIDS). If a participant has taken NSAIDS for 7 consecutive days in any prior 28 day period, we will require additional monthly blood draws of 10 ml to monitor serum creatinine for the duration of the participant's intercurrent medication use. Participants who begin taking any medication during the trial that is listed as an exclusionary medication at screening will temporarily discontinue study drug. Study drug may be resumed if no contraindicated medication (as defined in Section 6.2.2.2) has been taken in the past 28 days, serum creatinine is ≤1.5 fold relative to baseline, and a rapid test for HIV-1 antibodies is negative.

12.10 Management of Infant Toxicity

Creatinine measurements for infants born to partner (HIV-1 uninfected) participants who had been taking study drug at the time of conception will be collected. Abnormal values will be graded according to the DAIDS AE Grading Table.

12.11 AE Reporting

Information on adverse events will be reported by the study Coordinating Center to the US FDA per appropriate regulations. Reporting on adverse events to relevant IRBs and local regulatory authorities will be performed by site investigators and/or the study Coordinating Center, as appropriate.

13. CRYOPRESERVATION OF SPECIMENS

Blood and genital tract specimens will be cryopreserved during the clinical trial and stored at the study site or central archive. These specimens may be used for (1) repeat and confirmatory analyses of safety and endpoint parameters; (2) analysis of viral nucleic acids and antigens of HIV-1 or other viruses that may be affected by PrEP; (3) analysis of plasma and intracellular TDF and FTC levels after the study is unblinded, (4) analysis of humoral and cellular immune responses, and (5) analysis of viral phenotypes that may include replication capacity and tropism, (6) analysis of other immunologic, virologic, genetic, and other factors (e.g., STIs) that may influence HIV-1 transmission within HIV-1 discordant couples, HIV-1 viral load and disease progression in HIV-1 infected individuals, and occurrence of adverse events among individuals receiving TDF or FTC/TDF PrEP.

Referral of specimens for repeat analysis of safety or efficacy parameters will be performed at the discretion of the principal investigator, which would be prompted by evidence of failed proficiency testing at the laboratory supporting the trial, or evidence that the selected assay systems may have systematically failed to identify clinically
relevant toxicity. Testing that has no known utility for medical management will not be shared with individual participants. Such tests include host genotyping, immune studies, and nucleic acid studies that are performed for research use only. Use of the specimens during the blinded phase of the study will require approval of the principal investigator, who will take steps to assure that the proposed analysis would not compromise the blinding of the study. Study participants will be asked to provide written informed consent for the preservation and analysis of archived specimens that are left over after the testing described in this protocol. Test results from archived specimens will not be reported to the participant. Storage and testing of left over specimens is optional, and participants will be able to indicate on the consent form if they do not wish to have left over specimens saved for future research.

An Ancillary Studies Committee, consisting of the protocol chair, co-investigators, and site PIs, will review protocols that involve laboratory testing of stored specimens. Protocols that have been scientifically approved by the Ancillary Studies Committee will be submitted to the UW IRB as the Coordinating Center, as well as the local site IRBs for ethical review, to ensure that ancillary study goals are consistent with the language for the consent for long-term storage and research testing.

14. DATA ANALYSIS

14.1 Review of Study Design

This study is a Phase III, multi-site, randomized, double-blind, placebo-controlled, three-arm trial evaluating the safety and efficacy of pre-exposure chemoprophylaxis with TDF and FTC/TDF, either administered orally once daily, for prevention of HIV-1 acquisition among HIV-1 uninfected individuals within an HIV-1 discordant partnership. Within the HIV-1 discordant partnerships, the HIV-1 infected partner must have a CD4 cell count of >250 cells/mm³ at screening and not be on ART, and the HIV-1 uninfected partner in the couple must report an average of 6 coital acts in the past 3 months. We will randomize 3900 eligible and consenting HIV-1 negative participants to receive once daily study drug in a 1:1:1 ratio to either 300 mg TDF (Viread®) or FTC 200 mg/TDF 300 mg (Truvada®) or placebo (thus, 1300 in each study arm). A total of 3900 couples will be enrolled in the study and maintained in follow-up for a minimum of 24 months and a maximum of 36 months, plus an additional 1 month of post-study drug follow-up for delayed endpoints identification. Additional follow-up will also be performed for HIV-1 seroconverters and infants with exposure to study drug in utero (during early pregnancy).

14.2 Random Assignment and Blinding

The HIV-infected partner in each couple will be assigned at random to one of the three study treatment groups in a 1:1:1 ratio. The randomization code will be generated and maintained by the Protocol Biostatistician or designee. A variable size block randomization scheme will be implemented. Participants will receive ID numbers in sequence.
The randomization codes will be linked to TDF, FTC/TDF, or placebo. Using this list, the drug manufacturer will fill the sequentially numbered study bottles with TDF, FTC/TDF, or placebo according to the assignment. Gilead will prepare 12 bottle kits (i.e., a 6-month supply, corresponding to TDF or placebo TDF plus FTC/TDF or placebo FTC/TDF. Kits will each be labeled with an identifying number, an operation number (which is coded for the study), the lot number (blinded), and an expiry date. Every 6 months, a computer or telephonic randomization system will be accessed by the study staff to assign an appropriate kit to each participant. None of the study staff or investigators will have access to lists of randomization codes or groups. Clinical Packaging and Quality Assurance (QA) at Gilead will be unblinded to the bottle assignments in order to coordinate the labeling operation with the contract labeling site and provide quality assurance review after the labeling operation. This is required by Gilead SOPs that are in compliance with FDA and ICH Good Manufacturing Practices. Any request for access to the unblinded randomization codes by anyone outside of the labeling and QA groups would have to follow Gilead SOP 10526.00 Unblinding Clinical Study Data for Analysis.

Unblinding is unlikely to be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. However, if a participant requires hemodialysis, unblinding may occur at the discretion of the investigators. In the event that an investigator is concerned that a participant might be put at undue risk by continuing product use, the investigator may discontinue product use by this participant, in discussion with the Protocol Chair and Medical Director; however, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an investigator feels that specific product knowledge is necessary to protect participant safety, the investigator may notify the Protocol Chair to consider and rule upon the request. Otherwise, participants will be unblinded to their drug only at the close of the trial. Participants who develop HIV-1 infections or drop out will not be unblinded early. The DSMB will be provided with the unblinded product coding information with study reports upon their request. However, the routine work of the DSMB will be carried out according to randomization codes (e.g., Groups A, B, and C) and without knowledge of the randomization groups (TDF, FTC/TDF, and placebo).

14.3 Endpoints

Incident HIV-1 infection will be defined as i) serologically confirmed incident HIV-1 infection, with the exception that the enrollment sample from any partner (HIV-1 uninfected) participant who is serologically positive at a visit within the first three months after enrollment will be tested for HIV-1 RNA by PCR. Detectable HIV-1 RNA at enrollment will indicate infection prior to randomization and this individual will be excluded from efficacy analyses; ii) HIV-1 RNA >50 copies/ml by PCR at the last study visit of any subject – in particular, individuals who are RNA positive at Stop Visit who then seroconvert at the post-study drug visit; iii) other incident HIV-1 infections as determined and documented by the endpoint review committee (see below). Sequence matching of index (HIV-1 infected) and seroconverting partner HIV-1 viral clones will be performed for the purpose of facilitating the secondary study objective of evaluating the impact of index (HIV-1 infected) participant factors (e.g., HIV-1 plasma viral load) on PrEP efficacy.
A study endpoint committee will review primary endpoint data, confirm all reported incident HIV-1 infections among HIV-1 uninfected partners, and, for secondary analyses, determine whether these infections were transmitted from the HIV-1 infected study partner, as determined by genotyping and sequencing. Based on a review of laboratory and clinical data, the endpoint committee may also recommend that persons who test positive by other laboratory measures of HIV-1 infection (e.g. HIV-1 PCR) be included as seroconverters in a secondary analysis of study data.

The proportion of study treatment doses missed, plasma HIV-1 viral load in the index (HIV-1 infected) partner, and frequency of key sexual behaviors (e.g., number of sex acts, number of new partners) will be assessed in secondary analyses. Other variables that will be considered in secondary analyses include gender of the HIV-1 uninfected partner, HSV-2 status of either partner, and male circumcision in either the HIV-1 infected or the HIV-1 uninfected partner.

### 14.4 Sample Size Estimates for Primary Endpoints

This trial will benefit from the use of a common placebo arm for comparison to each of two active arms, and will aim to demonstrate efficacy of each regimen separately against placebo. Although biologic plausibility of efficacy as well as direct estimation of efficacy in macaque challenge studies suggest potentially very high levels of protection, our study design calculations use a conservative efficacy of 60%. Because the intention is for results from this trial to impact public health practice, we will test for a minimum level of efficacy that will have significant public health benefit when balanced against the risks and cost. Concordant with Phase III trial designs for HIV vaccines, we set this minimum level of efficacy at 30%, and therefore will test a null hypothesis of 30% (or less) efficacy for each PrEP regimen with the standard Type I error rate of 0.05. Duration of follow-up will be a minimum of 24 months, and a maximum of 36 months. We anticipate loss to follow-up of ~18% over the course of the follow-up period for this study (7% per year), based on our previous work with HIV-1 discordant couples in East Africa.

Sample sizes required for rejecting the null hypothesis of 30% efficacy (with 80% power) are given in Table 3 when the true efficacy of each PrEP arm (TDF or FTC/TDF) is assumed to be 60%. Ultimately, the trial design is event-driven so that each treatment arm will be tested separately against placebo. Endpoints may accrue at different rates for testing the efficacy of each arm compared to placebo so efficacy data may mature at somewhat different times for each regimen.

### Table 3: Sample size estimates for 80% power to distinguish 60% from 30% efficacy of each PrEP arm relative to placebo

<table>
<thead>
<tr>
<th>Incidence in placebo arm</th>
<th>Total Sample Size</th>
<th>Total HIV Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>4%</td>
<td>3150</td>
<td>191 (147 in each 2 arm comparison)</td>
</tr>
<tr>
<td>3.5%</td>
<td>3590</td>
<td>191 (147 in each 2 arm comparison)</td>
</tr>
<tr>
<td>3.25%</td>
<td>3860</td>
<td>191 (147 in each 2 arm comparison)</td>
</tr>
<tr>
<td>3%</td>
<td>4170</td>
<td>191 (147 in each arm comparison)</td>
</tr>
</tbody>
</table>

In additional calculations not shown here, assuming possible HIV incidence rates between 3% and 4% in the placebo arm, we will have 90% power to detect an efficacy of
between 61% and 65% for each PrEP arm vs. placebo, against a null hypothesis of 30% efficacy.

Thus, assuming 3-4% HIV incidence in the placebo arm, which is consistent with our observed HIV incidence in the Partners’ HSV-2 trial, we estimate achieving at least 80% power to detect ≥60% efficacy for TDF and FTC/TDF, separately, compared to placebo, ruling out <30% efficacy.

Of note, these sample size estimates are designed using the intent-to-treat approach to the primary efficacy endpoint, as detailed in Section 14.5.1 below. We anticipate that pregnancy and breastfeeding will require that ~10% of study time among female participants will be off of study drug, or 5% of total study time, assuming equal enrollment of female and male partner (HIV-1 uninfected) participants. We have anticipated that person-time from women who become pregnant but who are off study drug will be included in the intent-to-treat analysis, with events in the intervention arms contributed at the placebo rate. Thus, effectively we have 80% power to detect efficacy of 57% rather than 60% for each active arm compared to placebo, which is reduced due to having 5% of total follow-up time off drug (60%*(1-5%) = 57%). This has been factored into the sample size estimates in Table 3.

In computations not shown, 3900 HIV-uninfected participants will also provide 90% power to test overall efficacy at the 60% level of the combined treatment effect of TDF and FTC/TDF relative to placebo (i.e., a test of the concept of PrEP, rather than a test of either specific PrEP drug).

For evaluating safety, with 1300 per arm of active drug, the 95% CI for the rate of AEs, if none observed, is 0-0.2%.

14.5 Analysis Plan

Data analyses will be performed on an intent-to-treat basis, unless otherwise specified. To assess the success of randomization, a summary of key baseline variables will be tabulated by treatment group. However no formal statistical testing of these variables will be performed.

14.5.1 Primary Endpoint: Efficacy of TDF and FTC/TDF

For the principal analyses of the primary study endpoint, participants will be included if they are randomized and receive any study drug. Those who do not adhere to study drug will be included in the intent-to-treat analyses to provide the most generalizable efficacy measure. However, HIV-1 seronegative participants found to be HIV-1 positive by PCR at the enrollment visit will be excluded from efficacy analyses.

Additional modified intent-to-treat analyses of the primary study endpoint will also be performed. These modified intent-to-treat analyses will exclude person-time contributed by study participants while off study medication for >3 consecutive months.
as a result of pregnancy and/or breastfeeding. These modified
intent-to-treat analyses will provide information more closely
related to on-drug efficacy.

Additional analyses will be performed on a per-protocol basis, and
will include participants reporting at least 90% adherence over
follow-up. Covariates of sexual behavior and condom use will be
described at enrollment and over follow-up. Categorical variables
will be described in tables, and continuous measures will be
summarized using means and standard deviations or medians
and ranges, as appropriate. Statistical testing will be performed to
assess any potential differences by randomization arm.

Analyses of the primary study endpoint will be performed to test
the rate of HIV-1 acquisition, both combined and separately,
between each TDF and FTC/TDF arm versus placebo using Cox
regression analysis. Only one predictor will be used in each
analysis: the randomization arm. The same reference arm
(placebo) will be used for each treatment arm; however, no
multiple comparison adjustment will be performed. The endpoint
used will be HIV-1 detection, calculated using the date of first
seropositivity.

14.5.2 Co-primary Endpoint: Safety of PrEP Compared to Placebo

Adverse events (AEs) will be compared by treatment arm and
rates will be compared using exact tests for differences in rates
(given the Poisson distribution). Since several AEs are of interest,
multiple comparison adjustments will be performed to avoid false
positive findings. Like for the analyses of the primary study
efficacy endpoint, analyses of the co-primary safety endpoint will
be by both intent-to-treat and as-treated approaches, the latter of
which will capture safety associated with actual product use.

14.5.3 Secondary Aims Analyses

Efficacy. Cox regression models will be used to examine the
efficacy of PrEP stratified by potential risk factors for acquisition in
addition to treatment arm. Baseline risk factors will be considered
including plasma HIV-1 viral load in the index (HIV-1 infected)
partner, gender, HSV-2 status, GUD history, and male
circumcision status. Time-varying measures will also be assessed
using Cox models for correlated data (including a robust variance
measure) and will allow assessment of the potential impact of
CD4 level and HIV-1 viral load of the transmitting partner as well
as incident STIs.

Adherence. Adherence to study drug will be described both by
self report and using pill counts from returned bottles. Reasons
for non-adherence will be collected, including sharing of drugs
with the index (HIV-1 infected) participant, alcohol use, illness, relationship change, and percent of missed pills due to each reported reason will be computed. Potential drug sharing in couples will be assessed by drug assays in index (HIV-1 infected) participants.

**Risk Compensation.** Sexual practices, including condom use, will be described at enrollment and all follow-up visits. Changes in sexual frequency and frequency of condom use will be assessed using, respectively, Poisson and binomial models for correlated data (generalized estimating equations, GEE). Correlated data techniques are appropriate as participants will contribute multiple visits. Time trends can be evaluated as well as differences in trends by treatment arm, using interaction terms, to determine whether potential changes in sexual practices are common to all or specific to a given treatment arms.

**Viral Resistance and ‘Set-point’ in Seroconverters.** Differences by treatment arms in resistance genotypic and phenotypic assays and viral set-point among those acquiring HIV-1 will be assessed using two-sample tests. For continuous measures such as CD4 count, non-parametric tests will be used to compare the clinical outcome in seroconverters by treatment arm, or t-tests if the outcome is centrally-distributed. Categorical measures will be compared using chi-square tests, or Fisher’s exact tests if the number of seroconverters in a given arm is very small (< 10).

**14.5.4 Analytic Considerations**

The primary analysis will be a survival analysis using Cox's proportional hazards model with time to detection of HIV-1 infection in the HIV-1 uninfected partner as the outcome. Since the follow-up schedule is the same for both treatment groups, it is sufficient and operationally simpler, to measure “time to detection” rather than “time to infection.” The principal analyses will be based on the "intent to treat infected" principle, by which couples will be included in their assigned treatment group (based on random assignment of the HIV-1 uninfected partner) regardless of adherence to treatment. All tests will be two-sided unless specified otherwise.

The unit of analysis is the partnership and in the primary analysis only confirmed HIV-1 acquisitions will be treated as endpoints.

If the couple should separate during the course of the study (i.e., the partnership dissolves), we will continue to follow both partners. The partners will remain in follow-up in the spirit of an intent to treat analysis, and because it is not possible to predict the durability of a partnership termination.
In secondary analyses we will estimate the treatment effect on HIV-1 seroconversions among the HIV-negative partners of key covariates (e.g., adherence, gender, plasma viral load in the index [HIV-1 infected] partner, condom use, use of ART) on transmission and the efficacy of the intervention.

Some secondary analyses will estimate the per-contact risk of transmission as a function of covariates. We will use the following model (based on the work of Jewell and Shiboski [91])

\[
\log(-\log(1-P(k,X))) = X\beta + \Sigma i \log(k_i) + \log(-\log(1-\lambda_i))
\]  (1)

where \(k_i\) is the number of contacts (episodes of intercourse) of type \(i\), \(X\) is a vector of covariates and \(P(k,X)\) is the probability of a transmission event in an interval during which \(k = \Sigma k_i\) contacts occur and the covariate values are given by \(X\). The parameter \(\lambda_i\) is the probability of transmission per coital act (infectivity) of type \(i\) (e.g. insertive or receptive vaginal sex) for an individual with covariates set at baseline levels (this is sometimes referred to as the "adjusted" infectivity).

Possible covariates include treatment group, condom use, circumcision status, HSV-2 serostatus, CD4/viral load of the HIV-1 positive partner in the preceding interval, slope of decline or increase in viral load after enrollment, duration of relationship as reported at enrollment, ART in the HIV-1 positive partner, and STIs in either partner. The possibility of declining or increasing infectivity over time can be incorporated using a "time since study enrollment" covariate. Note that we obtain separate infectivity estimates for each level of the covariate (i.e. if CD4 is categorized into 4 intervals then the model estimates four infectivity values - one for each CD4 quartile). For binary or categorical covariates, this is effectively the same model used by Gray, et al. [85], to estimate infectivity in the Rakai cohort.

The model (1) has the form of a generalized linear model and can be fit with standard software. The data used for model fitting includes the number of coital acts of each type (the \(k_i\)) and HIV-1 serostatus of the susceptible partner for each testing interval for each partnership in the study. The fitted model provides estimates of the baseline infectivities (\(\lambda_i\)) and the effect of covariates (\(\beta\)). Straightforward calculation yields estimates of infectivity for any combination of covariates. Since each couple may contribute multiple "observations" (i.e. intervals between testing) to these data, robust variance estimates [92] will be used to evaluate statistical significance and form confidence intervals.

The analysis of adherence will be structured to estimate the adherence rate, test for a difference in adherence between the placebo and treatment groups, test for a trend over time in the adherence rate and examine the relationship between adherence and markers of risky sexual behavior. Specifically, we will use a logistic
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regression with proportion of pills taken each month or the pattern (clustering or consecutive missed doses) of non-adherence as the outcome and treatment group, and time on study and markers of risky sexual behavior as predictors. Since the analysis will involve repeated observations on individuals, robust variance estimates will be used to evaluate statistical significance and compute confidence intervals. Standard methods for model checking will be used to check the assumption of a linear trend in adherence.

To determine if the intervention has had any measurable effect on sexual behavior, we will compare endpoints such as partnership dissolution, number of new partners and number of sex acts per unit time, as well as longitudinal change in these parameters after enrollment, between study arms. As these can all be measured on a per individual basis, the units of analysis are independent and a t-test or chi-squared test, as appropriate, can be used for the comparison.

Both the Cox model used for the primary analysis and model (1) may be extended to include additional covariates that may influence transmission. To ascertain the importance of immunologic, genetic, and virologic determinants of HIV-1 transmission, factors such as viral clade, heterogeneity, and SI phenotype, HIV-1 coreceptor polymorphisms, and HLA match between partners or other host genetic factors can be added to the model.

14.5.5 Interim Analyses

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that will advise the sponsor and the study investigators. The DSMB for the HPTN 039 and Partners in Prevention HSV/HIV Transmission Trials will monitor this trial, with the addition of members with pediatric expertise and knowledge of East Africa. The primary responsibilities of the DMSB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and efficacy, and 2) make recommendations to the study investigators and the sponsor concerning the continuation, modification, or termination of the trial. The DSMB will consider study-specific data as well as relevant background knowledge about the disease, study medications, and/or patient population under study. The DSMB will maintain the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

Following study initiation, the DSMB will review data on safety, study conduct, and scientific validity and integrity of the trial approximately every 6 months. One DSMB review to assess safety and study conduct will be scheduled prior to 6 months after study initiation, to allow an early review of these issues.

Additional reviews of efficacy will also be performed; these may
coincide with DSMB reviews of safety and study conduct, or these may occur separately. Prior to study initiation, the schedule of efficacy review will be established. It is anticipated that there will be 2-3 interim scheduled efficacy reviews – for example at 30, 60, and 90 total endpoints (out of the expected 122 study endpoints across the 3 study arms).

Analyses presented to the DSMB will include participant accrual rates, comparability of the two study treatment groups at enrollment, adherence to the study drug regimen, loss-to-follow-up rates, AE rates, and HIV-1 incidence by treatment group. Analyses of HIV-1 incidence rates will utilize an O’Brien-Fleming stopping rule.

The DSMB will specifically review safety information related to infants exposed to study drug in utero. Evaluation of HIV-1 incidence among women who become pregnant and/or initiate breastfeeding (and who will thus be off study drug) will be assessed.

The DSMB will also assess the performance of overall study operations and other relevant issues. Additional information about the DSMB composition and review procedures will be contained in a separate DSMB charter.

Prior to study implementation the DSMB will define its stopping guidelines, procedures for unmasking (unblinding), event triggers that would call for an unscheduled review, and voting procedures. Guidelines for evaluation of futility will also be developed.

The DSMB will make recommendations regarding adjustment of sample size, if required, if HIV-1 incidence or follow-up rates are different than anticipated. If loss to follow-up is less than anticipated, or the HIV-1 incidence rate is higher, fewer subjects may be needed to observe the required number of acquisition events. Based on unblinded safety and efficacy data in closed reports, the DSMB will make recommendations as to whether to continue or halt the study.

In developing procedures related to study continuation or discontinuation as part of the DSMB charter, several scenarios will be considered, including:

- Decision rules for stopping the study if both active study drug arms demonstrate efficacy

- Decision rules for stopping the study if both active study drug arms demonstrate substantial adverse event rates, compared with the placebo arm, including rare but significant adverse events
• Demonstration of efficacy in one of the two active study drug arms without (or prior to) demonstration of efficacy in the other active study drug arm, including parameters for the level of efficacy to stop follow-up in one arm early while continuing follow-up of the remaining arm

• Demonstration of efficacy in another ongoing PrEP trial

• Differential rates of adverse events, including rare but significant adverse events, in either or both of the active study drug arms

• Lower than expected HIV-1 incidence, lower than expected study drug adherence, or higher than expected loss to follow-up in any of the study arms

• Possible futility in one or both of the active study drug arms

15. HUMAN SUBJECTS CONSIDERATIONS

Human subjects are the focus of the work outlined in this proposal, which is designed to study the use of ART for prevention of HIV-1 infection. Approvals from all applicable regulatory authorities will be obtained prior to initiating any study procedures. The applicable regulatory authorities include the local site IRBs; the University of Washington IRB; the Health Ministries that govern study sites; and the FDA. The primary IRB for the study is the University of Washington Human Subjects Review Committee.

15.1 Ethical Review

The study protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will be reviewed and approved by the IRBs/ECs responsible for oversight of research conducted at the study sites. Subsequent to initial review and approval, the responsible IRBs/ECs will review the study at least annually.

Each site Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, all AEs, and all unanticipated problems involving risks to human subjects or others. The results of all DSMB reviews of the study also will be provided to the IRBs/ECs.
15.2 Informed Consent

Written informed consent will be obtained from each study participant prior to both screening and enrollment. In addition to consent to participation in the study, a separate initial line will allow participants to agree or disagree to having their specimens placed in the local and central repositories for future testing to identify host and viral factors associated with transmission of HIV-1 and other sexually transmitted diseases. HIV-1 infected participants will be allowed to participate in the study even if they are unwilling to provide genital tract specimens (semen or endocervical swabs) for HIV-1 viral load measurement. Participants will be offered copies of the informed consent forms.

Each study site is responsible for developing study informed consent forms for local use that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations, based on the samples provided in Appendices VIII, IX, X, and XII. Each site also is responsible for translating the forms into local languages and verifying the accuracy of the translation by performing an independent back-translation, which will be reviewed and approved by the Coordinating Center.

The informed consent process will include an assessment of each potential participant’s understanding of concepts identified by the Protocol Team members as essential to the informed consent decision prior to the participant signing an informed consent. Assessment of comprehension will include a quiz for each prospective participant. Participants who are not able to demonstrate adequate understanding of key concepts after educational efforts will not be enrolled in the study. Assessments of participant understanding will be repeated throughout the accrual period; results will be used to identify participants who need additional counseling regarding the study. Participants who are able to comprehend the study and want to participate will be asked to sign an informed consent form. Additionally, the counselor will sign the informed consent form to document the consent process and their belief that the participant understands the informed consent form. If the individual is unable to read or write, a witness will be present throughout the consenting process and sign the consent document as a witness. Acceptance or declination of consent will be noted in the source document.

In addition to the informed consent forms, 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 the study site. Written educational materials as well as other more innovative approaches will be considered. The process and materials will be pilot-tested prior to study start-up to ensure cultural appropriateness at the site.

15.3 Key Elements of the Informed Consent

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

(1) The unknown safety and unproven efficacy of the study agent.
(2) The need to practice safer sex behaviors during the study.
(3) The importance of partner (HIV-1 uninfected) participants in all three study groups to the success of the study, as well as the important contribution of index (HIV-1 infected) participants.

(4) The importance of adherence to the study visit and procedures schedule.

(5) The potential medical risks of study participation (and what to do if such risks are experienced).

(6) The potential social harms associated with study participation (and what to do if such harms are experienced).

(7) The probable direct and indirect, but uncertain, benefits of study participation.

(8) The distinction between research and clinical care.

(9) The right to withdraw from the study at any time.

15.4 Risks

15.4.1 Risks Common to Both Partner (HIV-1 Uninfected) and Index (HIV-1 Infected) Participants

Study participants may experience discomfort during genital exams, swabbing of genital ulcers, and/or collection of genital tract specimens. Participants may experience discomfort or pain when undergoing phlebotomy. They also may feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle is inserted.

Participants may become embarrassed, worried, or anxious when completing their HIV-1 risk assessment and/or receiving HIV-1 counseling. They also may become worried or anxious while waiting for their (and their partner’s) HIV-1 test results. Couples-based counseling and discussions of study participation may raise issues between partners, particularly related to blame (from the HIV-1 uninfected partner) and potential termination of the partnership. Participants who learn that they have HIV-1 may experience anxiety or depression related to their test results. At all study sites, individual and couples-based HIV-1 counseling will be provided by counselors and clinicians who have been trained in specific issues related to HIV-1 discordant couples, including stigma, blame, methods to avoid transmission, and available support services.

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 participating in a trial involving HIV-1 infected persons). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

15.4.2 Toxicity Risks Specific to Partner (HIV-1 Uninfected) Participants
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Risks and side effects related to the study drugs TDF and FTC/TDF include the following:

**Less Likely**
- Gastrointestinal intolerance, such as nausea, diarrhea or vomiting
- Flatulence
- Rash

**Rare but serious**
- Lactic acidosis/ severe hepatomegaly with steatosis
- Renal impairment, including cases of acute renal failure and Fanconi’s syndrome (renal tubular injury with severe hypophosphatemia)
- Increase in bone metabolism leading to osteopenia
- Hypersensitivity reaction

15.5 Benefits

There may be no direct benefits to participants in this study. However, participants and others also may benefit in the future from information learned from this study.

15.5.1 Potential Benefits to Participants

Participants will receive couples counseling at screening, enrollment, and during follow-up that will include counseling about risks for transmission and strategies to reduce the risk of transmission. Participants will receive genital exams, HIV-1 and STI counseling and testing, STI treatment, and HBV vaccination if indicated. They may be offered participation in support groups for HIV-1 infected and HIV-1 uninfected persons (e.g., "post-test clubs" focusing on issues pertinent to HIV-1 discordant couples) and will be provided condoms (male condoms, as well as female condoms as available) and STI treatment free of charge.

Notably, we have found that the prevalence of curable STIs (i.e., *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, syphilis) among stable, heterosexual HIV-1 discordant couples in this setting is <10%. Assessment and syndromic management of STIs will be a part of all study visits. Yearly testing will also be conducted, in batched testing in Seattle, to assess the prevalence of curable STIs over the course of the study.

Based on the local standard of care, participants also may be offered certain clinical services available through the study staff, including contraceptives, malaria screening, Bactrim prophylaxis,
chest x-rays for TB case detection, and — when consistent with TB prevalence and local TB program objectives — isoniazid for TB prophylaxis. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community.

### 15.5.2 HIV-1 Counseling and Testing

Best prevention practices will be provided to all couples screened for this study. HIV-1 pre-test, risk reduction, and post-test counseling will be provided to all potential study participants who consent to undergo HIV-1 screening to determine their eligibility for this study, and to all enrolled HIV-1 uninfected participants at each follow-up visit including counseling and HIV-1 testing. Counseling will be provided in accordance with local standards of practice at each study site.

Site counselors will receive training in specific methods for counseling of couples. Couples counseling will include:

- **Approaches to risk assessment with couples**

- **Pre-test counseling points:**
  - Possible scenarios of being HIV-1 positive concordant, HIV-1 negative concordant, or HIV-1 discordant
  - Risks of transmission
  - Implications/strategies for each outcome prior to actual testing

- **Post-test counseling points:**
  - Approximately 50% of couples tested in Africa in which one partner is HIV-1 infected are HIV-1 discordant
  - HIV-1 transmission risk is variable, depending on factors like stage of HIV-1 infection in the HIV-1 infected partner, plasma viral load, male circumcision, and STIs
  - Methods couples can use to protect themselves, such as condoms and avoidance of sex during menses
  - Family planning considerations and options to reduce risk of HIV-1 transmission during conception

- **Issues related to HIV-1 discordant couples, including stigma, blame, and disclosure to relatives and children**

- **Support services for couples, possibly including “post-test clubs” for couples who are HIV-1 positive concordant, HIV-1 negative concordant, and HIV-1 discordant**

All couples will be provided with HIV-1 prevention services, including condoms, STI treatment, and ongoing support, including
counseling and referral to other support services.

15.5.3  HIV Prevention Services

The primary aim of this study is to assess the safety and efficacy of PrEP in prevention HIV-1 acquisition among HIV-1 uninfected partners within HIV-1 discordant couples who are receiving standard-of-care HIV-1 prevention services. Best prevention practices, according to national guidelines, will be provided to all couples enrolled in this study. This will include risk reduction counseling, treatment of sexually transmitted infections (STIs), and condoms. As other efficacious prevention strategies (e.g., male circumcision) are translated into national policies in areas in which the study is being conducted, study participants will be counseled about these interventions, and either offered by the site or referred to local centers with appropriate expertise. If additional prevention strategies (e.g., acyclovir herpes suppression) are found to be efficacious and national policies are developed for implementation, participants will be counseled and receive or be referred for these strategies as well.

15.5.4  Care for Participants Identified as HIV-1 Infected

This study will identify persons who are infected with HIV-1, either as part of the study screening process or during follow-up of enrolled participants. Study staff will provide participants with their HIV-1 test results in the context of post-test counseling.

Persons identified as HIV-1 infected during the study screening process, but who do not meet eligibility criteria or who do not wish to enroll in the study, will be referred to local HIV-1 care services and/or other agencies that provide care or access to treatment. Sites will establish referral procedures with clinical care providers and HIV support programs, including services after the trial ends. They also will be referred to any available HIV-1 treatment clinical trials and/or other research studies for HIV-1 infected persons. An algorithm for referral or provision of services for HIV-1 infected persons who are ineligible for the trial (using the example of current guidelines, which recommend ART at CD4 <200 cells/mm$^3$) or refuse participation is summarized as follows:

- If CD4 cell count is less than 250 cells/mm$^3$ or clinical AIDS diagnosis: refer to care program or ARV clinical trial(s).

- If CD4 cell count is > 250 cells/mm$^3$ but individual or couple otherwise ineligible, provide or refer to Bactrim D/S and TB screening/INH prophylaxis, according to national guidelines.

- If pregnant (whether enrolled or not), refer to preventive
mother-to-child-transmission program (PMTCT)

HIV-1 infected persons who enroll in the study will be provided or referred for HIV-1 clinical care, including primary care, screening and treatment for a variety of disease manifestations, and antiretroviral therapy, according to national guidelines. This clinical care will be provided under the best clinical judgment of the study clinicians, and will be either provided at the study site during the trial or through well-established referral to clinical care programs. During the course of the study, it is possible that guidelines will change regarding clinical care of persons with HIV-1 (including timing of initiation of ART, optimal therapy, prophylaxis, etc.). At all times during the study, treatment and referral practices for HIV-1 infected persons in the study will adhere to national guidelines for HIV-1 infected persons.

After the study ends, HIV-1 infected participants (including those who seroconvert to HIV-1 during the trial) will be provided referrals to other care programs for ongoing HIV-1 primary care. This type of care will also be offered to initially HIV-1 uninfected study participants who become infected during follow-up. The results of batched HIV-1 resistance assays for HIV-1 seroconverters will be made available to the research sites to be considered in ART regimen selection when seroconverters meet national guidelines for ART initiation.

For participants who are HIV-1 infected and who also become pregnant during follow-up, every effort will be made to facilitate access to programs for preventing mother-to-child HIV transmission for appropriate antiretroviral treatment to reduce the probability of HIV-1 transmission from mother to child. Women who seroconvert to HIV-1 and subsequently become pregnant during the course of the study will have expedited HIV-1 resistance testing to facilitate appropriate antiretroviral treatment to reduce the probability of mother-to-child HIV-1 transmission.

15.5.5 Benefits to the Community

An important goal of this study is to achieve the study objectives in a way that provides benefits to the community that endure beyond the proposed study lifetime regardless of the specific outcome of the study. Some of these community benefits are listed below:

Development of couples HIV counseling and testing (CHCT): Infrastructure to effectively counsel and test couples for HIV will be needed for this study to effectively recruit discordant couples. CHCT capacity developed at participating sites in collaboration with existing local VCT programs through training of local counselors will be a beneficial resource to the community well after the study is completed. Given recent data that 70% of
incident HIV-1 cases are transmitted from regular partners, creating awareness, increasing demand and constructing facilities for couples VCT should reduce transmission of HIV-1 among couples. This will have consequent benefits to the family and community by maintaining one healthy partner.

Enhanced laboratory capacity: The study will enhance local laboratory specimen and data management infrastructure through use of electronic databases and networks. The study will also provide technical training to ensure sustainable proficiency testing and quality control for HIV, CD4, and other testing.

Sustainable infrastructure for future HIV-1 prevention and treatment trials: A sustainable infrastructure allowing high quality behavioral and laboratory research with HIV-1 discordant couples is needed to study vaccines and other preventive and treatment strategies for HIV-1. This will be developed in communities participating in this trial making them attractive sites for future studies (e.g., microbicide and vaccine trials) with consequent direct and indirect individual and community benefits.

Knowledge of community-specific biological factors for HIV-1 transmission: This study may identify specific biological and social risk factors for HIV-1 transmission that are unique to specific ethnic groups. Knowledge about specific genetic and immunologic factors may lead to therapies, vaccines or other preventive tools that may specifically benefit such groups in participating communities.

15.6 Treatment for Injury

Participants will be asked to inform the study staff if they feel they have been injured because of taking part in the study. Injuries may also be identified during laboratory testing, medical histories, and physical examinations. These injuries will be reported as AEs. Treatment for AEs related to study participation will be provided by the study clinic. If treatment is required that is beyond the capacity of the study clinic, the study doctors will refer the participant to appropriate services or organizations that can provide care for the injury. If the study doctors determine that the injury is related to the study, the study will pay for the medical care.

15.7 Access To Effective Products

Should this study provide evidence of the effectiveness of TDF and/or FTC/TDF in preventing HIV-1 infection, it will be important to provide appropriate access to TDF and/or FTC/TDF to study participants, their communities, and the worldwide population at risk for HIV-1 infection in a timely manner. In preparation for this study, Protocol Team members have had discussions with Gilead regarding access to TDF and FTC/TDF in the future. Gilead has committed to providing TDF and/or FTC/TDF for the placebo participants for 12 months free of charge. As the study is ongoing, the study investigators will explore options for provision of TDF and/or FTC/TDF to participants in
the active arms of the study, should the study demonstrate efficacy.

Gilead has provided technology transfer for TDF and FTC/TDF to generic companies and has established an international access program in which TDF and FTC/TDF will be provided at cost in resource-poor countries. While this program is currently intended to facilitate access to TDF and FTC/TDF for those who are already HIV-1-infected and require treatment, the drug may be accessed through this program for other indications as well. Considerations under discussion include licensing agreements and preferred pricing arrangements for the study communities and other resource-poor settings. While this study is ongoing, discussions will be initiated with other public and private funding sources such as the WHO, UNAIDS, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and appropriate site government agencies that may be able to purchase product supplies in bulk and offer them at low or no cost to the study communities and other resource-poor communities most in need of TDF and FTC/TDF. Operations and marketing research may also be conducted to determine how best to package and distribute TDF and FTC/TDF and maximize the utility for at-risk populations.

15.8 Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent possible. Personal identifying information will be retained at the local study site and not forwarded to the UW coordinating center. Each study site will establish a standard operating procedure for confidentiality protection that reflects the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in areas with limited access. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified only by a coded number 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 participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participants’ study information will not be released without their written permission, except as necessary for oversight by:

- The Protocol Chair or designees
- Study monitors
- The Bill and Melinda Gates Foundation
- Site IRBs/ECs
- The U.S. Food and Drug Administration
15.9 Incentives

Participants may be compensated for their time and effort in this study, and/or be reimbursed for costs associated with travel to study visits, time away from work, and childcare. Site-specific reimbursement schedules and amounts will be specified in the local study informed consent forms and approved by all responsible IRBs/ECs.

15.10 Communicable Disease Reporting Requirements

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

15.11 Study Discontinuation

This study may be discontinued at any time by the Protocol Chairs, the Bill and Melinda Gates Foundation, government or regulatory authorities, and/or site IRBs/ECs. Sites will be supported to provide time for exit visits for study participants and to close out study records before locking the database.

16. LABORATORY CONSIDERATIONS

All specimen transport, processing, testing, and results reporting will be conducted in accordance with standards of good clinical and laboratory practice. Each study site will establish standard operating procedures, including specimen chain of custody and QC/QA procedures, for all protocol-specified laboratory tests prior to study initiation. All specimens will be transported and/or shipped in accordance with International Air Transport Association.

Laboratory study specific procedures (SSPs) will dictate the maximum number of aliquots for any given specimen type that will be retained for this protocol in local or central archives. SSPs will also dictate the priority for distributing aliquots when specimen volume is limiting. Until the appropriate number of aliquots are received at the central archive, samples at the local archive should be maintained as a back-up for the central archive. Any specimen aliquots beyond the maximum required by the study protocol can be retained in the local archive for future testing with permission of the local IRB.

16.1 Local Laboratory Specimens

The following types of specimens will be collected for testing at the local laboratory:

- Blood for HIV-1, HSV-2, syphilis, and HBV serologies, as well as CD4 cell counts, serum chemistries, and CBC
- Urine for pregnancy testing
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- STI diagnostic testing (syphilis serologies at all sites, and, at selected sites where such testing is available, including gonorrhea, chlamydia, trichomonas by culture or PCR, and endocervical Pap smears)

16.2 Central Laboratory Specimens

The following types of specimens will be collected for testing at the University of Washington, which serves as the Central Laboratory for this study:

- Urine (men) and cervical swabs (women) for STI testing to assess STI prevalence across all sites (gonorrhea, chlamydia, and trichomonas PCR)
- Vaginal swabs and slides prepared from vaginal swabs for evaluation of bacterial vaginosis (women only)
- Sera and plasma for HIV-1 WB confirmation of HIV-1 infection among enrolled index (HIV-1 infected) participants and incident HIV-1 infection in partner (HIV-1 uninfected) participants, HIV-1 RNA PCR, HIV-1 genotyping and phenotyping, TDF and FTC/TDF drug levels in partner (HIV-1 uninfected) and index (HIV-1 infected) participants to monitor study drug adherence and drug sharing, respectively
- Seminal plasma and cells for HIV-1 RNA PCR
- Endocervical swab for HIV-1 RNA PCR
- Whole blood and dried blood spot archives for DNA for HLA typing and analysis of polymorphisms in genes affecting innate/adaptive immunity

16.3 Quality Control and Quality Assurance Procedures

Quality control will be coordinated through Contract Laboratory Services (CLS) at University of Witswatersrand and will consist of proficiency specimen panels for HIV-1, HBV, and HSV-2 ELISA and CD4 tests, as well as serum chemistries and CBC. These will be distributed to all laboratories for participating sites at regular intervals during the study enrollment and follow-up periods.

The Protocol Chair will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through confirmatory HIV-1 testing performed by the UW Lab.

16.4 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 United States Centers for Disease Control and Prevention.
17. ADMINISTRATIVE PROCEDURES

17.1 Protocol Compliance

This study will be conducted in full compliance with the protocol. Site Investigators will not amend the protocol without prior written approval from the protocol chair. Any protocol amendments will be reviewed and approved by the relevant IRBs/ECs prior to implementing the amendments except when necessary to protect the safety, the rights, or welfare of participants, or to eliminate apparent immediate hazards to participants.

17.2 Study Coordination

Study implementation will be directed by this protocol. Case report forms will be developed by the Protocol Team. Data will be transferred, entered, and cleaned using the DataFax data management system. Data quality control reports and queries will be generated routinely and distributed to study sites for verification and resolution.

Close coordination between the Protocol Chair, site Investigators, 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. The team will closely monitor rates of participant accrual, study drug adherence, follow-up, and incidence of reportable AEs. The Protocol Co-Chairs and other designated Protocol Team members 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.

17.3 Study Activation

Following IRB/EC review and approval, study sites will submit required administrative documentation (specified in the study procedures manual) to the Protocol Chair or designees. The Chair or designees will review the documents for accuracy and completeness. Upon confirmation of the adequacy of these documents, the Chair or designees will “activate” the site to begin study operations. Study implementation may not be initiated until a formal study activation notice is issued for the site.

17.4 Study Monitoring

Study monitors will complete periodic visits to each study site to:

- Verify compliance with human subjects and other research regulations and guidelines
- Assess adherence to the study protocol and study procedures manual
- 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 (if participants consent). Investigators also will allow inspection of all study-related documentation by individuals authorized by the Protocol Chair as well as representatives of the study Sponsor. A site visit log will be maintained at the study site to document all visits.

17.5 Study Records

Site Investigators will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. The investigator will retain all study records for at least five years after completion of the study, unless directed otherwise by the Protocol Chair. Study records include administrative documentation and regulatory documentation 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.

17.6 Use of Information and Publications

Publication of the results of this study will be governed by the policies of the Gates Foundation and the University of Washington. A publications committee will be formed to which concept sheets, analysis plans, conference abstracts, and manuscripts will be submitted for review.
18. REFERENCES

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples


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Appendix II  Study Visits and Procedures for Index (HIV-1 Infected) Participants
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## Appendix I  Study Visits and Procedures for Partner (HIV-1 Uninfected) Participants

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Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

a  At Enrollment and every 12 months, STI screening (syphilis serology and for women, an endocervical swab and a Pap smear and for men, a urine sample) will be performed, in addition to usual monthly, quarterly, and 6-monthly procedures. STI symptoms will be collected quarterly. If clinically indicated, based on genital symptoms, STI screening and syndromic or laboratory-based diagnosis and management will be provided at any study visit.

b  Participants who are not immune to hepatitis B will be offered hepatitis B vaccination (at enrollment, 3 and 6 months). Those who are not immune but who decline vaccination will have hepatitis B testing repeated annually and at the Stop Visit. In addition, as needed hepatitis B testing will be performed at the time study drug is stopped during the study (e.g., for pregnancy, for side effects) for individuals who are hepatitis B susceptible at enrollment and who either declined vaccination or did not complete the vaccine series. If HBsAg positive, they will be counseled about the risk of hepatitis flare and serum chemistries will be monitored monthly for 2 months after they stop study drug.

c  At Screening, Month 1, and every 3 months (quarterly), serum chemistries and blood counts will be performed, as defined in the Protocol, in addition to the standard monthly procedures (e.g., HIV-1 testing and provision of study drug).

d  HSV-2 serology will be done at the Local Lab if results of on-going studies of HSV-2 suppressive therapy to prevent HIV-1 acquisition demonstrate efficacy. Prior to those results becoming available, or if those results do not demonstrate efficacy, testing will be done in a batched fashion at the Central Laboratory.

e  Pap smears will be performed at sites where Pap smears are the standard of care and where cytopathology and referral for dysplasia management are available.

f  Archived samples for the Central Lab will include:
   1) Serum and plasma for eligibility and endpoint confirmation, and for secondary and tertiary study objectives. Batched HIV-1 Western blot testing will be performed for QC purposes in 10% of enrolled participants and to confirm local rapid HIV-1 tests in HIV-1 seroconverters
   2) Samples for STI and BV (for women) testing will be performed from Enrollment and every 12 months thereafter to assess the prevalence of genital tract infections in participants.
   3) Whole blood and blood spot samples for secondary and tertiary study objectives. As detailed in the protocol, participants will consent to storage of samples for future research and IRB approval will be obtained prior to additional testing.

g  After completing follow-up on study drug, participants will be followed for an additional 1 month, to observe for delayed endpoints.

h  Blood volumes are maximums. Explanation of blood volumes:

At all visits, sites will have the option to perform HIV-1 serologic testing by blood draw or finger stick. One 4 mL plasma (e.g., EDTA) blood tube will be obtained for this purpose at sites that choose to use a blood draw. At the Screening Visit, a blood draw sample will be collected, to allow confirmatory EIA testing.

At visits at which serum chemistries will be performed (i.e., Screening, Month 1, Month 3 and quarterly thereafter, Stop, Post-Study Drug), one 8.5 mL serum (e.g., SST) tube will be collected.
for this purpose. If study sites determine that a smaller tube (e.g., 4 mL) is sufficient to perform the required tests, a smaller tube can be drawn.

At visits at which hematologic testing will be performed (i.e., Screening, Month 1, Month 3 and quarterly thereafter, Stop), one 8.5 mL plasma (e.g., EDTA) tube will be collected for this purpose. If study sites determine that a smaller tube (e.g., 4 mL) is sufficient to perform the required tests, a smaller tube can be drawn.

At visits at which serum aliquots will be archived (i.e., Enrollment, Month 1, Month 3 and quarterly thereafter, Stop, Post-Study Drug), one 8.5 mL serum (e.g., SST) tube will be collected. Separate tubes for serum chemistry testing and for serum aliquotting are required to allow for sufficient sample to be available for chemistry testing and to accommodate research sites that will utilize separate laboratories for testing and aliquot preparation. At the Enrollment Visit, a small amount of serum will be used for HSV-2 and syphilis testing.

At visits at which plasma aliquots will be archived (i.e., Enrollment, Month 1, Month 3 and quarterly thereafter, Stop, Post-Study Drug), one 8.5 mL plasma (e.g., EDTA) tube will be collected. Separate tubes for hematology testing and for plasma aliquotting are required to allow for sufficient sample to be available for hematology testing and to accommodate research sites that will utilize separate laboratories for testing and aliquot preparation. Given the importance of plasma samples for the secondary and tertiary aims of the study, an additional 8.5 mL plasma tube will be collected at Enrollment and yearly thereafter (e.g., at Month 12, Month 24, etc., and at Stop), which will be used for archived aliquot preparation.

sites will have the option to obtain blood for HIV-1 testing by blood draw or by finger stick. For those sites that obtain blood by blood draw, a small blood tube will be used to minimize sample required.

[] = if clinically indicated, based on participant history
## Appendix II  Study Visits and Procedures for Index (HIV-1 Infected) Participants

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<tr>
<td>Collect blood specimen</td>
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<tr>
<td>Provide test results</td>
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<tr>
<td>Provide counseling about not sharing study drug</td>
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<td><strong>Local Lab</strong></td>
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<tr>
<td>HIV-1 serology (rapid test and EIA)</td>
<td>X</td>
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<tr>
<td>Syphilis serology</td>
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<td>CD4+ cell countf</td>
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<td><strong>Central Lab / Specimen Repositoryg</strong></td>
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<td>HIV-1 Western Blot quality control (batch testing)</td>
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<td>HIV-1 plasma viral load (batch testing)</td>
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<td>Plasma archive</td>
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<tr>
<td>Whole blood &amp; blood spot archives</td>
<td>X</td>
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<td>Urine archive</td>
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<tr>
<td>Seminal plasma and seminal cells archives (men only), for HIV-1 PCR (M6&amp;12 only)</td>
<td></td>
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<tr>
<td>Endocervical swab archive (women only), for HIV-1 PCR</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Endocervical swab for gonorrhoea, chlamydia &amp; trichomonas PCR (women only)b</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vaginal swab and slide for bacterial vaginosis evaluation (women only)b</td>
<td>X</td>
<td></td>
<td>X</td>
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<td></td>
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</tr>
<tr>
<td>Urine archive for gonorrhoea, Chlamydia and trichomonas PCR (men only)b</td>
<td>X</td>
<td></td>
<td>X</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BLOOD VOLUME (mL)g</strong></td>
<td>16.5</td>
<td>25.5</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>29.5</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>29.5</td>
<td>29.5</td>
</tr>
</tbody>
</table>

*Note: M = Month, E = Every.*

b: For HIV-1 positive participants only.
c: For HBV seronegative persons only.
d: For HSV-2 seropositive persons only.

---

**Partners PrEP Protocol**

Version 3.0, 12 October 2007
a. Routine follow-up for HIV-1 infected partners will be every 3 months (quarterly), although they will be encouraged to come to their partner’s monthly visits.

b. At Enrollment and every 12 months, STI screening (syphilis serology and for women, an endocervical swab and a Pap smear and for men, a urine sample) will be performed, in addition to usual monthly, quarterly, and 6-monthly procedures. If clinically indicated, STI screening will be performed at any study visit.

c. Participants who are not infected with and not immune to hepatitis B will be offered hepatitis B vaccination (at enrollment, 3 and 6 months).

d. HSV-2 serology will be done at the Local Lab if results of on-going studies of HSV-2 suppressive therapy to prevent HIV-1 transmission demonstrate efficacy. Prior to those results becoming available, or if those results do not demonstrate efficacy, testing will be done in a batched fashion at the Central Laboratory.

e. Pap smears will be performed at sites where Pap smears are the standard of care and where cytopathology and referral for dysplasia management are available.

f. Every 6 months, CD4 determination will be completed.

g. Archived samples for the Central Lab will include:

1) Serum and plasma for eligibility and endpoint confirmation, and for secondary and tertiary study objectives (including study drug levels and HIV-1 genotypic and phenotypic resistance testing among a subset of participants). Batched HIV-1 Western blot testing will be performed for QC purposes in 10% of enrolled participants.

2) Samples for STI and BV (for women) testing will be performed from Enrollment and every 12 months thereafter to assess the prevalence of genital tract infections in participants.

3) A semen sample will be requested from male HIV-1 infected participants at the Month 6 and Month 12 visits. Endocervical swabs from HIV-1 infected female participants will be obtained every 12 months.

4) Whole blood and blood spot samples for secondary and tertiary study objectives. As detailed in the protocol, participants will consent to storage of samples for future research and IRB approval will be obtained prior to additional testing.

h. Blood volumes are maximums. Explanation of blood volumes:

At the Screening Visit, one 4 mL plasma (e.g., EDTA) tube will be obtained for HIV-1 testing, including confirmatory ELISA testing. In addition, one 8.5 mL serum (e.g., SST) tube will be obtained for HBV testing and one 4 mL plasma (e.g., EDTA) tube will be obtained for CD4 testing. If able, sites may consolidate the blood volume for this visit – for example, by collecting a smaller volume (e.g., 4 mL) for HBV testing and/or by performing HIV-1 serologic testing using the serum or plasma collected for HBV or CD4 testing.

At 6-monthly visits, CD4 testing will be performed, using one 4 mL plasma (e.g., EDTA) tube.

At visits at which serum aliquots will be archived (i.e., Enrollment and 6-monthly thereafter), one 8.5 mL serum (e.g., SST) tube will be collected. At the Enrollment Visit, a small amount of serum will be used for HSV-2 and syphilis testing.
At visits at which plasma aliquots will be archived (i.e., Enrollment and 6-monthly thereafter), one 8.5 mL plasma (e.g., EDTA) tube will be collected. Given the importance of plasma samples for the secondary and tertiary aims of the study, an additional 8.5 mL plasma tube will be collected at Enrollment and yearly thereafter (e.g., at Month 12, Month 24, etc., and at Stop), which will be used for archived aliquot preparation.

[] = if clinically indicated, based on participant history
Appendix III  Study Visits and Procedures in the Event of HIV-1 Seroconversion

<table>
<thead>
<tr>
<th>Visits at seroconversion, &lt;1 month later, then quarterly for at least 12 months*</th>
<th>SC</th>
<th>SC&lt;1</th>
<th>SC3</th>
<th>SC6</th>
<th>SC9</th>
<th>SC12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMINISTRATIVE, BEHAVIORAL AND REGULATORY PROCEDURES</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Collect/update locator information</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Provide HIV-1 counseling, including couples counseling</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CLINICAL PROCEDURES</td>
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<td></td>
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</tr>
<tr>
<td>Collect medical history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Perform physical exam, including genital exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Collect urine specimen (women for pregnancy testing, only at SC visit; men at SC and SC+12 months, for STI testing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Collect genital swab specimens (women only – men provide semen specimen at SC3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Collect blood specimen</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>Stop study drug</td>
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</tr>
<tr>
<td>Provide test results</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>LABORATORY PROCEDURES</td>
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<tr>
<td>Local Lab</td>
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<tr>
<td>Chemistries</td>
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<tr>
<td>CBC</td>
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<tr>
<td>Syphilis serology</td>
<td></td>
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<tr>
<td>CD4 count</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HIV-1 serology (confirmatory EIA)</td>
<td>X</td>
<td></td>
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<tr>
<td>Urine pregnancy test (women only)</td>
<td>X</td>
<td>[X]</td>
<td>[X]</td>
<td>[X]</td>
<td>[X]</td>
<td>[X]</td>
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<tr>
<td>Check hepatitis B serology if not immune and declined vaccination</td>
<td>X</td>
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<tr>
<td>Central Lab / Specimen Repository</td>
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<tr>
<td>Confirmary HIV-1 Western Blot (batched testing at the end of the study)</td>
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<tr>
<td>Serum archive</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Plasma archive</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Genotypic and phenotypic resistance assays (batched testing), on first two time points, with ultrasensitive testing if standard genotypic resistance testing is negative, with the possibility of additional resistance testing on later samples</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Whole blood &amp; blood spot archives</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Endocervical swab archive for gonorrhea, chlamydia &amp; trichomonas PCR (women only)</td>
<td>X</td>
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<tr>
<td>Vaginal swab &amp; slide for bacterial vaginosis evaluation (women only)</td>
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<tr>
<td>Urine archive for gonorrhea, chlamydia and trichomonas PCR (men only)</td>
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<tr>
<td>Seminal plasma and seminal cells archives (men only), for HIV-1 PCR</td>
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</tr>
<tr>
<td>Endocervical swab archive (women only), for HIV-1 PCR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BLOOD VOLUME (mL)</td>
<td>42</td>
<td>17</td>
<td>21</td>
<td>21</td>
<td>17</td>
<td>29.5</td>
</tr>
</tbody>
</table>

* All seroconverters will be followed for 12 months after seroconversion. Those who seroconvert earlier in the study will be followed until the trial completes follow-up; thus, some will be followed for >12 months post-seroconversion. After 12 months, quarterly and annual procedures will mirror those in the above table – e.g., procedures at 18 months will reflect those at 6 months, procedures at 21 months will reflect those at 9 months.

Index participants whose partners seroconvert to HIV-1 will have one set of samples collected as close in time to the seroconversion visit as possible (ideally, either at the SC or SC<1 month visits). Samples will be collected:

- Blood sample (21 mL) for:
  - CD4 count
  - Plasma and serum archive (for secondary and tertiary endpoints, including resistance assays)
  - Whole blood and blood spot archives
  - Endocervical swab for HIV-1 PCR (women) or seminal plasma and seminal cells for HIV-1 PCR (men)
Individual and couples counseling and risk-reduction services will also be provided to the index participants at this visit. Index participants will be encouraged to attend subsequent post-seroconversion visits with their partner and will thereafter continue on with their scheduled index follow-up procedures.
Appendix IV Study Visits and Procedures for Pregnancy and Follow-up of Infants Exposed to Study Drug

Pregnancy

- Visit at which pregnancy is detected
  - Stop study medication
  - Counseling about study medication and pregnancy risk
  - Complete all other procedures as at that visit, with the exception of dispensing of new study drug and adherence counseling
  - Provide or refer for antenatal care

- Visits while pregnant
  - All scheduled study procedures, except those related to study medication
  - If HIV-1 seroconversion occurs, treat or refer to program for prevention to mother-to-child HIV-1 transmission

- If pregnancy does not go to term,
  - Collect information on timing of pregnancy loss and nature of pregnancy loss (e.g., stillbirth, spontaneous or elective termination)
  - Participants may resume study medication, after a negative pregnancy test.
  - Participants should continue on in follow-up through end of their scheduled study time.

- If pregnancy does go to term,
  - Schedule visit for mother and infant within 1 month of birth:
    - Measure infant weight, height, head circumference
    - Blood from infant for measurement of renal function
  - Schedule additional visits for infant for every 3 months for 1 year:
    - Measure infant weight, length, head circumference
    - Blood from infant for measurement of renal function at the 3 month visit
  - Participants may resume study medication, if still within study medication follow-up period, after completion of breastfeeding
  - Women who are breastfeeding will not receive study medication
Appendix V  Local Laboratory Normal Ranges and Panic Values

Each study site will define local laboratory normal ranges, in concert with the Study Coordinating Center and the reference laboratory. The International AIDS Vaccine Initiative (IAVI) tables of normal laboratory values for sub-Saharan African populations will guide the development of site-specific tables. In all cases, site-specific tables will reflect the criteria as defined by the DAIDS toxicity tables. In addition, each site will develop criteria for panic laboratory results (i.e., those requiring immediate contact of the on-call study clinician).
## Appendix VI  Hepatitis B Virus Serology Interpretation

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Interpretation and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>HBV susceptible. Offer vaccination series. If accepted, flag chart as &quot;vaccine series.&quot;</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>negative</td>
<td>If vaccination is refused, then test the HBV panel annually and when stopping study drug and counsel on HBV flare risk accordingly (if HBsAg positive).</td>
</tr>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>Immune due to natural infection or hepatitis B vaccination. Flag chart as &quot;HBV Immune.&quot; No further action.</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>positive</td>
<td>HBV infected If potential partner (HIV-1 uninfected) participant → not eligible for the study</td>
</tr>
</tbody>
</table>
Appendix VII  
HIV-1 Testing Algorithm

Paired HIV rapid assays performed in parallel

- Paired rapid assay results are concordant positive
- Results of paired rapid assays are discordant
- Paired rapid assays are concordant negative

**HIV EIA performed with two wells using a single kit**

- Paired EIA wells are concordant positive
- Paired EIA wells are concordant negative or discordant

**HIV**

**seropositive**

- Has paired rapid assay/EIA set been run twice for this visit

    - No
      - Contact participant to obtain new specimen return visit in 1-2 weeks to repeat paired rapid assays
    - Yes
      - Contact study PI

**HIV seropositive**

**HIV seronegative**

**Results of paired rapid assays are discordant**

**Results of paired rapid EIA tests are concordant+ ++ positive**

**Results of paired EIA wells are concordant- negative**

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Appendices VIII – XI Study Consent Forms

Each study site is responsible for developing study informed consent forms for local use that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations, based on the samples provided in the following appendices. Each site also is responsible for translating the forms into local languages and verifying the accuracy of the translation by performing an independent back-translation, which will be reviewed by the Coordinating Center before submission to the local IRB.
Appendix VIII  Human Immunodeficiency Virus (HIV) Antibody Test Consent Form

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Version 3.0  
12 October 2007

INVESTIGATOR’S STATEMENT

Purpose and Benefits

A virus called HIV (Human Immunodeficiency Virus) causes AIDS (Acquired Immunodeficiency Syndrome). Any person with HIV can spread it to others through unprotected sex, needle sharing, or donating blood or other tissues. Infected mothers can spread HIV to their newborns. The test for HIV detects the body’s reaction to the virus (antibody). It does not detect the virus itself. You are not required to have the test. Testing for HIV is voluntary. This test is being done for a research study. You should be tested only if you are well informed about the risks and benefits of testing. Please read this consent form carefully so that you can make an informed decision about having the blood test.

What the Test Means?

If you test POSITIVE, you have the HIV virus. That means you can pass it to others. The test cannot tell how long a person has been infected. A positive test does not mean that you have AIDS, which is the most advanced stage of HIV infection.

If the test is NEGATIVE, you probably do not have the HIV virus. A negative test usually means that a person is not infected with HIV; however, recently infected persons can have a negative test, which becomes positive in three months after infection. This would mean that your body has not yet made antibody to fight the virus.

False results (a negative test in an infected person, or a positive result in an uninfected person) are rare. Indeterminate (unclear) results are also rare. When a test result does not seem to make sense, a repeat test or another kind of blood test is done to find out if the person is infected or not.

Procedures

This is what will happen if you decide to have the test. First, you will meet with a counselor to get more information about the risks and benefits of the test. They will explain the meaning of test results. They will teach you how to reduce the chance of spreading HIV. They will explain the dangers of HIV infection. Then, they will take collect blood, either from your arm or from your finger, with a sterile needle. They will
test your blood for HIV. It will take about 20 minutes to get your test result. You will be
told your result on the same day that you give blood and have the test. The study staff
will talk with you about the meaning of your result and how you feel about it. Sometimes
HIV tests are not clearly positive but also not negative. In that case, we will do more
tests until we know the result for sure. If the test result is positive, you will learn how to
notify anyone with whom you have sex, and how to get services for yourself.

Risk and Benefits

The needle used to draw blood for the test may cause discomfort. A bruise may form
where the needle enters the vein, and if you get a bruise, it usually goes away within a
week.

Learning the test results may cause stress, anxiety and depression for people being
tested and for their partners. You might be tempted to have unsafe sex if the result is
negative. This would increase your risk of becoming infected with HIV. It is possible
that you may feel nervous about the information you are going to give us and concerned
about any links between this information and your name or identity.

Many people are afraid that their test results will get into the wrong hands. For example
someone might see the test results who might tell others that you have HIV, and
prejudice and discrimination, such as gossip, may cause problems in keeping your job or
the place where you live. We will take precautions to protect your identity and prevent
the study results from being used in this fashion. One risk is that your partner may
become upset or leave you after hearing that you are HIV-infected. We encourage you
to be tested with your partner so that the counselor can provide information and support
to both of you, regardless of your results. If you want to be tested without your partner,
and you test positive for HIV, we will provide you with support to avoid negative
reactions of your partner, if you decide to notify him/her about your HIV infection. There
may be other risks and stresses of being tested that we don’t know about now.

Otherwise, the benefits of being tested are personal. Test results may help diagnose a
medical problem, guide your health care, help you follow strategies to improve your
health, and may help you avoid transmitting HIV to other people. If you are worried
about AIDS, you might feel better if you have a negative test. Sometimes knowing that
the test is positive can relieve stress. You may want to know your test results before you
have sex with a new partner. There may be other benefits of testing that we don’t know
about now.

Confidentiality

Your HIV antibody test result must be held in the strictest confidence, and no identifying
information of any kind will be released to any other person or agency without your
specific written permission. No publication or public discussion of the testing will contain
information that could identify you.

Other Information

We will tell you the results of the test in person. If you test positive, we will encourage
you to notify your sexual partners. The investigator or his representative can answer all
your questions about this study. If you have any additional questions, you can ask them now, or contact a study representative at the telephone number on this form.

We will give you a copy of this form.

_________________________________  _____________________ ___________
Signature of Investigator   Printed Name   Date

VOLUNTEER’S STATEMENT

The benefits and risk about HIV test on the preceding page has been explained to me, and I voluntarily agree to participate. I have had an opportunity to ask questions. I have been told that if I have future questions about the research, I can ask one of the investigators listed above. If I have questions about my rights as a research subject, I may call [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

[Insert signature blocks as required by the local IRB/EC:]

____________________  __________________________  ______________
Participant Name    Participant Signature/Thumbprint Date
(print)

____________________ _____________________ _____________
Study Staff Conducting Study Staff Signature Date
Consent Discussion (print)

____________________ _____________________ _____________
Witness Name    Witness Signature Date
(print)
Appendix IX  Screening Consent Form

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Version 3.0
12 October 2007

PRINCIPAL INVESTIGATOR:  [insert name]
[insert physical address and relevant contact info]

INFORMED CONSENT

We are asking you to volunteer to have screening tests to find out if you are eligible for a research study. The study is for partners between whom one person has HIV and the other person does not have HIV. HIV is the virus that causes AIDS. The study is sponsored by the Bill and Melinda Gates Foundation and the University of Washington, which are located in Seattle, Washington, USA.

If you decide to participate in the screening procedures you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

PURPOSE OF THE RESEARCH

This research is studying two medications that suppress the HIV virus. One medication is called tenofovir. The second medication is a combination of tenofovir and another medication called emtricitabine. This combination is known as Truvada®. Both tenofovir and Truvada® are pills that are used to treat people already infected with HIV. Studies have shown that these medications are safe when used once per day as treatment of HIV by HIV-infected people. Tenofovir and Truvada® are not cures for HIV, but they are very effective in suppressing the HIV virus in people who are HIV-infected and in improving their health and immune function.

The purpose of this study is to find out if taking tenofovir or Truvada® every day can prevent HIV-uninfected men and women from getting the HIV virus from their partner. This is called **pre-exposure prophylaxis**. The study also will learn whether tenofovir and Truvada® are safe (meaning that they do not produce significant health problems in persons who take them) when taken by HIV-uninfected men and women. We do not know if taking tenofovir or Truvada® will prevent HIV infection in a safe way.

Approximately 3900 couples, all from Africa, will be in the study. All the couples will be HIV-discordant, meaning that one person has HIV and the other person does not have HIV. This will be the largest of this kind of study ever. 500-800 couples are planned to
be in the study here at [clinic].

Each couple will be in the study for a minimum of 24 months and up to a maximum of 36 months. The total length of time will depend on how quickly the study meets its objectives. Those who become HIV infected during the study will be asked to continue for one year after infection, regardless of when during the 36 months of maximum follow-up the HIV infection occurs.

SCREENING

The screening tests for this study will include questions and tests done from samples of blood and urine. Some people may not be able to join the study because of information found during the screening process. You and your partner must both be willing and eligible to participate in the study.

YOUR PARTICIPATION IS VOLUNTARY

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

- You do not have to be in this study if you do not want to,
- You may decide not to have the screening tests, or to stop the screening tests at any time, without losing your regular medical care.
- If you decide not to have the screening tests, you can still join other research studies later, if available and you qualify.
- You may be asked about joining other studies. Due to the time commitment from being in this study, you may not be eligible to join this study if you are in other studies. If you do not agree to join these other studies, you may still take part in this study.
- We are only asking you to have the screening tests at this time. Even if you agree to have the screening tests and are eligible to join the study, you do not have to join the research study.
- You will receive the results of the screening tests even if you are not eligible to join the research study.

SCREENING PROCEDURES

Screening procedures will begin today, after you read, discuss, and sign or make your mark on this form. The screening procedures will include the following:

- The study staff will ask you where you live and other questions about you and your sexual practices.
• We will counsel you about HIV and other infections passed during sex, and how to avoid these infections.

• Even if you have recently been tested for HIV, we will need to repeat the HIV test today as part of screening for the study. You will sign a separate form to consent for HIV testing. The study staff will talk with you about the HIV test, what it may mean to know your HIV test results, including issues for partners when one partner is HIV-infected and the other is HIV-uninfected. We will then ask your partner and you whether you are ready to be tested today and receive your HIV test results. You must receive your HIV test results to be in the research study.

• If you are in an HIV discordant couple and you do not have HIV infection:
  
  • We will ask you questions about your medical history and you will have a physical examination.

  • You will be asked to give us permission to obtain a blood sample for laboratory tests. No more than 21 ml (about 1 ½ tablespoons) will be collected for all the screening tests, including the HIV test.

    o Some of the blood sample will be used to test for the presence of infection with the hepatitis B virus. If you are found to have hepatitis B infection, you will not be eligible for the study.

    o Some of the blood sample will be used to test the function of your kidneys, your liver, your pancreas, and your bone marrow. Abnormalities in any of these tests may make you ineligible to participate in this study.

  • You will be asked to provide a urine sample.

    o Some of the urine sample will be tested to evaluate your kidney function. If the testing on this sample shows the presence of proteins and/or glucose (sugar) in your urine, you will be asked to provide another sample on a different day. If testing of this second sample also shows the presence of proteins and/or glucose, you will not be eligible to participate in this study.

    o For women, a pregnancy test will also be done on the urine sample. Women who do not have HIV and who are pregnant, or who are planning to become pregnant during the study period, are not eligible for this study.

• If you are in an HIV discordant couple and you do have HIV infection:

  • We will ask you questions about your medical history. As part of these questions, you will be asked about symptoms of AIDS. People with AIDS are not eligible for the study, but will be referred to local providers for clinical care and further evaluation for services for persons with AIDS.
You will be asked to give us permission to obtain a blood sample for laboratory tests. No more than 16.5 ml (about 1 tablespoon) will be collected for all the screening tests, including the HIV test.

- Some of the blood sample will be used to test for the presence of infection with the hepatitis B virus.
- Some of the blood sample will be used for a test called a CD4 cell count. The CD4 count is a measure of how well your immune system is functioning. The lower the CD4 count in persons who are HIV-infected, the more at risk they are for having problems from AIDS.

You may need to come back to this clinic more than once over the next few weeks to complete all screening procedures. The number of visits will depend on whether you and your partner have already been tested for HIV as a couple, your test results, and the time it takes to provide counseling to you and your partner about the results and available services.

If both you and your partner are found to be eligible for the research study, the study staff will fully explain the study to you and answer any questions you have. You and your partner must have at least one other visit here at the clinic together to learn about the study. You also may have additional separate visits. If more than 56 days pass after starting the screening process, you will need to repeat all screening procedures to be considered for the research study. If you and your partner decide to take part in the research study, each of you will be asked to sign another consent form.

**RISKS AND/OR DISCOMFORTS**

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise where the sterile instrument (needle) goes into your arm.

You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or anxious while waiting for your test results. Having the screening tests, talking about HIV, and finding out your and your partner’s results could cause problems between you and your partner. Sometimes partners experience anger and blame when one partner learns that s/he is HIV-positive and the other is HIV-negative (“HIV-discordant”), sometimes leading to the relationship ending. The counseling that you will receive through the study staff will help you understand this situation. Previous studies have shown that counseling is important to help HIV-discordant partners stay together and to reduce the chances of HIV transmission. Trained counselors are available through the study who will help you and your partner deal with any feelings or questions you may have.

The study staff will make every effort to protect your privacy and confidentiality while you are having the screening tests. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.
BENEFITS

You may get no direct benefit from the screening tests. However, you and your partner will get counseling and testing for HIV. You will get information on how to protect against HIV and other infections passed during sex. You will get free condoms. For other health problems that cannot be treated at this clinic, the study staff will tell you about other places you can go for treatment. The study staff will also tell you about other places that provide care and support for people with HIV/AIDS. You may also contribute to understanding about HIV in couples in Africa, which will help others in the future.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING PROCESS

You may be removed from the screening process without your consent for the following reasons:

- The research study is stopped or canceled.
- You are not willing to find out your HIV test result.
- You are not willing to talk about HIV and your HIV test result with your partner.
- You or your partner are not able to attend clinic visits or complete the screening tests.
- You or your partner are found to not be eligible for the research study, for any of a number of reasons. We may not be able to tell you why you and your partner are not eligible.
- The study staff feel that having the screening tests would be harmful to you or your partner.

COSTS TO YOU

There is no cost to you for the screening tests.

REIMBURSEMENT

[Sites to insert information about local incentives:] You will receive [site specified amount] for your time and effort at each scheduled screening visit. You also will receive payment for the costs of [lost work, travel, and/or childcare] due to your visits.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if...
required by law. Any sample from you or information about you will be identified only by
code and not by name. The link between your name and code will be kept in a secure
location at the clinic only. Any publication of this study will not use your name or identify
you personally.

The records of your screening tests may be reviewed by study staff and representatives
of:

- the University of Washington, including study monitors
- the Bill and Melinda Gates Foundation
- the United States Food and Drug Administration
- [insert applicable local authorities, e.g., Ministry of Health]
- [insert names of applicable IRBs/ECs]

RESEARCH-RELATED INJURY

[Sites to amend this sample text as needed, and/or specify institutional policy:] It is
unlikely that you will be injured as a result of having the screening tests. If you are
injured as a result of having the screening tests, the study staff will give you immediate
necessary treatment for your injuries, free of charge. The study staff also will tell you
where you can get additional treatment for your injuries, if needed. There is no program
for monetary compensation or other forms of compensation for such injuries. You do not
give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

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

I have read this form or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the screening tests is voluntary. I understand that if I decide to have the screening tests I may withdraw at any time. By signing this form I do not give up any rights that I have as a research participant.

[Insert signature blocks as required by the local IRB/EC:]

____________________  __________________________  ______________
Participant Name    Participant Signature/Thumbprint Date
(print)

____________________ _____________________ _____________
Study Staff Conducting Study Staff Signature Date
Consent Discussion (print)

____________________  ________________________  ______________
Witness Name    Witness Signature    Date
(print)
Appendix X  Study Enrollment Consent for Partner (HIV-1 Uninfected) Participants

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Version 3.0
12 October 2007

PRINCIPAL INVESTIGATOR:  [insert name]
[insert physical address and relevant contact info]

INFORMED CONSENT

We are asking you to volunteer for a research study. This study is for partners in which one person has HIV and the other does not. HIV is the virus that causes AIDS. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, and what would be expected of you if you agree to be in the study. This study is sponsored by the Bill and Melinda Gates Foundation and the University of Washington, which are located in Seattle, Washington, USA.

If you decide to participate in the research study, you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

PURPOSE OF THE STUDY

This research is studying two medications that suppress the HIV virus. One medication is called tenofovir. The second medication is a combination of tenofovir and another medication called emtricitabine. This combination is known as Truvada®. Both tenofovir and Truvada® are pills that are used to treat people already infected with HIV. Studies have shown that these medications are safe when used once per day as treatment of HIV by HIV-infected people. Tenofovir and Truvada® are not cures for HIV, but they are very effective in suppressing the HIV virus in people who are HIV-infected and in improving their health and immune function.

The purpose of this study is to find out if taking tenofovir or Truvada® every day can prevent HIV-uninfected men and women from getting the HIV virus from their partner. This is called pre-exposure prophylaxis. The study also will learn whether tenofovir and Truvada® are safe (meaning that they do not produce significant health problems in persons who take them) when taken by HIV-uninfected men and women. We do not know if taking tenofovir or Truvada® will prevent HIV infection in a safe way.

Approximately 3900 couples, all from Africa, will be in the study. All the couples will be HIV-discordant, meaning that one person has HIV and the other person does not have HIV. This will be the largest of this kind of study ever. Approximately 500-800 couples...
are planned to be in the study here at [clinic].

Each couple will be in the study for a minimum of 24 months and up to a maximum of 36 months. Those who become HIV infected during the study will be asked to continue for one year after infection, regardless of when during the 36 months of maximum follow-up the HIV infection occurs. The whole study will take at about 5 years to finish.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that we will discuss with you. Once you understand the study, and if you agree to take part, we will ask you to sign your name or make your mark on this form. We will offer you a copy to keep.

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

- You do not have to be in this study if you do not want to join.

- You may decide not to take part in the study, or to withdraw from the study at any time, without losing the benefits of your or your partner’s routine medical care.

- If you decide not to take part in the study, you can still join another research study later, if one is available and you qualify.

STUDY MEDICATION

Tenofovir at a dose of 300 mg once per day and the combination of emtricitabine at 200 mg once per day and tenofovir at 300 mg once per day (known as Truvada®) are medications approved by the United States Food and Drug Administration for the treatment of HIV infection. In this study, we will evaluate if taking tenofovir or Truvada® every day prevents men and women who are not infected with HIV from getting the HIV virus.

Tenofovir and Truvada® were chosen for this study for several reasons:

- We know that they have low levels of side effects compared to other medications used to treat HIV.

- They can be taken once a day.

- HIV does not easily become resistant to tenofovir or Truvada®.

- Studies done in animals have shown that tenofovir and Truvada® can sometimes prevent infection with a virus similar to HIV.

Tenofovir and Truvada® have not been approved by the US FDA for the prevention of HIV. Gilead Sciences is the pharmaceutical company that produces tenofovir and Truvada®, and Gilead Sciences will supply the medications for this study.
We do not know if taking tenofovir or Truvada® can prevent you from getting HIV. That is why we are conducting the study.

STUDY GROUPS

In this research study, you will be assigned to one of three study groups – one group will receive tenofovir, one group will receive Truvada®, and one group will receive placebo. You will take two pills of study medication each day. The placebo group will receive pills that have the same physical appearance and have the same taste as tenofovir and Truvada® but the pills will not contain a medication that is used to treat HIV infection or any other medication.

The two pills that you will take each day will look different. Everyone in the study will receive pills that look the same as the pills you will receive. You will get the same type of study medication throughout the study. A computer program will randomly decide which type of study medication you receive. You will have an equal chance of being assigned to the tenofovir group, the Truvada® group, or the placebo group. Neither you nor any of the research staff in this clinic will know who is taking tenofovir, who is taking Truvada®, and who is taking the placebo. You cannot be told which group you are in until 6-24 months after the end of the study. This means you may have to wait up to 7 years to find out which pills you were randomly assigned to take.

All three groups are very important to this study. Couples in all three groups will have the same study visits. All couples will get condoms, treatment for other STDs, and counseling on how to avoid HIV and other infections passed during sex.

No matter what study group you are in, you must remember that we do not know if tenofovir or Truvada® work to prevent passing HIV from one person to another. The only known way to protect against getting HIV during sex is to use a condom every time you have sex.

It is very important that you do not share the study medication with anyone, including your partner. If the drugs that are used in this study are used alone in someone who has HIV, the HIV virus can become resistant to these medications. If you share the study medications with your partner, the HIV virus your partner could become resistant to these medications, which could limit your partner’s treatment options for the future.

STUDY PROCEDURES

If you decide to take part in the study, your first visit will continue today, after you read, discuss, and sign or make your mark on this form. At today’s visit, several things will happen:

- The study staff will ask you questions about your medical history and your sexual practices
• You will undergo a physical exam, including a genital exam to look for sexually transmitted infections.
  
  o For women, the study staff will collect swab samples during the genital exam from your genital area to test for sexually transmitted infections. These will be collected using soft, sterile swabs. A Pap smear may also be performed.

• We will ask your permission to obtain a blood sample [up to 29.5 ml / less than 2 tablespoons]. We will obtain the sample using a sterile instrument (needle) inserted into a vein in your arm. The blood sample will be used for tests at the clinic and by study researchers at the University of Washington.
  
  o Some of the blood will be used to test for HIV. When we do HIV testing for this study, we first do a test that gives results in about 20 minutes. You will get the result of that test when it is available, on the same day you give blood and have the test. If the test shows that you may have HIV infection, we will do another different test to confirm this result. This test takes about 1-2 weeks, so you will have to come back here at that time to get the results. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will do more tests until we know the result for sure. You must receive your HIV test results to stay in the study. If the HIV test is positive today, you will not be able to enroll in the study.
  
  o Some of the blood will be used to test for syphilis.

  o Some of the blood may be used to test for infection with herpes simplex virus, another sexually transmitted infection.

  o Some of the blood will be used to confirm the results of the HIV tests that we do here and will look for other genetic, infectious, and immune factors that affect the chances of becoming HIV-infected.

• You will be asked to provide a urine sample.
  
  o For men, the urine sample will be tested for sexually transmitted diseases by researchers at the University of Washington.

  o For women, the urine sample will be used for a pregnancy test. You are not eligible for this study if you are pregnant.

• If your blood sample from the Screening Visit showed no evidence of hepatitis B infection, and no evidence of immunity to hepatitis B, you will be given information about the disease and also offered to begin the hepatitis B vaccination series. This will include vaccine injections also at 3 and 6 months.

• You will then be randomly assigned to receive study medication.
The study pharmacy staff will give you two bottles of study medication pills. You should take one pill from each bottle, once every day, by mouth, until your next scheduled visit. The study staff will give you information on the possible side effects and will teach you methods to not forget to take the pills every day.

After today's visit, you will have scheduled study follow-up every month. You will take the study medications every day. Your partner will also have regular follow-up visits scheduled, for every 3 months. During the months when you and your partner both have a visit, you should come to the clinic together, for your convenience and so you can have counseling together as a couple. If that is not possible, you can come for your visits by yourself if you wish. Each visit will take about 60 minutes.

At each of your monthly visits you will:

- Be asked questions about your health and medical history, including whether you have any clinical symptoms or side effects from the study drug.

- Be asked questions about your sexual practices.

- Talk with study staff about ways to avoid HIV and other infections passed during sex. We encourage you to have this counseling with your partner, but you can have it by yourself if you wish.

- Talk with study staff about the HIV test and give blood [up to 4 ml / 1/3 of a tablespoon or less], either from a finger stick and/or from your arm, for the test.
  
  - If the HIV test in the clinic is positive or not clear positive or negative, you will stop study medication until more tests are done to know for sure. If further testing demonstrates that you are HIV negative, you will be allowed to resume study medication.
  
  - Some of the blood may be used to confirm the results of the HIV tests that we do here and will look for other genetic, infectious, and immune factors that affect the chances of becoming HIV-infected.

- Get condoms.

- Get medical care or referrals for medical care and other services if you need them.

- Give updated information on where you live and how to keep in contact with you. The study staff will use this information to remind you of scheduled visits. If you miss a visit, the study staff will try to contact you by [describe site-specific methods]. 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.
Receive study medication. At your first monthly visit you will return the bottles of study medication pills that were dispensed at your Enrollment Visit. You will be asked to answer questions about the pills you took during the previous month and be counseled about methods for not forgetting to take your pills during the following month. The pharmacy staff will provide you with new bottles with pills for the following month. This process will be repeated each month.

You will be counseled about the importance of not sharing the study medication with anyone, including your partner.

Women will be asked to provide a urine sample. This will be used for a pregnancy test.

Some of your monthly visits may take place at your home. The study staff will talk with you about whether this will be an option.

At the first month and 3 months:

You will undergo a physical exam.

Give more blood [up to a total of 46.5 ml / about 3 tablespoons]. This will be used:

- For an HIV test, the same as at each monthly visit.
- To test the function of your kidneys, your liver, your pancreas, and your blood counts. This is to check the safety of the study drug. The study staff will provide you with the results of these laboratory tests. If at any time you have a result of a test that is abnormal, we will contact you so that you will know. If you have an abnormal result of a laboratory, you will be evaluated at the study clinic and appropriate treatment will be provided to you. If you need treatment that is not available at the study clinic, the staff will refer you for additional care.
- Some of the blood will be sent to study researchers at the University of Washington to look for genetic, infectious and immune factors that affect the chances of becoming HIV-infected.

Every 12 months:

You will undergo a genital exam to look for sexually transmitted infections.

- For women, the study staff will collect swab samples during the genital exam from your genital area to test for sexually transmitted infections. These will be collected using soft-tipped, sterile swabs. A Pap smear may also be performed to look for pre-cancerous or cancer cells from the cervix.
- For men, you will be asked to provide a urine sample that will be tested
for sexually transmitted diseases by researchers at the University of Washington.

- A blood sample will also be checked for syphilis.

At end of follow-up, which will occur at a minimum of 24 months and up to a maximum of 36 months, depending on how quickly the overall study meets its objectives:

- You will be finished with taking study drug.
- You will undergo the same study procedures as at a usual monthly visit, including counseling, a symptom questionnaire, condoms, medical care or referral, and collection of information on where you live.
- A blood sample [up to 46.5 cc / about 3 tablespoons] will be requested for HIV testing. Some of this blood will be sent to study researchers at the University of Washington to look for genetic, infectious and immune factors that affect the chances of becoming HIV-infected.
- You will be asked to continue monthly follow-up for an additional 2 months to monitor you for HIV and health status after stopping the study medication. At these visits after stopping study medication, you will be asked to provide a blood sample [up to 29.5 cc / less than 2 tablespoons] for HIV testing. Some of this blood will be sent to study researchers at the University of Washington to look for genetic, infectious and immune factors that affect the chances of becoming HIV-infected. You will undergo the same study procedures as at a usual monthly visit, including counseling, a symptom questionnaire, condoms, medical care or referral, and collection of information on where you live.

At any time in the study:

- If you or the study staff think you may be having any health problems, you may need to undergo a physical exam and may need to provide blood or other samples for testing.
- If you are having health problems that may be due to a sexually transmitted infection, you will have a genital exam and receive medicine to treat the infections as needed.
- You can have extra counseling and testing for HIV if needed between scheduled visits, either with your partner or by yourself.
- If you and your partner end your relationship before your last scheduled study visit, we will ask you to stay in the study as originally scheduled and continue the study medication (for a minimum of 24 months, or until the study has met its objectives).
- If you decide to leave the study before your last scheduled study visit, we will ask
you to have a final study visit with all the exams and tests listed above.

PREGNANCY (women only)

Although infants born to HIV-infected women taking tenofovir or Truvada® during pregnancy have not been found to have a greater chance of having birth defects, we do not know for sure if these drugs are safe to the fetus in women who become pregnant.

During this study, you will receive counseling at each visit about the potential that you may become pregnant. You will also receive counseling about your options for contraception. You can receive some forms of contraception from the study clinic. You may choose whether or not you want to receive contraception.

If you become pregnant at any time during the study, your study medication will be stopped and the study staff will counsel you. You will continue to be followed in the research clinic. You will also receive, or be referred for, antenatal care. If you do not carry the pregnancy successfully to term, you will be allowed to resume study drug once you are no longer pregnant. If you become pregnant and give birth, we will ask that you bring the infant to the clinic within the first month after birth and then every 3 months for the first year. At each visit, we will measure the weight and growth of the child. At two of those visits, we will ask to obtain a small blood sample from the child, to check the function of the kidneys.

If you are breastfeeding, you will not be allowed to enroll in the study or take the study medication. If you begin breastfeeding during the study, your study medication will be stopped. You will continue to be followed in the research clinic. You will be allowed to resume the study medication when you are no longer breastfeeding.

The effect on infants of tenofovir or Truvada® when taken during pregnancy and breastfeeding by HIV-uninfected women is unknown.

It will be important that we monitor infants whose mothers have taken the study medications during early pregnancy, so we can learn if taking tenofovir or Truvada® during pregnancy is safe.

IF YOU BECOME HIV INFECTED

During the course of the study we will provide you with condoms and other materials to help prevent your partner from getting HIV. However it is possible that you can become HIV infected.

If you have a positive HIV test during the study:

- The study staff will talk with you about this test result and what this means for you.
- You will stop the study medication.
- The staff will ask your permission to obtain a second blood test [42 ml / less than 3...
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

drugs] that will be used to confirm the initial positive test.

- Some of the blood will be used to test the function of your kidneys, your liver, your pancreas, and your blood counts.
- Some of the blood will be used to test for syphilis.
- If you were not immune to hepatitis B at study enrollment and you declined the hepatitis B vaccine, some of the blood will be used to test for hepatitis B.
- Some of the blood will be used to perform a CD4 count, a measure of your immune function.
- Some of the blood will be sent to study researchers at the University of Washington to look for genetics, infectious and immune factors that affect the chances of becoming HIV-infected.

• You will undergo a physical exam, including a genital exam to look for sexually transmitted infections.
  - For women, the study staff will collect swab samples during the genital exam from your genital area to test for sexually transmitted infections. These will be collected using soft-tipped, sterile swabs.
  - For women, an additional swab will be obtained from your genital area. This will be sent to study researchers at the University of Washington to test for HIV in the genital area.

• You will be asked to provide a urine sample.
  - For men, the urine sample will be tested for sexually transmitted diseases by researchers at the University of Washington.
  - For women, the urine sample will be used for a pregnancy test.

• You will then be asked to return for another visit after about 2 weeks. At that visit, results from the confirmatory HIV test will be available. If those results confirm that you have become infected with HIV, we will ask that you continue follow-up at this clinic every 3 months until the study is finished, or for at least 12 months.
  - Note that if you become infected with HIV, depending on when that occurs, your total duration of follow-up in this clinic may be longer than 36 months.
  - For example, if you are found to be infected with HIV at your 32 month visit, you will be requested to continue your follow-up for an additional 12 months. In that case, the maximum follow-up in this clinic may be 44 months.
• At each of the visits after HIV infection is confirmed:
  
  o You will undergo a physical examination.
  
  o You will be asked to provide a blood sample [17 – 29.5 ml / under 2 tablespoons].
    
    ▪ Some of the blood will be sent to study researchers at the University of Washington to look for genetics, infectious and immune factors that affect the chances of becoming HIV-infected. Tests will also be done to look for resistance to HIV medications and other characteristics of early HIV infection. If we find that you have laboratory results that might be useful to your medical care, those results will be provided to you and your doctor.

    ▪ Some of the blood will be used to perform a CD4 count, a measure of your immune system.

  o For women, we will perform a genital exam and obtain a swab from your genital area. These will be sent to study researchers at the University of Washington to test for HIV in the genital area.

  o For men, we will ask you to provide a semen sample once, 3 months or later after HIV infection is detected.

• We will also request samples from your partner to help us understand HIV transmission from one person to another.

IMPORTANCE OF NOT SHARING THE STUDY MEDICATION

In this research study, you will take study medication each day. Your partner will not take any study medication. Your partner will come for follow-up visits every three months, for a total of 2-4 years. At your partner’s visits to the research clinic, the study staff will ask your partner questions about his/her health and will collect samples of his/her blood and genital secretions. These samples will be used to investigate whether there are factors that either increase or decrease the chances that HIV is transmitted from one person to another. They will also be used to determine whether some factors about the HIV infection your partner has increase or decrease the chance that the study medication you are taking works to prevent you from acquiring HIV infection.

It is very important that you do not share your study medication with your partner or with anyone else. Although tenofovir and Truvada® are used to treat HIV infection, they are only effective for treating people who already HIV infection if they are used in combination with other medications. If your partner takes your study medication, he/she may be exposed to tenofovir or Truvada®. If he/she is exposed to tenofovir or Truvada®, his/her HIV could become resistant to tenofovir, emtricitabine (one of the components of Truvada®), or lamivudine (a medication similar to emtricitabine). Resistance to these antiretroviral medications reduce the effectiveness of HIV treatment for your partner and may limit your partner’s HIV treatment options. If your partner
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

requires HIV treatment during the course of this research study, we will refer him/her for appropriate treatment or, if treatment is not available elsewhere, provide treatment at the research clinic.

Hepatitis B infection

Hepatitis B is an infection that affects the liver. It can be transmitted sexually. Many people who become infected with hepatitis B clear the infection. Some fail to clear the infection and develop chronic hepatitis B infection.

If the results of your tests done at the Screening Visit show no evidence of chronic hepatitis B infection, you may have been previously infected but do not have persistent infection, you may have been previously immunized, or you may not be immune. If you are not immune, we will offer you hepatitis B vaccination as part of this study to protect you from getting hepatitis B in the future. If you do not want the vaccine, or do not complete the three injections required for the vaccine to work completely, we will test you for hepatitis B later in the study and may ask you to provide additional blood samples (up to 8.5 cc / less than 1 tablespoon) each month for 2 months.

SPECIMEN STORAGE AND USE OF SAMPLES AND DATA FOR FUTURE STUDIES

We would like to save data from this study and samples of your blood, urine, semen, and genital secretions at [local site] and at the University of Washington for future research by us and by other researchers. We will use these samples only for research related to HIV, HIV-related diseases, and sexually-transmitted infections. This will include testing for genes which may affect whether a person is more or less likely to get these infections, have more severe infection, or how people respond to the medications used in this study. Gene studies may test for a specific gene to understand these effects or help researchers find new genes that may have these effects. This research is experimental and these tests are not useful for your clinical care. Before your samples leave the clinic, they will be assigned a code and your name will not be on them. Your name will be linked to the code only at this clinic and only for five years after the study is completed. After that time, the link between your name and the code on your data and samples will be destroyed. An Institutional Review Board or Independent Ethics Committee, which watches over the safety and rights of research participants, must approve any future research studies using your data and samples. If you agree to store your samples, we will keep them for as long as sample remains that can be used for future research. If you do not want to have your samples saved for future research, you can still be in this study and your samples will be destroyed once testing for this study is completed. If you agree to store your samples now, but change your mind before the end of the study, let the study staff know and we will make sure that your samples do not get stored for future research. We will not sell your data or samples. Tests done on your samples may lead to a new invention or discovery. We have no plans to share any money or other benefits resulting from this invention or discovery with you.

RISKS AND/OR DISCOMFORTS

Partners PrEP Protocol
Version 3.0, 12 October 2007
You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise where the needle goes into your arm. You may feel discomfort during genital exams.

You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against HIV and other infections passed during sex, and your HIV test results. You may become worried or anxious while waiting for your test results. If you become infected with HIV, knowing this could make you worried or anxious. Talking about HIV and finding out your test results could cause problems between you and your partner. Trained counselors will help you and your partner deal with any feelings or questions you may have.

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

**Risks potentially related to the study medication**

You may have symptoms or adverse effects while participating in the study. These symptoms or adverse effects may be due to participation in the study or due to illnesses that have no relation to the study, like a cold or flu. All persons who participate in this study will be watched carefully to monitor their health. The medical team in charge of your health care may give you medicines to treat the adverse effects. Many adverse effects disappear as soon after you stop taking the study pills. In some cases, the adverse effects can be serious, long-lasting, or may never disappear.

You should tell the doctor of the study clinic about any symptoms that you feel while you are participating in the study. If you have any symptoms, especially frequent vomiting, swollen feet, or abnormal shortness of breath, you should visit the clinic immediately and not wait for your next scheduled visit. You will be given a telephone number where the study doctors will be available 24 hours a day, 7 days a week. You should call them if you experience any serious symptoms.

The adverse effects that can occur in a small proportion of people taking tenofovir or Truvada® are well known because the medication has been used by many people. The following adverse events have been associated with taking tenofovir: fever, achesiness and a general feeling of illness associated with allergic reaction. The following adverse effects have been associated with emtricitabine (one of the two medicines contained in Truvada®): headache, tiredness, difficulty sleeping, unusual dreams, skin darkening (palms and/or soles of the feet), increased cough, runny nose and increased triglycerides in the blood (a substance derived from the metabolism of fat in your body).

Some mild adverse effects are expected to occur in up to 1 in 10 persons who take tenofovir or Truvada®. Other adverse effects are more serious, but are expected to occur in less than 1 in 100 persons who take tenofovir or Truvada®.

**Occasional adverse effects (expected to occur in 1-10% of the participants in this**
study)

- Mild problems of kidney function that are only detected by laboratory tests (changes in creatinine and phosphate in the blood that do not cause you to feel different in any way)
- Lack of energy/general body weakness
- Upset stomach, vomiting, soft or liquid stools
- Abdominal pain
- More intestinal gas than normal
- Dizziness

Rare adverse effects (expected to occur in less than 1% of the participants in this study)

These adverse effects have been rarely observed in persons with HIV infection who are receiving tenofovir or Truvada®, plus other medications. It is not known whether these adverse effects will also occur in people like you, who do not have HIV infection and who are not taking other drugs for the treatment of HIV.

- Rash
- Liver function problems
- Serious kidney damage or failure
- Low phosphate levels (which is a chemical in the blood) or protein or sugar in the urine
- Inflammation or swelling and possible damage to the pancreas. The pancreas is an organ located in the abdomen that produces insulin and substances that aid in digestion.
- Allergic reaction
- Small changes in the mineral density of bones were observed in studies of HIV-infected people who were given tenofovir or Truvada®, plus other drugs used for HIV treatment. The changes in the mineral density of the bones did not cause any fractures, or other problems that bothered the patients. It is unknown if tenofovir or Truvada® can decrease the strength of bones in HIV-uninfected persons like you.
- Lactic acidosis has occurred in HIV-infected persons taking tenofovir or Truvada®, in combination with other drugs. Lactic acidosis is a condition that can produce shortness of breath, nausea, and liver failure. This is a serious adverse effect of some treatments used for HIV infection.

You should call or come to the study clinic if you have unexplained urination, weight loss, cramps, muscle pain, dizziness, excessive fatigue, nausea, vomiting, or shortness of breath. If you have these symptoms, or any other symptoms that concern you, the study staff will evaluate your symptoms and determine whether you should stop your study pills.

Tenofovir and Truvada® have been studied in many people so the possible adverse effects are well known. Still, it is possible that tenofovir or Truvada® may have rare adverse effects that are not yet recognized. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. You should notify the study doctors if you feel that the study medication is causing you to have any symptoms.

Other medications
Many medications can be taken in parallel with the study medication used in this research study. However, some medications should not be taken while you are taking the study medication. If you take other medications during your participation in the study, there is a chance that we will need to obtain additional blood, undergo medical evaluations and laboratory tests. While taking some medications, you will need to temporarily stop taking the study medication. If so, you would continue to participate in the study visits in order to monitor your health. In addition, you should tell the team of researchers if you plan to enroll in any other clinical trial while you are participating in this study. When you visit the study clinic, we will provide you with a list of medications that you should not take while you are participating in this study, and if you authorize us to, we will send this information to any doctor that you consider necessary to be informed. Please ask your study doctor about these medications if you have any questions.

Unknown risks

The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about continuing to participate in the study.

Risk of acquiring HIV infection and drug resistance

If you are receiving tenofovir or Truvada® during the study, we do not know if it will protect you from becoming infected with HIV. If you are receiving the placebo, we definitely know that this pill will not protect you from becoming infected with HIV. You may become infected with HIV during this study from your HIV-infected partner or from other sexual partners you may have. It is very important to use all the known risk reduction strategies to prevent the acquisition of HIV, like using condoms for all sexual relations and keeping your number of sexual partners low.

If you are receiving tenofovir or Truvada® and you become infected with HIV during the study, you could become infected with a strain of the HIV virus that could be resistant to tenofovir, emtricitabine (one of the components of Truvada®), or lamivudine (a medication similar to emtricitabine). These three medications are used for HIV treatment. Resistance to antiretroviral medications may make effective HIV treatment more difficult and may limit your treatment options. Resistance to antiretroviral medications can affect the response of the virus in such a way that the virus may become resistant to tenofovir, emtricitabine, or to both. You will be able to discuss treatment and the generation of resistance to medications with the study doctor.

For more information about risks of this study, ask your study doctor.

BENEFITS

You may get no direct benefit from being in this study. **We do not know if tenofovir or**
Truvada® help HIV-uninfected individuals who have HIV-infected partners from getting HIV. Plus, you may receive placebo, and not the tenofovir or Truvada® pills. Study staff will remind you of the importance of using condoms to protect against HIV.

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

You will get counseling and testing for HIV. You will get free condoms. If you are not immune to hepatitis B, you will be offered hepatitis B vaccination. If you or your partner have health problems that may be due to infections passed during sex, you will get medicine to treat them, if needed. For other health problems, the study staff will give you care and treatment that is available at the clinic. For care and treatment that is not available at the clinic, study staff will tell you about other places where care and treatment may be available.

Your partner will receive care and support related to his/her HIV infection while this study is ongoing. Depending on when you and your partner join the study, this care will be available to your partner for 2 to 4 years. This care will be either be provided through a referral clinic or, if not otherwise available, will be paid for by the study and will be provided [by the study staff or by the xxx organization]. Medications used to treat HIV will be given per national guidelines.

If you become infected with HIV while in this study, you will be offered counseling and clinical services for HIV while the study is ongoing. After the study is over, the study staff will no longer be able to provide this care to you or your partner. You and your partner will be referred to other HIV care programs that are available to you.

NEW FINDINGS

You will be told any new information learned during this study that is important for your health or might cause you to change your mind about staying in the study. You will be told when the results of the study may be available, and how to learn about them.

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you from the study will be given free of charge.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY

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

- The study is stopped or canceled.
- The study staff feel that staying in the study would be harmful to you.
• You are not able to attend study visits or complete the study procedures.

ALTERNATIVES TO PARTICIPATION

We do not know if tenofovir or Truvada® work to prevent HIV-uninfected persons from getting HIV from their HIV-infected partners. The only way to prevent getting HIV 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 or your partner 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.]

REIMBURSEMENT

[Sites to insert information about local incentives:] You will receive money for your transportation costs, time and effort at each scheduled study visit. You also will receive payment for the costs of travel due to your visits.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any sample from you or information about you will be identified only by code. The link between your name and code will be kept in a secure location at the clinic only. We will not discuss any information about you with your partner unless you give written permission, and will encourage you to be present during the discussion. Any publication of this study will not use your name or identify you personally.

Your study records may be reviewed by study staff and representatives of:

• the University of Washington, including study monitors
• the Bill and Melinda Gates Foundation
• the United States Food and Drug Administration
• [insert applicable local authorities, e.g., Ministry of Health]
• [insert names of applicable IRBs/ECs]

RESEARCH-RELATED INJURY

[Sites to amend this sample text as needed, and/or specify institutional policy]
The study staff will monitor your health and the health of your partner while you are in this study.

You will have a study visit every month. Your partner will have a visit every 3 months. If you or your partner have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions].

If you are injured from participating in this study, you will be offered care at the study clinic, free of charge. It is important that you tell the members of team of researchers at this clinic if you feel that you have been injured because of taking part in this study.

There is not a program of monetary compensation through this institution. If you require medical care that that the study clinic cannot provide, the study doctors will refer you to the appropriate services or organizations that can provide care for the injury. If the study doctors determine that the injury is a consequence of your participation in the study, study funds will be used to pay for the medical care that you need.

You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

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

STATEMENT OF CONSENT AND SIGNATURES

I have read this form or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the study is voluntary. I understand that if I decide to join the study I may withdraw at any time. By signing this form I do not give up any rights that I have as a research participant.

[Insert signature blocks as required by the local IRB/EC:]

<table>
<thead>
<tr>
<th>Participant Name (print)</th>
<th>Participant Signature/Thumbprint</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Staff Conducting</td>
<td>Study Staff Signature</td>
<td>Date</td>
</tr>
</tbody>
</table>

Partners PrEP Protocol
Version 3.0, 12 October 2007

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CONSENT FOR OFF-SITE VISITS

It may be necessary for the members of the team of researchers of this clinic to visit you at your home or another location or to contact you via telephone as part of the study. Some of the scheduled study visits may take place at your home. In addition, if you have missed visits, study staff may visit you at your home. The study personnel will explain in greater detail the requirements to do these visits (like the conditions of the place, the type of visit and the duration of it) and the procedures to maintain your information in a confidential manner. However it is important that you know that home visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

To do this we will need you to authorize us to do so, please read carefully the following statement and initial and date one option. Choosing not to be visited outside of the study clinic will not affect your participation in this study.

___________        I DO agree to be contacted or visited at a site other than the study clinic

___________        I DO NOT agree to be contacted or visited at a site other than the study clinic

[Insert signature blocks as required by the local IRB/EC:]

Participant Name (print)                  Participant Signature/Thumbprint                  Date

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

Witness Name (print)                  Witness Signature                  Date
SPECIMEN STORAGE AND USE OF YOUR DATA AND SAMPLES FOR FUTURE STUDIES:

Please initial and date one option:

___________  I DO agree to store my data and samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

___________  I DO NOT agree to store my data and samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

[Insert signature blocks as required by the local IRB/EC:]

<table>
<thead>
<tr>
<th>Participant Name (print)</th>
<th>Participant Signature/Thumbprint</th>
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<tr>
<th>Study Staff Conducting Consent Discussion (print)</th>
<th>Study Staff Signature</th>
<th>Date</th>
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<tr>
<th>Witness Name (print)</th>
<th>Witness Signature</th>
<th>Date</th>
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</table>
Appendix XI  Study Enrollment Comprehension Questionnaire for Partner (HIV-1 Uninfected) Participants

<table>
<thead>
<tr>
<th></th>
<th>The study seeks to find out if taking 2 pills daily can prevent the acquisition of HIV.</th>
<th>True</th>
<th>False</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>This study also seeks to find out if it is safe for HIV-uninfected men and women to take a pill daily to prevent the acquisition of HIV.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Once you initiate your participation in the study, you will be assigned to take either tenofovir, Truvada, or placebo.</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>Tenofovir and Truvada have been authorized for use in the treatment of HIV and not for the prevention of HIV.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>You and the study staff will not be able to tell whether you have been assigned tenofovir, Truvada, or placebo.</td>
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</tr>
<tr>
<td>6</td>
<td>Once you begin your participation in the study, we will ask that you come to our clinic for monthly visits, for the next approximately 24 to 48 months.</td>
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</tr>
<tr>
<td>7</td>
<td>(women only) If you become pregnant during the study, you will stop taking the study medication. We do not know the effects of tenofovir and Truvada taken during pregnancy.</td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>(women only) If you are breastfeeding now, you will not be allowed in the study. If you decide to start breastfeeding during the study, you will stop taking the study medication. We do not know the effects of tenofovir and Truvada taken during breastfeeding.</td>
<td></td>
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<tr>
<td>9</td>
<td>It is very important that you do not share your study drug with anyone, including your partner.</td>
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<tr>
<td>10</td>
<td>Participating in this study will prevent you from getting HIV infection.</td>
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</tr>
<tr>
<td>11</td>
<td>There are many possible side effects that could occur as a result of taking the study medications. One of these is that the study medications may affect the function of the kidneys.</td>
<td></td>
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<tr>
<td>12</td>
<td>You can come to this clinic at any time if you feel that you have a health problem. If you need more specialized care, the study staff will arrange for you to receive the needed medical attention.</td>
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<tr>
<td>13</td>
<td>If you develop a health problem potentially related to the study medication, the study staff may instruct you to stop the medication, either temporarily or permanently.</td>
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<tr>
<td>14</td>
<td>If during the study you have a positive test result for HIV, you will cease using the study medication. You will continue to receive medical attention.</td>
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<tr>
<td>15</td>
<td>If you do not wish to participate in this study, you will not lose any benefit offered by this institution.</td>
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<tr>
<td>16</td>
<td>You can go to the Ethical Review Committee to provide any comment or complaint that you have regarding your participation in the study.</td>
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<tr>
<td>17</td>
<td>The study can be terminated at any moment if the investigators and authorities that regulate the conduct of this study decide this.</td>
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<tr>
<td>18</td>
<td>If you need, there is a telephone number available 24 hours a day for you to call and contact a study physician.</td>
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<tr>
<td>19</td>
<td>You cannot withdraw from the study once you have agreed to participate in it.</td>
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</tr>
<tr>
<td>20</td>
<td>Using a condom every time you have sex will reduce your chances of getting HIV.</td>
<td></td>
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</tbody>
</table>
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Appendix XII  Study Enrollment Consent for Index (HIV-1 Infected) Participants

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Version 3.0
12 October 2007

PRINCIPAL INVESTIGATOR: [insert name]
[insert physical address and relevant contact info]

INFORMED CONSENT

We are asking you to volunteer for a research study. This study is for partners in which one person has HIV and the other does not. HIV is the virus that causes AIDS. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, and what would be expected of you if you agree to be in the study. This study is sponsored by the Bill and Melinda Gates Foundation and the University of Washington, which are located in Seattle, Washington, USA.

If you decide to participate in the research study, you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

PURPOSE OF THE STUDY

This research is studying two medications that suppress the HIV virus. One medication is called tenofovir. The second medication is a combination of tenofovir and another medication called emtricitabine. This combination is known as Truvada®. Both tenofovir and Truvada are pills that are used to treat people already infected with HIV. Studies have shown that these medications are safe when used once per day as treatment of HIV by HIV-infected people. Tenofovir and Truvada are not cures for HIV, but they are very effective in suppressing the HIV virus in people who are HIV-infected and in improving their health and immune function.

The purpose of this study is to find out if taking tenofovir or Truvada every day can prevent HIV-uninfected men and women from getting the HIV virus from their partner. This is called pre-exposure prophylaxis. The study also will learn whether tenofovir and Truvada are safe (meaning that they do not produce significant health problems in persons who take them) when taken by HIV-uninfected men and women. We do not know if taking tenofovir or Truvada will prevent HIV infection in a safe way.

Approximately 3900 couples, all from Africa, will be in the study. All the couples will be HIV-discordant, meaning that one person has HIV and the other person does not have
HIV. This will be the largest of this kind of study ever. Approximately 500-800 couples are planned to be in the study here at [clinic].

Each couple will be in the study for a minimum of 24 months and up to a maximum of 36 months. Those who become HIV infected during the study will be asked to continue for one year after infection, regardless of when during the 36 months of maximum follow-up the HIV infection occurs. The whole study will take at about 5 years to finish.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that we will discuss with you. Once you understand the study, and if you agree to take part, we will ask you to sign your name or make your mark on this form. We will offer you a copy to keep.

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

• You do not have to be in this study if you do not want to join.

• You may decide not to take part in the study, or to withdraw from the study at any time, without losing the benefits of your or your partner’s routine medical care.

• If you decide not to take part in the study, you can still join another research study later, if one is available and you qualify.

STUDY GROUPS

In this research study, your partner will be assigned to one of three study groups – one group will receive tenofovir, one group will receive Truvada, and one group will receive placebo. Your partner will take two pills of study medication each day. The placebo group will receive pills that have the same physical appearance and have the same taste as tenofovir and Truvada but do not contain a medication that is used to treat HIV infection or any other medication.

A computer program will randomly decide which type of study medication your partner receives. Your partner will have an equal chance of being assigned to tenofovir, Truvada, or placebo. Neither you, your partner, nor any of the research staff in this clinic will know if your partner is taking tenofovir, Truvada, or placebo.

All three groups are very important to this study. Couples in all three groups will have the same study visits. All couples will get condoms, treatment for other STDs, and counseling on how to avoid HIV and other infections passed during sex.

We do not know if taking tenofovir or Truvada can prevent your partner from getting HIV. That is why we are conducting the study.

The only known way to protect your partner against getting HIV during sex is to use a condom every time you and your partner have sex.
IMPORTANCE OF NOT SHARING THE STUDY MEDICATION

In this research study, your partner will take study medication each day. You will not take any study medication. Instead, you will come for follow-up visits every three months, for a total of 2 years. At your visits to the research clinic, the study staff will ask you questions about your health and your sexual practices and will collect samples of your blood and genital secretions. These samples will be used to investigate whether there are factors that either increase or decrease the chances that HIV is transmitted from one person to another. They will also be used to determine whether some factors increase or decrease the chance that the study medication your partner is taking works to prevent your partner from acquiring HIV infection.

It is very important that you do not share your partner’s study medication. Although tenofovir and Truvada are used to treat HIV infection, they are only effective for treating HIV infection if they are used in combination with other medications used for treating HIV infection. If you take your partner's study medication, you may be exposed to tenofovir or Truvada, or you may be exposed only to placebo. If you are exposed to tenofovir or Truvada, your HIV could become resistant to tenofovir, emtricitabine (one of the components of Truvada), or lamivudine (a medication similar to emtricitabine). Resistance to these antiretroviral medications may reduce how well future HIV treatment will work for you.

During this study, we will test your blood every 6 months to monitor your immune function. If those tests show that you require HIV treatment during the course of this research study, we will either provide treatment at the research clinic or refer you for appropriate treatment.

STUDY PROCEDURES

If you decide to take part in the study, your first visit will continue today, after you read, discuss, and sign or make your mark on this form. At today's visit, several things will happen:

- The study staff will ask you questions about your medical history and your sexual practices

- You will undergo a physical exam, including a genital exam to look for sexually transmitted infections.
  
  - For women, the study staff will collect swab samples during the genital exam from your genital area to test for sexually transmitted infections. These will be collected using soft-tipped, sterile swabs. A Pap smear may also be performed.
  
  - For women, an additional swab will be obtained from your genital area. This will be sent to study researchers at the University of Washington to test for HIV in the genital area.
For both women and men, you will be asked to provide a urine sample that will be used by researchers at the University of Washington for tests related to HIV and other sexually transmitted infections.

- We will ask your permission to obtain a blood sample [up to 25.5 ml / less than 2 tablespoons]. We will obtain the sample using a sterile instrument (needle) inserted into a vein in your arm. The blood sample will be used for tests at the clinic and by study researchers at the University of Washington.
  - Some of the blood will be used to test for syphilis.
  - Some of the blood may be used to test for infection with herpes simplex virus, another sexually transmitted infection.
  - Some of the blood will be used by researchers at the University of Washington to confirm the results of the HIV tests that we do here, to measure the levels of HIV in your blood, and to look for other genetic, infectious, and immune factors that affect the chances of transmitting HIV to your partner.

- If your blood sample from the Screening Visit showed no evidence of hepatitis B infection, and no evidence of immunity to hepatitis B, you will be given information about the disease and also offered to begin the hepatitis B vaccination series. This will include vaccine injections also at 3 and 6 months.

After today’s visit, you will have scheduled study follow-up every 3 months. Your partner will have scheduled follow-up every month. During the months when you and your partner both have a visit, you should come to the clinic together, for your convenience and so you can have counseling together as a couple. If that is not possible, you can come for your visits by yourself if you wish. Each visit will take about 60 minutes. You are also encouraged to come to your partner’s monthly visits with your partner.

**At each of your 3-monthly visits you will:**

- Be asked questions about your health and medical history.
- Be asked questions about your sexual practices.
- Talk with study staff about ways to avoid HIV and other infections passed during sex. We encourage you to have this counseling with your partner, but you can have it by yourself if you wish.
- Get condoms.
- Get medical care or referrals for medical care and other services if you need them.
• Give updated information on where you live and how to keep in contact with you. The study staff 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]. 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.

Every 3 months:

• You will undergo a physical exam.

Every 6 months:

• We will ask your permission to obtain a blood sample [up to 29.5 ml / less than 2 tablespoons]. We will obtain the sample using a sterile instrument (needle) inserted into a vein in your arm. The blood sample will be used for tests at the clinic and by study researchers at the University of Washington.

  o Some of the blood sample will be used for a test called a CD4 cell count. The CD4 count is a measure of how well your immune system is functioning. The lower the CD4 count in persons who are HIV-infected, the more at risk they are for having problems from AIDS.

  o Some of the blood will be used by researchers at the University of Washington to confirm the results of the HIV tests that we do here, to measure the levels of HIV in your blood, and to look for other genetic, infectious, and immune factors that affect the chances of transmitting HIV to your partner.

• Only at the visits that are scheduled to take place six and twelve months after joining the study, men will be asked to give a semen sample that will be sent to the University of Washington for tests of the HIV that may be in the semen. Men who choose not to give this sample may remain in the study.

Every 12 months:

• You will undergo testing to look for sexually transmitted infections.

  o This will include a blood test for syphilis.

  o For women, the study staff will collect swab samples during a genital exam from your genital area to test for sexually transmitted infections. These will be collected using soft-tipped, sterile swabs. A Pap smear may also be performed.

  o For women, an additional swab will be obtained from your genital area. This will be sent to study researchers at the University of Washington to
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

test for HIV in the genital area.
  o For men, you will be asked to provide a urine sample that will be used by researchers at the University of Washington to test for sexually transmitted infections.

At any time in the study:

- If you or the study staff think you may be pregnant, you will give urine for a pregnancy test (for women only).

- If you become pregnant, you can still participate in the study. You will be counseled about HIV and pregnancy. You will receive, or be referred for antenatal care for pregnant women with HIV (for women only).

- If you or the study staff think you may be having any health problems, the study staff can perform a physical examination and may offer additional testing and treatment, or referral for testing and treatment.

- If you are having health problems that may be due to a sexually transmitted infection, you will have a genital exam and receive medicine to treat the infections as needed.

- You can have extra counseling about HIV if needed between scheduled visits, either with your partner or by yourself.

- If you and your partner end your relationship before your last scheduled study visit, we will ask you to stay in the study as originally scheduled.

- If you decide to leave the study before your last scheduled study visit, we will ask you to have a final study visit with all the exams and tests listed above.

IF YOUR PARTNER BECOMES HIV INFECTED

During the course of the study we will provide you with condoms and other materials to help prevent transmission of HIV to your partner. However it is possible that your partner can become HIV infected.

If your partner has a positive HIV test during the study, The study staff will talk with your partner, and with you, about this test result. We will ask that you provide one set of blood and genital samples to help us understand HIV transmission from one person to another. If your partner has a positive HIV test on a day at which you are not attending the research clinic, we will ask you, either directly or via your partner, to come back to the clinic within a couple of weeks to provide these samples. The samples will include:

- A blood sample [up to 21 ml / less than 2 tablespoons]. We will obtain the sample using a sterile instrument (needle) inserted into a vein in your arm. The blood sample will be used for tests at the clinic and by study researchers at the University
of Washington.

- Some of the blood sample will be used for a CD4 cell count test.
- Some of the blood will be used by researchers at the University of Washington to measure the levels of HIV in your blood and to look for other genetic, infectious, and immune factors that affect the chances of transmitting HIV from one person to another.

- For women, you will undergo a genital exam, during which a swab will be obtained from your genital area. This will be sent to study researchers at the University of Washington to test for HIV in the genital area.

- For men, you will be asked to give a semen sample that will be sent to the University of Washington for tests of the HIV that may be in the semen.

After you provide these samples, you will then resume your usual follow-up. Your partner will be asked to continue follow-up every three months, for one year, after his/her HIV infection is detected. You are welcome to come to those visits with your partner.

SPECIMEN STORAGE AND USE OF SAMPLES AND DATA FOR FUTURE STUDIES

We would like to save data from this study and samples of your blood, urine, semen, and genital secretions at [local site] and at the University of Washington for future research by us and by other researchers. We will use these samples only for research related to HIV, HIV-related diseases, and sexually-transmitted infections. This will include testing for genes which may affect whether a person is more or less likely to get these infections, have more severe infection, or how people respond to the medications used in this study. Gene studies may test for a specific gene to understand these effects or help researchers find new genes that may have these effects. This research is experimental and these tests are not useful for your clinical care. Before your samples leave the clinic, they will be assigned a code and your name will not be on them. Your name will be linked to the code only at this clinic and only for five years after the study is completed. After that time, the link between your name and the code on your data and samples will be destroyed. An Institutional Review Board or Independent Ethics Committee, which watches over the safety and rights of research participants, must approve any future research studies using your data and samples. If you agree to store your samples, we will keep them for as long as sample remains that can be used for future research. If you do not want to have your samples saved for future research, you can still be in this study and your samples will be destroyed once testing for this study is completed. If you agree to store your samples now, but change your mind before the end of the study, let the study staff know and we will make sure that your samples do not get stored for future research. We will not sell your data or samples. Tests done on your samples may lead to a new invention or discovery. We have no plans to share any money or other benefits resulting from this invention or discovery with you.

RISKS AND/OR DISCOMFORTS
You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise where the needle goes into your arm. You may feel discomfort during genital exams.

You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against HIV and other infections passed during sex, and your HIV test results. You may become worried or anxious while waiting for your test results. If you have or become infected with HIV, knowing this could make you worried or anxious. Talking about HIV and finding out your test results could cause problems between you and your partner. Trained counselors will help you and your partner deal with any feelings or questions you may have.

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

Your partner will receive study medication during this research study. It is important that you do not share that study medication.

**BENEFITS**

You may get no direct benefit from being in this study. Study staff will remind you of the importance of using condoms to protect against HIV.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV.

You will get counseling and testing for HIV. You will get free condoms. If you or your partner have health problems that may be due to infections passed during sex, you will get medicine to treat them, if needed. For other health problems, the study staff will give you care and treatment that is available at the clinic. For care and treatment that is not available at the clinic, study staff will tell you about other places where care and treatment may be available.

You will receive care and support related to your HIV infection while this study is ongoing. Depending on when you join the study, this care will be available for a minimum of 2 years. This care will be either be provided through a referral clinic or, if not otherwise available, will be paid for by the study and will be provided [by the study staff or by the xxx organization]. Medications used to treat HIV will be given per guidelines of the World Health Organization for at least two years.

**NEW FINDINGS**

You will be told any new information learned during this study that is important for your health or might cause you to change your mind about staying in the study. You will be told when the results of the study may be available, and how to learn about them.
COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you from the study will be given free of charge.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY

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

- The study is stopped or canceled.
- The study staff feel that staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.

ALTERNATIVES TO PARTICIPATION

The only way to prevent getting HIV 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 or your partner 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.]

REIMBURSEMENT

[Sites to insert information about local incentives:] You will receive money for your transportation costs, time and effort at each scheduled study visit. You also will receive payment for the costs of travel due to your visits.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any sample from you or information about you will be identified only by code. The link between your name and code will be kept in a secure location at the clinic only. We will not discuss any information about you with your partner unless you give written permission, and will encourage you to be present during the discussion. Any publication of this study will not use your name or identify you personally.
Your study records may be reviewed by study staff and representatives of:

- the University of Washington, including study monitors
- the Bill and Melinda Gates Foundation
- the United States Food and Drug Administration
- [insert applicable local authorities, e.g., Ministry of Health]
- [insert names of applicable IRBs/ECs]

RESEARCH-RELATED INJURY

[Sites to amend this sample text as needed, and/or specify institutional policy]

The study staff will monitor your health and the health of your partner while you are in this study.

You will have a study visit every 3 months. Your partner will have a visit every month. If you or your partner have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions].

If you are injured from participating in this study, you will be offered care at the study clinic, free of charge. It is important that you tell the members of team of researchers at this clinic if you feel that you have been injured because of taking part in this study.

There is not a program of monetary compensation through this institution. If you require medical care that that the study clinic cannot provide, the study doctors will refer you to the appropriate services or organizations that can provide care for the injury. If the study doctors determine that the injury is a consequence of your participation in the study, study funds will be used to pay for the medical care that you need.

You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

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

STATEMENT OF CONSENT AND SIGNATURES

Partners PrEP Protocol
Version 3.0, 12 October 2007

Page 161 of 165
I have read this form or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the study is voluntary. I understand that if I decide to join the study I may withdraw at any time. By signing this form I do not give up any rights that I have as a research participant.

[Insert signature blocks as required by the local IRB/EC:]

<table>
<thead>
<tr>
<th>Participant Name</th>
<th>Participant Signature/Thumbprint</th>
<th>Date</th>
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</tbody>
</table>

| Study Staff Conducting    | Study Staff Signature            | Date |
| Consent Discussion (print)|                                  |      |

| Witness Name              | Witness Signature                | Date |
| (print)                   |                                  |      |

CONSENT FOR OFF-SITE VISITS

It may be necessary for the members of the team of researchers of this clinic to visit you at your home or another location as or to contact you via telephone as part of the study. Some of the scheduled study visits may take place at your home. In addition, if you have missed visits, study staff may visit you at your home. The study personnel will explain in greater detail the requirements to do these visits (like the conditions of the place, the type of visit and the duration of it) and the procedures to maintain your information in a confidential manner. However it is important that you know that this procedure may eventually affect your confidentiality.

To do this we will need you to authorize us to do so, please read carefully the following statement and initial and date one option. Choosing not to be visited outside of the study clinic will not affect your participation in this study.

___________ I DO agree to be contacted or visited at a site other than the study clinic

___________ I DO NOT agree to be contacted or visited at a site other than the study clinic

[Insert signature blocks as required by the local IRB/EC:]

<table>
<thead>
<tr>
<th>Participant Name</th>
<th>Participant Signature/Thumbprint</th>
<th>Date</th>
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</table>
SPECIMEN STORAGE AND USE OF YOUR SAMPLES FOR FUTURE STUDIES:

Please initial and date one option:

_________ I DO agree to store my data and samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

_________ I DO NOT agree to store data and my samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

[Insert signature blocks as required by the local IRB/EC:]

Participant Name  (print)  Participant Signature/Thumbprint  Date

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

Witness Name  (print)  Witness Signature  Date
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Appendix XIII Viread® (tenofovir disoproxil fumarate) Package Insert

Appendix XIV Truvada® (emtricitabine/tenofovir disoproxil fumarate) Package Insert

Appendix XV Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

These appendices follow as separate documents.
PROTOCOL ADDENDUM

# 1

16 October 2008

For study:

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

IND #75,365
Version 3.0
12 October 2007

Purpose of this addendum: Modifications to the Protocol Team Roster

Section 1.1 Coordinating Center

Add:

Deborah Donnell, PhD
Co-Investigator, Study Statistician
Statistical Center for HIV/AIDS Research and Prevention & University of Washington

James Hughes, PhD
Co-Investigator, Study Statistician
University of Washington

Section 1.3 Site Principal Investigators

Under site Uganda – Mbale, add:

James Campbell, MD
CDC Uganda

Under site Uganda – Tororo, add:

James Campbell, MD
CDC Uganda
Purpose of this addendum: Addition of a study site in Jinja, Uganda and modification of protocol team roster to reflect Jinja site principal investigators.

To protocol team roster, **Section 1.3 Site Principal Investigators**, add:

**Uganda – Jinja**

Patrick Ndase, MBChB, MPH  
University of Washington

Elly Katabira, MBChB, FRCP  
Makarere University School of Medicine

Couples House  
Plot 27B, Kiira Road (opp Jinja Main Hospital)  
Jinja, Uganda
Summary

This addendum details the addition of peripheral blood mononuclear cell (PBMC) collection from HIV-1 susceptible, infected, and seroconverting participants in the Partners PrEP Study. At a minority of scheduled study visits, the blood volume collected will be increased to permit collection of this additional sample type. This addendum does not modify the objectives of the study protocol or substantially change participant risks and benefits.

PBMC collection will occur at the following visits:

<table>
<thead>
<tr>
<th>HIV-1 uninfected participants</th>
<th>HIV-1 infected participants</th>
<th>HIV-1 seroconverters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment*</td>
<td>Enrollment*</td>
<td>Possible seroconversion (SC)</td>
</tr>
<tr>
<td>Month 6</td>
<td>Month 12</td>
<td>SC + 3 months</td>
</tr>
<tr>
<td>Month 12</td>
<td></td>
<td>SC + 6 months</td>
</tr>
<tr>
<td>Month 24</td>
<td></td>
<td>SC + 12 months</td>
</tr>
</tbody>
</table>

* Participants already enrolled at the time this addendum is implemented will be offered study reconsent to participate in PBMC collection and will embark on the schedule above (e.g., already-enrolled HIV-1 uninfected participants will not have enrollment samples collected but can have Month 6, 12, and 24 samples collected).

PBMC collection will increase the blood volume collected by a maximum of 51-53.5 ml at these visits.
Rationale

The Partners PrEP Study clinical trial cohort offers a unique opportunity to understand PrEP efficacy and adherence, as well as the fundamental biologic mechanisms that underlie sexual HIV-1 transmission. These goals are detailed in the Secondary and Tertiary Objectives of the study protocol. PBMC collection at a small number of scheduled study visits for the Partners PrEP Study will permit better exploration of these important questions.

Specifically, the addition of PBMC collection to Partners PrEP Study will allow the Protocol Team to:

1. Measure intracellular concentrations of study drug, to better understand study drug adherence, the relationship between study drug adherence and HIV-1 protection, and the frequency and correlates of study drug sharing between HIV-1 uninfected individuals taking PrEP and their HIV-1 infected partners. This is consistent with Secondary Objective #2 in the study protocol.

2. Test the hypothesis that PrEP, by having sufficient levels of antiretroviral drugs in the blood and genital tract, can abort early infections and may in turn permit the induction of HIV-1 specific immunity, a situation analogous to a vaccine “prime-boost” strategy. This is consistent with Secondary Objective #1 and the Tertiary Objectives of the study protocol.

3. Characterize innate and specific immune responses in exposed HIV-1 seronegative persons (partner participants) who remain uninfected. This understanding may inform novel strategies for HIV-1 prevention. This is consistent with the Tertiary Objectives of the study protocol.

4. Determine the clinical and immunological consequences of PrEP in recipients who either contain integrated HIV-1 at very low levels or who go on to seroconvert and develop systemic infection. This is consistent with Secondary Objective #5 of the study protocol.

Ethical considerations

PBMC collection will occur only after Institutional Review Board (IRB) / Ethical Committee (EC) approval and with participant consent. This additional sample collection will increase the blood volume at a limited number of scheduled follow-up visits; it does not alter the visit schedule or protocol objectives. The study consent documents will be modified to reflect the increased blood volume. The blood volumes proposed for this addendum are equivalent or lower to those collected routinely in prospective studies of HIV-1 infected and at-risk persons participating in other prospective studies (e.g., HIV-1 vaccine studies) occurring in East Africa.
Implementation of PBMC collection at study sites

The specific protocol and consent addenda required to implement PBMC collection are detailed below. PBMC collection will be conducted at sites with the technical capacity to perform PBMC separations. Each study site, in collaboration with the University of Washington Coordinating Center, will determine if there is technical capacity and interest in adding PBMC collection. All study sites will submit this protocol addendum to their IRBs/ECs for review and approval. Sites intending to perform PBMC collection will notify their IRBs/ECs of that intention and will also submit revised informed consent documents. Thus, notification and submission of revised consent materials will distinguish those sites that will collect PBMCs.

Detailed Listing of Protocol Addendum Points

PBMC collection requires modification of protocol sections 8.2.3, 8.3.3, 9.2.3, 9.3.3, 16.2, and Appendices I, II, III, X and XII.

Section 8.2.3, Laboratory Procedures, add:
- Peripheral blood mononuclear cell (PBMC) archive

Section 8.3.3, Laboratory Procedures, add:
- PBMC archive
  - At Months 6, Month 12, and Month 24

Section 9.2.3, Laboratory Procedures, add:
- PBMC archive

Section 9.3.3, Laboratory Procedures, add:
- PBMC archive
  - At Month 12

Section 16.2, Central Laboratory Specimens, add:
- PBMC archive from partner (HIV-1 uninfected), index (HIV-1 infected), and seroconverting participants
Appendix I  Study Visits and Procedures for Partners (HIV-1 Uninfected Participants)

- In the section entitled LABORATORY PROCEDURES, subsection Central Lab/Specimen Repository, add the following rows:

<table>
<thead>
<tr>
<th>SCREENING, ENROLLMENT, MONTHS 1-12</th>
<th>S</th>
<th>E</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
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<tr>
<th>MONTHS ≥13, STOP VISIT, POST-STUDY DRUG FOLLOW-UP</th>
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- At the bottom of each table, add an additional row:

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<tr>
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<th>S</th>
<th>E</th>
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<th>M2</th>
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<tr>
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<tr>
<td>TOTAL MAXIMUM BLOOD VOLUME (mL), including PBMC collection</td>
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<th>MONTHS ≥13, STOP VISIT, POST-STUDY DRUG FOLLOW-UP</th>
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<td>97.5#</td>
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- To the footnotes:

Footnote # modify first subpoint to be “Serum, plasma, and PBMCs…”

Add new footnotes:
At sites performing PBMC collections, and for participants who consent to PBMC collection, these rows detail the blood volume for PBMC collection and the total blood volume for the visit. For all other visits, the blood collection is unchanged.

The Month 6 PBMC collection will include and additional 2.5 mL for PaxGene blood archive.

Only the Month 24 visit.

Appendix II  Study Visits and Procedures for Index (HIV-1 Infected Participants)

- In section titled LABORATORY PROCEDURES, subsection Central Lab/Specimen Repository, add the following row:

<table>
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<tr>
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<th>M3</th>
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<th>M9</th>
<th>M12</th>
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<th>M18</th>
<th>M21</th>
<th>M24</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC archive</td>
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</tr>
</tbody>
</table>

- At the bottom of the table, add an additional row:

<table>
<thead>
<tr>
<th></th>
<th>S</th>
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<th>M9</th>
<th>M12</th>
<th>M15</th>
<th>M18</th>
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<th>Stop</th>
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<tbody>
<tr>
<td>ADDITIONAL MAXIMUM BLOOD VOLUME (mL) for PBMC collection visits</td>
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<tr>
<td>TOTAL MAXIMUM BLOOD VOLUME (mL), including PBMC collection</td>
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</tr>
</tbody>
</table>

- To the footnotes:

Footnote modify first subpoint to be “Serum, plasma, and PBMCs…”

Add new footnotes:

i At sites performing PBMC collections, and for participants who consent to PBMC collection, these rows detail the blood volume for PBMC collection and the total blood volume for the visit. For all other visits, the blood collection is unchanged.

j Only the Month 12 visit.
Appendix III  Study Visits and Procedures in the Event of HIV-1 Seroconversion

- In section titled **LABORATORY PROCEDURES**, subsection **Central Lab/Specimen Repository**, add the following rows:

<table>
<thead>
<tr>
<th>Visits at seroconversion, &lt;1 month later, then quarterly for at least 12 months*</th>
<th>SC</th>
<th>SC&lt;1</th>
<th>SC3</th>
<th>SC6</th>
<th>SC9</th>
<th>SC12</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBMC archive</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td></td>
</tr>
</tbody>
</table>

- At the bottom of the table, add an additional row:

<table>
<thead>
<tr>
<th>Visits at seroconversion, &lt;1 month later, then quarterly for at least 12 months*</th>
<th>SC</th>
<th>SC&lt;1</th>
<th>SC3</th>
<th>SC6</th>
<th>SC9</th>
<th>SC12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDITIONAL MAXIMUM BLOOD VOLUME (mL) for PBMC collection visits**</td>
<td>53.5***</td>
<td>51</td>
<td>51</td>
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<tr>
<td>TOTAL MAXIMUM BLOOD VOLUME (mL), including PBMC collection***</td>
<td>95.5***</td>
<td>72</td>
<td>72</td>
<td>80.5</td>
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</tbody>
</table>

- Add new footnotes:

** At sites performing PBMC collections, and for participants who consent to PBMC collection, this row details the maximum blood volume. For all other visits, the blood collection is unchanged.

*** The Possible Seroconversion PBMC collection will include an additional 2.5 mL for PaxGene blood archive.

NOTE: The following edits apply to the protocol template consent forms. Each study site will modify their consent forms in accordance with their individual IRB/EC requirements.

Appendix X  Study Enrollment Consent for Partner (HIV-1 Uninfected) Participants

In the section entitled **STUDY PROCEDURES** change blood volumes:

- 3rd bullet point. Change “up to 29.5 ml / less than 2 tablespoons” to “up to 80.5 ml / less than 4 tablespoons”

- In subsection entitled, **At the first month and every 3 months**, the 2nd bullet point. Change “up to 46.5 ml / about 3 tablespoons” to “up to 97.5 ml / less than 7 tablespoons”

Partners PrEP Protocol  Page 6 of 7  Protocol Addendum #3
Version 3.0, 12 October 2007  03 June 2009
In the section entitled **IF YOU BECOME HIV INFECTED** change blood volumes:

- 3rd bullet point. Change “42 ml / less than 3 tablespoons” to “up to 95.5 ml / less than 7 tablespoons”

- Subsection entitled “At each of the visits after HIV infection is confirmed”, 2nd sub-bullet. Change “17 – 29.5 ml / under 2 tablespoons” to “17 – 80.5 ml / under 6 tablespoons”

**Appendix XII  Study Enrollment Consent for Index (HIV-1 Infected) Participants**

In the section entitled **STUDY PROCEDURES** change blood volumes:

- 3rd bullet point. Change “up to 25.5 ml / less than 2 tablespoons” to “up to 76.5 ml / less than 6 tablespoons”

- In subsection entitled **Every 6 months**, the 1st bullet point. Change “up to 29.5 ml / about 2 tablespoons” to “up to 80.5 ml / less than 6 tablespoons”
PROTOCOL ADDENDUM

# 4

2 November 2009

For study:

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

IND #75,365
Version 3.0
12 October 2007

Purpose of this addendum: Modification of protocol team roster to remove Christine Nabiryo, MBChB as site principal investigator at the Mbale and Tororo, Uganda sites. Dr. Nabiryo has left The AIDS Support Organization (TASO) for other employment and has requested to be removed as site investigator. The other investigators of record at Mbale and Tororo remain unchanged.

To protocol team roster, Section 1.3 Site Principal Investigators, remove:

Uganda – Mbale

Christine Nabiryo, MBChB
The AIDS Support Organization (TASO)

Uganda – Tororo

Christine Nabiryo, MBChB
The AIDS Support Organization (TASO)
PROTOCOL ADDENDUM

# 5

20 November 2009

For study:

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

IND #75,365
Version 3.0
12 October 2007

Purpose of this addendum: Modification of protocol team roster to update the address for the Coordinating Center. The phone numbers and email addresses remain unchanged.

To protocol team roster, Section 1.1 Coordinating Center, update address only:

1.1 Coordinating Center

Connie Celum, MD, MPH
Principal Investigator, Protocol Chair
Professor of Global Health and Medicine and Adjunct Professor of Epidemiology
University of Washington
Box 359927
325 Ninth Avenue, 12th floor
Seattle, Washington 98104
T: (206) 520-3825
F: (206) 520-3831
E: ccelum@u.washington.edu
PROTOCOL ADDENDUM

# 6

11 January 2010

For study:

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

IND #75,365
Version 3.0
12 October 2007

Purpose of this addendum: Increase of sample size from 3900 HIV-1 serodiscordant couples to 4700 HIV-1 serodiscordant couples

Rationale: This study (the Partners PrEP Study) is a randomized, double-blind, placebo-controlled, three-arm trial of tenofovir disoproxil fumarate (TDF) and combination emtricitabine (FTC)/TDF antiretroviral pre-exposure prophylaxis (PrEP) for the prevention of HIV-1 acquisition by HIV-1 uninfected members of HIV-1 serodiscordant couples. The study is end-point driven – i.e., a specific number of HIV-1 seroconversion endpoint events are necessary to achieve the trial’s pre-specified objectives for evaluating whether TDF and/or FTC/TDF PrEP are efficacious for HIV-1 prevention. As detailed in the trial’s Interim Analysis Plan (version 1.5, 9 June 2008), a total of 191 HIV-1 seroconversion endpoints – broken out as 147 per pair-wise comparison (i.e., TDF vs. placebo, FTC/TDF vs. placebo) – are required. The trial sample size (3900 HIV-1 discordant couples) was calculated to be sufficient to achieve the required 191 HIV-1 seroconversions, based on an estimated HIV-1 seroincidence of 3.2 per 100 person-years in the placebo arm and other estimates about the degree of efficacy of the study product, average length of follow-up, overall loss to follow-up, and time off study drug due to pregnancy, as detailed previously. Since the trial initiated, additional information has become available from another HIV-1 prevention trial among HIV-1 serodiscordant couples (the Partners in Prevention HSV/HIV Transmission Study) to estimate HIV-1 seroincidence among HIV-1 serodiscordant couples; in that study, the HIV-1 incidence was 2.8 per 100 person-years in the placebo arm. If an HIV-1 incidence of 2.8 per 100 person-years for the placebo arm is used for estimating HIV-1 incidence in the current trial, then a sample size of 4700 HIV-1 serodiscordant couples is required to achieve 191 HIV-1 seroconversion endpoints, holding all other assumptions approximately constant.
The sample size of the trial will be increased to 4700 (1566 per arm), which should permit the trial to be completed successfully. The increase has been reviewed with and recommended by the study Data and Safety Monitoring Board. The increase in sample size poses no additional risk to study participants, and study procedures are not altered by this change.

Note: As previously defined, changes to the study protocol that do not substantially change study procedures and do not change safety procedures are presented as protocol addenda. This sample size change (<25%) is thus presented as an addendum, rather than as a protocol revision.

In several places in the protocol, the total sample size (3900) or number of subjects per arm (1300) is mentioned, listed below (underlined for emphasis). These should be replaced by 4700 and 1566, respectively.

Section 3. Study Summary subsection Study Size (page 17)

3900 HIV-1 seronegative partners within HIV-1 discordant couples (1300 in each treatment arm) are estimated to be needed for this endpoint-driven trial.

Section 6.1 Overall Design (page 39)

We will randomize 3900 eligible and consenting HIV-1 negative participants to receive once daily study drug in a 1:1:1 ratio to either 300 mg TDF (Viread®) or FTC 200 mg/TDF 300 mg (Truvada®) or placebo (thus, 1300 in each study arm).

Section 6.2.1 Description of Population (page 40)

The study will enroll 3900 heterosexual HIV-discordant couples, with approximately 500-800 couples from each participating study site. The final sample size will be determined by the rate of accrual of confirmed endpoints in this endpoint-driven trial.

Section 14.1 Review of Study Design (page 79)

We will randomize 3900 eligible and consenting HIV-1 negative participants to receive once daily study drug in a 1:1:1 ratio to either 300 mg TDF (Viread®) or FTC 200 mg/TDF 300 mg (Truvada®) or placebo (thus, 1300 in each study arm). A total of 3900 couples will be enrolled in the study and maintained in follow-up for a minimum of 24 months and a maximum of 36 months, plus an additional 1 month of post-study drug follow-up for delayed endpoints identification.

Section 14.4 Sample Size Estimate for Primary Endpoints (page 82)

In computations not shown, 3900 HIV-uninfected participants will also provide 90% power to test overall efficacy at the 60% level of the combined treatment effect of TDF and FTC/TDF relative to placebo (i.e., a test of the concept of PrEP, rather than a test of either specific PrEP drug).

For evaluating safety, with 1300 per arm of active drug, the 95% CI for the rate of AEs, if none observed, is 0-0.2%.
Appendix IX  Screening Consent Form (page 125)

Approximately 3900 couples, all from Africa, will be in the study.

Appendix X  Study Enrollment Consent for Partner (HIV-1 Uninfected) Participants (page 132)

Approximately 3900 couples, all from Africa, will be in the study.

Appendix XII  Study Enrollment Consent for Index (HIV-1 Infected) Participants (page 152)

Approximately 3900 couples, all from Africa, will be in the study.

As detailed in the study protocol, the consent documents in the protocol are template documents only. Each study site, as directed by its Institutional Review Board (IRB) / Ethics Review Committee (ERC), determines the structure of the consent forms. Whether the sample size change necessitates revision of the consent documents will be determined for each site in discussion with its IRB/ERC. The University of Washington IRB (the Coordinating Center IRB) does not feel that participants already participating in the trial need to be reconsented as a result of this sample size change.
PROTOCOL ADDENDUM

# 7

14 February 2011

For study:

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

IND #75,365
Version 3.0
12 October 2007

Purpose of this addendum: Modification of protocol team roster to update the address for the Site Principal Investigators of Kenya-Nairobi.

To protocol team roster, Section 1.3 Site Principal Investigators, Kenya-Nairobi, update address only:

1.3 Site Principal Investigators

Kenya –Nairobi

Kenyatta National Hospital
Couples Counseling Centre
Opposite the Police Post
Nairobi, 00200, Kenya
For study:

*Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples*

*IND # 75, 365*  
*Version 3.0*  
*12 October 2007*

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**Summary**

On 10 July 2011, the Partners PrEP Study independent Data and Safety Monitoring Board (DSMB) recommended, after review of the study data, that the study results be publically reported and the placebo arm be discontinued, because of clear demonstration of HIV-1 protection from pre-exposure prophylaxis (PrEP) in the study population. Both TDF and combination FTC/TDF PrEP significantly reduced HIV-1 risk, compared with placebo, by 62% and 73%, respectively; the HIV-1 protection effects of TDF and FTC/TDF were statistically similar. Both medications were safe.

Following the recommendations of the DSMB, the Partners PrEP Study initiated discontinuation of the study placebo arm. Placebo arm participants are completing the protocol-defined ‘Stop Visit’ and the two monthly ‘Post-Stop’ visits (called P1 and P2 in the study protocol). Participants in the TDF and FTC/TDF (active PrEP) arms are continuing their protocol-defined trial follow-up in a blinded fashion, as recommended by the DSMB, in order to gather additional strength of information regarding the comparative efficacy, safety, and tolerability of TDF versus FTC/TDF as PrEP. Participants in the active PrEP arms are informed that they are receiving active PrEP and that PrEP was found in the study to be partially protective against HIV-1, when provided in combination with other HIV-1 prevention strategies, such as individual and couples HIV-1 and risk reduction counseling and condom use. The potential for differential cost, safety, resistance, and tolerability of TDF versus FTC/TDF presents a strong scientific rationale for increasing the amount of data about their relative efficacy, resistance, and safety by continuing the evaluation of these two medications. The statistically similar HIV-1 prevention effects of TDF and FTC/TDF provide clear equipoise to continue both arms.

This protocol modification and template consent offer an ethical and logistical research mechanism to provide active PrEP to the placebo arm, under the provision of the protocol that detailed the commitment of the study team to provide active PrEP to the placebo arm for 12 months should PrEP demonstrate efficacy for HIV-1 protection (section 15.7 [Access to Effective Products]).
Rationale

The present protocol addendum details mechanisms by which consenting placebo arm participants in the Partners PrEP Study will receive active PrEP for an additional 12 months. PrEP will be assigned as TDF or FTC/TDF, randomly allocated, given the compelling interest in obtaining additional comparative information of these two products as PrEP agents. Randomization to either TDF or FTC/TDF is justifiable given the statistical equivalence of the two agents for HIV-1 protection, and continuing to gather information on both TDF and FTC/TDF as PrEP will allow data on these two strategies to bolster data collected through continuation of the active arms.

Specifically, this protocol addendum will permit the study team to:

1. Provide active PrEP to placebo arm participants under section 15.7 of the study protocol, in which access to active PrEP for 12 months was committed if PrEP demonstrated efficacy for HIV-1 protection.

2. Collect additional information on the relative safety, efficacy, and HIV-1 resistance related to TDF versus FTC/TDF as PrEP. Given the potential for different cost, safety, efficacy, and HIV-1 resistance, continued comparative information on these two PrEP strategies will provide critically important information to policymakers to assist in decision-making regarding PrEP implementation.

3. Assess tolerability, adherence, and sexual risk behavior in placebo arm participants initiating PrEP, which has been demonstrated to have efficacy for the prevention of HIV-1. It is important to understand the impact of known efficacy of PrEP on sexual behavior and condom use, how participants perceive side effects, and adherence to daily PrEP medications.

Implementation of placebo arm conversion to active PrEP

The specific procedures and consent template required to implement placebo arm conversion to active PrEP are detailed below. All study sites will submit this protocol addendum, as well as site-specific consent documents, to their IRBs/ECs for review and approval, and placebo arm participants will consent to initiate active PrEP once their site obtains full regulatory approval of this.

Except as detailed otherwise in this addendum, procedures for placebo arm couples participating in this conversion to active PrEP will be identical to follow-up procedures described in the study protocol — including procedures for study drug management and safety, HIV-1 seroconversion, risk-reduction messaging, and pregnancy, as they are being applied to participants continuing in the active PrEP arms in the trial.
The HIV-1 uninfected partners in all couples initially randomized to placebo will be eligible for to receive active PrEP except 1) couples in which the partner (HIV-1 uninfected) participant was on a permanent study drug hold at the time of the study Stop visit, in order to protect participant safety (this is expected to be less than five placebo arm couples in total), 2) couples in which the partner (HIV-1 uninfected) participant is pregnant or breastfeeding, consistent with the procedures in the study protocol, and 3) couples in which the partner (initially HIV-1 uninfected) participant has become seropositive for HIV-1.

The study team will be working on separate protocols to collect safety information on PrEP use through pregnancy and breastfeeding, as this is critically important for PrEP implementation given the high risk of HIV-1 acquisition during pregnancy and breastfeeding, but continuation of PrEP through pregnancy and breastfeeding is not permitted within the Partners PrEP Study protocol (version 3.0, 12 October 2007).

Partner (HIV-1 uninfected) participants who were on protocol-defined temporary study drug holds at the time of the study Stop visit, or who had laboratory studies at the Stop, P1, or P2 visits that would mandate a temporary drug hold (e.g., a Grade 4 laboratory event), will be eligible for active PrEP, if they meet protocol definitions for study drug resumption. Those participants on temporary drug holds at the time of the Stop visit will require clearance by the Safety Monitor and Medical Director, who may instruct on protocol-defined laboratory testing to be done for participant safety, before initiating active PrEP.

Eligibility assessment and enrollment into this conversion phase will generally be expected to occur on the same day, although this is not required. No formal screening visit is expected, since placebo arm couples have been in active follow-up, with ongoing monitoring of safety laboratory studies, including at the Stop, P1, and P2 visits. Placebo arm participants will be counseled about the prevention benefits of PrEP as observed in the Partners PrEP Study. Those who decline active PrEP will be referred to local HIV-1 prevention services and reasons for declining will be recorded.

The active PrEP conversion phase enrollment visit will have specific procedures as described here. Post-enrollment visits will otherwise be identical to the first 12 months of visits as detailed in the study protocol – i.e., monthly visits for partner (HIV-1 uninfected) participants and quarterly visits for index (HIV-1 infected) participants, with the exception that peripheral blood mononuclear cells (PBMCs) will be collected only from partner (HIV-1 uninfected) participants and only at Month 6, at sites collecting PBMCs, and semen will not be routinely collected from index (HIV-1 infected) men. At monthly follow-up visits, HIV-1 rapid testing will be performed, in the context of pre-test, risk reduction, and post-test counseling; for women, pregnancy testing will be performed. Participants will be assessed with respect to clinical symptoms; laboratory measurements of chemistry and hematology parameters will be done at baseline, Month 1, and quarterly thereafter, consistent with the study protocol. At the baseline visit, no genital examination will be required, since genital examination was part of the study Stop visit. Participants will complete follow-up at 12 months, or at less than 12 months if they choose to exit the study early.

Partner (HIV-1 uninfected) participants will be randomized to receive TDF or FTC/TDF PrEP and will be monitored for HIV-1 seroconversion and adverse events, with procedures that will be identical to that as otherwise detailed in the study protocol.

Participants who become infected with HIV-1 during follow-up will continue follow-up, according to seroconverter procedures. Those who become pregnant will continue procedures for pregnant women as defined in the protocol.
Index (HIV-1 infected) participants will be followed, with the same monitoring of HIV-1 clinical status and active referral for HIV-1 care as in the study protocol.

Importantly, both members of the couple do not need to consent to this active PrEP continuation phase in order for each member to be eligible – i.e., they may enroll or not enroll as individuals and may enroll on separate days. This recognizes that some couples have had relationship dissolution or partner death during the study but those situations should not adversely affect access to 12 months of active PrEP and continued research clinic access as committed in the study protocol.

**Enrollment procedures for placebo arm conversion for partner (HIV-1 uninfected) participants**

**Administrative, Behavioral, and Regulatory Procedures**

- Obtain informed consent
- Update locator information
- Individual/couples HIV-1 counseling
- Provision of condoms, other HIV-1 prevention supplies
- HIV-1 risk behavior interview
- Interview regarding attitudes about PrEP and about fertility intentions
- Risk reduction counseling
- Contraception counseling and provision/referral
- HIV-1 pre- and post-test counseling
- Randomization

**Clinical Procedures**

- Medical history questionnaire
- Blood collection
- Physical examination
- Urine collection (women only, for pregnancy testing)
- Study drug supplies, instructions for use, and adherence counseling

**Laboratory Procedures**

- HIV-1 serology
- Serum chemistries
- CBC
- Serum for local site archive and central archive
- Plasma for local site archive and central archive
- Urine pregnancy test (women only)

These procedures, plus procedures at Month 1-12 visits (which are otherwise identical to the
study protocol Month 1-12 procedures and are thus not otherwise detailed here), are listed in protocol Appendix XVI.

_Enrollment procedures for placebo arm conversion for index (HIV-1 infected) participants_

**Administrative, Behavioral, and Regulatory Procedures**

- Obtain informed consent
- Update locator information
- Individual/couples HIV-1 counseling
- Provision of condoms, other HIV-1 prevention supplies
- HIV-1 risk behavior interview
- Interview regarding attitudes about PrEP and about fertility intentions
- Contraception counseling and provision/referral
- Risk reduction counseling

**Clinical Procedures**

- Medical history, including HIV-1 staging, use of opportunistic infection prophylaxis, and use of antiretroviral therapy
- Blood collection
- Physical exam
- Urine collection (women only, when clinically indicated for pregnancy testing)

**Laboratory Procedures**

- CD4 cell count
- Serum for local site archive and central archive
- Plasma for local site archive and central archive
- Urine pregnancy test, if indicated (women only)

These procedures, plus procedures at Month 3-12 visits (which are otherwise identical to the study protocol Month 1-12 procedures and are thus not otherwise detailed here), are listed in protocol Appendix XVIII.
## Appendix XVI

### Study Visits and Procedures for Partner (HIV-1 Uninfected) Participants in the Placebo Conversion Phase to Active PrEP

**ENROLLMENT, MONTHS 1-12**

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<td>Apply eligibility criteria</td>
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<td>Collect/update locator information</td>
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<td>Provide STI treatment(a)</td>
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<td>Administer study drug adherence questionnaire; collect prior drug supplies for pill count</td>
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<td><strong>BLOOD VOLUME (mL)</strong>(e)</td>
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<td>38</td>
<td>38</td>
<td>38</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>38 / 91.5 PMBCs</td>
<td>4</td>
<td>4</td>
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a At 12 months, STI screening (syphilis serology and for women, an endocervical swab and a Pap smear and for men, a urine sample) will be performed, in addition to usual monthly, quarterly, and 6-monthly procedures. If clinically indicated, based on genital symptoms, STI screening and syndromic or laboratory-based diagnosis and management will be provided at any study visit.

b Participants who are not immune to hepatitis B and who declined vaccination will have hepatitis B testing repeated at Month 12, as defined in the main study protocol. In addition, as needed hepatitis B testing will be performed at the time study drug is stopped during the study (e.g., for pregnancy, for side effects) for individuals who are hepatitis B susceptible who either declined vaccination or did not complete the vaccination series. If HBsAg positive, they will be counseled about the risk of hepatitis flare and serum chemistries will be monitored monthly for 2 months after they stop study drug.

c Pap smears will be performed at sites where Pap smears are the standard of care and where cytopathology and referral for dysplasia management are available.

d Archived samples for the Central Lab will include:
   1) Serum and plasma for eligibility and endpoint confirmation, and for secondary and tertiary study objectives.
   2) Samples for STI and BV (for women) testing will be performed at 12 months to assess the prevalence of genital tract infections in participants.
   3) Whole blood and blood spot samples for secondary and tertiary study objectives. As detailed in the protocol, participants will consent to storage of samples for future research and IRB approval will be obtained prior to additional testing.

e Blood volumes are maximums.

[ ] = if clinically indicated, based on participant history
Appendix XVII  TEMPLATE CONSENT: Enrollment Consent for Partner (HIV-1 Uninfected) Participants in the Placebo Conversion Phase to Active PrEP

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples
Version 3.0
12 October 2007

Consent for 12 months of active PrEP for the placebo arm

PRINCIPAL INVESTIGATOR:  [insert name]
[insert physical address and relevant contact info]

INFORMED CONSENT

We are asking you to volunteer to continue in this research study. This study is for partners in which one person has HIV and the other does not. HIV is the virus that causes AIDS. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, and what would be expected of you if you agree to be in the study. This study is sponsored by the Bill and Melinda Gates Foundation and the University of Washington, which are located in Seattle, Washington, USA.

If you decide to participate in the research study, you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

PURPOSE OF THE STUDY

This research is studying two medications that suppress the HIV virus. One medication is called tenofovir. The second medication is a combination of tenofovir and another medication called emtricitabine. This combination is known as Truvada®. Recently, the research study you participated in showed that tenofovir and Truvada® can reduce the chances for HIV-uninfected men and women to get the HIV virus from their partner by 62 to 73 percent. This is called pre-exposure prophylaxis. The study also learned that tenofovir and Truvada® are safe (meaning that they do not produce significant health problems in persons who take them) when taken by HIV-uninfected men and women. In that study, you did not receive tenofovir or Truvada® but instead received placebo medication. Because you received placebo, you are now being offered to enter a new phase of the study in which you will receive 12 months of tenofovir or Truvada®. The purpose of this new phase of the study is to find out more information about tenofovir and Truvada® when used every day by HIV-uninfected men and women. All couples who received placebo, approximately 1600 in total, are being offered this new phase of the study.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that we will discuss with you. Once you understand the study, and if you agree to take part, we will ask you to sign your name or

Partners PrEP Protocol
Version 3.0, 12 October 2007
Page 8 of 36
Protocol Addendum #8
28 July 2011
Before you learn about the study procedures, it is important that you know the following:

- You do not have to be in this phase of the study if you do not want to join.

- You may decide not to take part in this phase of the study, or to withdraw from the study at any time, without losing the benefits of your or your partner’s routine medical care.

- If you decide not to take part in this phase of the study, you can still join another research study later, if one is available and you qualify.

**STUDY MEDICATION**

Tenofovir at a dose of 300 mg once per day and the combination of emtricitabine at 200 mg once per day and tenofovir at 300 mg once per day (known as Truvada®) are medications approved by the United States Food and Drug Administration for the treatment of HIV infection. In this study, we will evaluate if taking tenofovir or Truvada® every day prevents men and women who are not infected with HIV from getting the HIV virus.

Tenofovir and Truvada® were chosen for this study for several reasons:

- We know that they have low levels of side effects compared to other medications used to treat HIV.

- They can be taken once a day.

- HIV does not easily become resistant to tenofovir or Truvada®.

- Studies done in animals have shown that tenofovir and Truvada® can sometimes prevent infection with a virus similar to HIV.

Tenofovir and Truvada® have not been approved by the US FDA for the prevention of HIV. Gilead Sciences is the pharmaceutical company that produces tenofovir and Truvada®, and Gilead Sciences will supply the medications for this study.

**STUDY GROUPS**

In this phase of the research study, you will be assigned to one of two study groups – one group will receive tenofovir and one group will receive Truvada®. In this phase of the study, no group will receive placebo. You will take two pills of study medication each day.

The two pills that you will take each day will look different. Everyone in the study will receive pills that look the same as the pills you will receive. You will get the same type of study medication throughout the study. A computer program will randomly decide which type of study medication you receive. You will have an equal chance of being assigned to the tenofovir group or the Truvada® group. Neither you nor any of the research staff in this clinic will know who is taking tenofovir and who is taking Truvada®. You cannot be told which group you are in until 6-24 months after the end of the study.
Both groups are very important to this study. Couples in both groups will have the same study visits. All couples will get condoms and counseling on how to avoid HIV and other infections passed during sex.

It is very important that you do not share the study medication with anyone, including your partner. If the drugs that are used in this study are used alone in someone who has HIV, the HIV virus can become resistant to these medications. If you share the study medications with your partner, the HIV virus your partner has could become resistant to these medications, which could limit your partner’s treatment options for the future.

STUDY PROCEDURES

If you decide to take part in the study, your first visit will continue today, after you read, discuss, and sign or make your mark on this form. At today’s visit, several things will happen:

- The study staff will ask you questions about your medical history and your sexual practices
- You will undergo a physical exam.
- We will ask your permission to obtain a blood sample [up to 38 ml / less than 3 tablespoons]. We will obtain the sample using a sterile instrument (needle) inserted into a vein in your arm. The blood sample will be used for tests at the clinic and by study researchers at the University of Washington.
  - Some of the blood will be used to test for HIV. When we do HIV testing for this study, we first do a test that gives results in about 20 minutes. You will get the result of that test when it is available, on the same day you give blood and have the test. If the test shows that you may have HIV infection, we will do another different test to confirm this result. This test takes about 1-2 weeks, so you will have to come back here at that time to get the results. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive but also not negative. In that case, we will do more tests until we know the result for sure. You must receive your HIV test results to stay in the study. If the HIV test is positive today, you will not be able to continue in the study.
  - Some of the blood will be used to confirm the results of the HIV tests that we do here and will look for other genetic, infectious, and immune factors that affect the chances of becoming HIV-infected.
- For women, you will be asked to provide a urine sample to be used for a pregnancy test. You are not eligible for this phase of the study if you are pregnant.
- You will then be randomly assigned to receive study medication.
  - The study pharmacy staff will give you two bottles of study medication pills. You should take one pill from each bottle, once every day, by mouth, until your
next scheduled visit. The study staff will give you information on the possible side effects and will teach you methods to not forget to take the pills every day.

After today’s visit, you will have scheduled study follow-up visits every month. You will take the study medications every day. Your partner will also have regular follow-up visits scheduled, for every 3 months. During the months when you and your partner both have a visit, you should come to the clinic together, for your convenience and so you can have counseling together as a couple. If that is not possible, you can come for your visits by yourself if you wish. Each visit will take about 60 minutes.

At each of your monthly visits you will:

- Be asked questions about your health and medical history, including whether you have any clinical symptoms or side effects from the study drug.

- Be asked questions about your sexual practices.

- Talk with study staff about ways to avoid HIV and other infections passed during sex. We encourage you to have this counseling with your partner, but you can have it by yourself if you wish.

- Talk with study staff about the HIV test and give blood [up to 4 ml / 1/3 of a tablespoon or less], either from a finger stick and/or from your arm, for the test.
  - If the HIV test in the clinic is positive or not clear positive or negative, you will stop study medication until more tests are done to know for sure. If further testing demonstrates that you are HIV negative, you will be allowed to resume study medication.
  - Some of the blood may be used to confirm the results of the HIV tests that we do here and will look for other genetic, infectious, and immune factors that affect the chances of becoming HIV-infected.

- Get condoms.

- Get medical care or referrals for medical care and other services if you need them.

- Give updated information on where you live and how to keep in contact with you. The study staff will use this information to remind you of scheduled visits. If you miss a visit, the study staff will try to contact you by [describe site-specific methods]. 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.

- Receive study medication. At your first monthly visit you will return the bottles of study medication pills that were dispensed at your Enrollment Visit. You will be asked to answer questions about the pills you took during the previous month and be counseled about methods for not forgetting to take your pills during the following month. The
pharmacy staff will provide you with new bottles with pills for the following month. This process will be repeated each month.

- You will be counseled about the importance of not sharing the study medication with anyone, including your partner.

- Women will be asked to provide a urine sample. This will be used for a pregnancy test.

Some of your monthly visits may take place at your home. The study staff will talk with you about whether this will be an option.

**At the first month and every 3 months:**

- You will undergo a physical exam.

- Give more blood [up to a total of 46.5 ml / about 3 tablespoons or 91.5 ml / less than 7 tablespoons for sites doing PBMC collections]. This will be used:

  o For an HIV test, the same as at each monthly visit.

  o To test the function of your kidneys, your liver, your pancreas, and your blood counts. This is to check the safety of the study drug. The study staff will provide you with the results of these laboratory tests. If at any time you have a result of a test that is abnormal, we will contact you so that you will know. If you have an abnormal result of a laboratory, you will be evaluated at the study clinic and appropriate treatment will be provided to you. If you need treatment that is not available at the study clinic, the staff will refer you for additional care.

  o Some of the blood will be sent to study researchers at the University of Washington to look for genetic, infectious and immune factors that affect the chances of becoming HIV-infected.

**At 12 months:**

- You will undergo a genital exam to look for sexually transmitted infections.

  o For women, the study staff will collect swab samples during the genital exam from your genital area to test for sexually transmitted infections. These will be collected using soft-tipped, sterile swabs. A Pap smear may also be performed to look for pre-cancerous or cancer cells from the cervix.

  o For men, you will be asked to provide a urine sample that will be tested for sexually transmitted diseases by researchers at the University of Washington.

- A blood sample will also be checked for syphilis.
At any time in the study:

- If you or the study staff think you may be having any health problems, you may need to undergo a physical exam and may need to provide blood or other samples for testing.

- If you are having health problems that may be due to a sexually transmitted infection, you will have a genital exam and receive medicine to treat the infections as needed.

- You can have extra counseling and testing for HIV if needed between scheduled visits, either with your partner or by yourself.

- If you and your partner end your relationship before your last scheduled study visit, we will ask you to stay in the study as originally scheduled and continue the study medication.

- If you decide to leave the study before your last scheduled study visit, we will ask you to have a final study visit with all the exams and tests listed above.

PREGNANCY (women only)

Although infants born to HIV-infected women taking tenofovir or Truvada® during pregnancy have not been found to have a greater chance of having birth defects, we do not know for sure if these drugs are safe to the fetus in women who become pregnant.

During this study, you will receive counseling at each visit about the potential that you may become pregnant. You will also receive counseling about your options for contraception. You can receive some forms of contraception from the study clinic. You may choose whether or not you want to receive contraception.

If you become pregnant at any time during this phase of the study, your study medication will be stopped and the study staff will counsel you. You will continue to be followed in the research clinic. You will also receive, or be referred for, antenatal care. If you do not carry the pregnancy successfully to term, you will be allowed to resume study drug once you are no longer pregnant. If you become pregnant and give birth, we will ask that you bring the infant to the clinic within the first month after birth and then every 3 months for the first year. At each visit, we will measure the weight and growth of the child. At two of those visits, we will ask to obtain a small blood sample from the child, to check the function of the kidneys.

If you are breastfeeding, you will not be allowed to enroll in the study or take the study medication. If you begin breastfeeding during the study, your study medication will be stopped. You will continue to be followed in the research clinic. You will be allowed to resume the study medication when you are no longer breastfeeding.

It will be important that we monitor infants whose mothers have taken the study medications during early pregnancy, so we can learn if taking tenofovir or Truvada® during pregnancy is safe.
IF YOU BECOME HIV INFECTED

During the course of the study we will provide you with condoms and other materials to help prevent you from getting HIV. However it is possible that you can become HIV infected.

If you have a positive HIV test during the study:

- The study staff will talk with you about this test result and what this means for you.
- You will stop the study medication.
- The staff will ask your permission to obtain a second blood test [up to 95.5 ml / less than 7 tablespoons] that will be used to confirm the initial positive test.
  - Some of the blood will be used to test the function of your kidneys, your liver, your pancreas, and your blood counts.
  - Some of the blood will be used to test for syphilis.
  - Some of the blood will be used to perform a CD4 count, a measure of your immune function.
  - Some of the blood will be sent to study researchers at the University of Washington to look for genetic, infectious and immune factors that affect the chances of becoming HIV-infected.
- You will undergo a physical exam, including a genital exam to look for sexually transmitted infections.
  - For women, the study staff will collect swab samples during the genital exam from your genital area to test for sexually transmitted infections. These will be collected using soft-tipped, sterile swabs.
  - For women, an additional swab will be obtained from your genital area. This will be sent to study researchers at the University of Washington to test for HIV in the genital area.
- You will be asked to provide a urine sample.
  - For men, the urine sample will be tested for sexually transmitted diseases by researchers at the University of Washington.
  - For women, the urine sample will be used for a pregnancy test.
- You will then be asked to return for another visit after about 2 weeks. At that visit, results from the confirmatory HIV test will be available. If those results confirm that you have become infected with HIV, we will ask that you continue follow-up at this clinic every 3 months until the study is finished, or for at least 12 months.
At each of the visits after HIV infection is confirmed:

- You will undergo a physical examination.
- You will be asked to provide a blood sample [17 – 80.5 ml / under 6 tablespoons].
  - Some of the blood will be sent to study researchers at the University of Washington to look for genetics, infectious and immune factors that affect the chances of becoming HIV-infected. Tests will also be done to look for resistance to HIV medications and other characteristics of early HIV infection. If we find that you have laboratory results that might be useful to your medical care, those results will be provided to you and your doctor.
  - Some of the blood will be used to perform a CD4 count, a measure of your immune system.
- For women, we will perform a genital exam and obtain a swab from your genital area. These will be sent to study researchers at the University of Washington to test for HIV in the genital area.
- For men, we will ask you to provide a semen sample once, 3 months or later after HIV infection is detected.
- We will also request samples from your partner to help us understand HIV transmission from one person to another.

**IMPORTANCE OF NOT SHARING THE STUDY MEDICATION**

In this research study, you will take study medication each day. Your partner will not take any study medication. Your partner will come for follow-up visits every three months. At your partner’s visits to the research clinic, the study staff will ask your partner questions about his/her health and will collect samples of his/her blood and genital secretions. These samples will be used to investigate whether there are factors that either increase or decrease the chances that HIV is transmitted from one person to another. They will also be used to determine whether some factors about the HIV infection your partner has increase or decrease the chance that the study medication you are taking works to prevent you from acquiring HIV infection.

**It is very important that you do not share your study medication with your partner or with anyone else.** Although tenofovir and Truvada® are used to treat HIV infection, they are only effective for treating people who already have HIV infection if they are used in combination with other medications. If your partner is exposed to tenofovir or Truvada®, his/her HIV could become resistant to tenofovir, emtricitabine (one of the components of Truvada®), or lamivudine (a medication similar to emtricitabine). Resistance to these antiretroviral medications reduce the effectiveness of HIV treatment for your partner and may limit your partner’s HIV treatment options. If your partner requires HIV treatment during the course of this research study, we will refer him/her for appropriate treatment or, if treatment is not available elsewhere, provide treatment at the research clinic.
SPECIMEN STORAGE AND USE OF SAMPLES AND DATA FOR FUTURE STUDIES

We would like to save data from this study and samples of your blood, urine, and genital secretions at [local site] and at the University of Washington for future research by us and by other researchers. We will use these samples only for research related to HIV, HIV-related diseases, and sexually-transmitted infections. This will include testing for genes which may affect whether a person is more or less likely to get these infections, have more severe infection, or how people respond to the medications used in this study. Gene studies may test for a specific gene to understand these effects or help researchers find new genes that may have these effects. This research is experimental and these tests are not useful for your clinical care. Before your samples leave the clinic, they will be assigned a code and your name will not be on them. Your name will be linked to the code only at this clinic and only for five years after the study is completed. After that time, the link between your name and the code on your data and samples will be destroyed. An Institutional Review Board or Independent Ethics Committee, which watches over the safety and rights of research participants, must approve any future research studies using your data and samples. If you agree to store your samples, we will keep them for as long as sample remains that can be used for future research. If you do not want to have your samples saved for future research, you can still be in this study and your samples will be destroyed once testing for this study is completed. If you agree to store your samples now, but change your mind before the end of the study, let the study staff know and we will make sure that your samples do not get stored for future research. We will not sell your data or samples. Tests done on your samples may lead to a new invention or discovery. We have no plans to share any money or other benefits resulting from this invention or discovery with you.

RISKS AND/OR DISCOMFORTS

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise where the needle goes into your arm. You may feel discomfort during genital exams.

You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against HIV and other infections passed during sex, and your HIV test results. You may become worried or anxious while waiting for your test results. If you become infected with HIV, knowing this could make you worried or anxious. Talking about HIV and finding out your test results could cause problems between you and your partner. Trained counselors will help you and your partner deal with any feelings or questions you may have.

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

Risks potentially related to the study medication

You may have symptoms or adverse effects while participating in the study. These symptoms
or adverse effects may be due to participation in the study or due to illnesses that have no relation to the study, like a cold or flu. All persons who participate in this study will be watched carefully to monitor their health. The medical team in charge of your health care may give you medicines to treat the adverse effects. Many adverse effects disappear as soon after you stop taking the study pills. In some cases, the adverse effects can be serious, long-lasting, or may never disappear.

You should tell the doctor of the study clinic about any symptoms that you feel while you are participating in the study. If you have any symptoms, especially frequent vomiting, swollen feet, or abnormal shortness of breath, you should visit the clinic immediately and not wait for your next scheduled visit. You will be given a telephone number where the study doctors will be available 24 hours a day, 7 days a week. You should call them if you experience any serious symptoms.

The adverse effects that can occur in a small proportion of people taking tenofovir or Truvada® are well known because the medication has been used by many people. The following adverse events have been associated with taking tenofovir: fever, achiness and a general feeling of illness associated with allergic reaction. The following adverse effects have been associated with emtricitabine (one of the two medicines contained in Truvada®): headache, tiredness, difficulty sleeping, unusual dreams, skin darkening (palms and/or soles of the feet), increased cough, runny nose and increased triglycerides in the blood (a substance derived from the metabolism of fat in your body).

Some mild adverse effects are expected to occur in up to 1 in 10 persons who take tenofovir or Truvada®. Other adverse effects are more serious, but are expected to occur in less than 1 in 100 persons who take tenofovir or Truvada®.

**Occasional adverse effects (expected to occur in 1-10% of the participants in this study)**

- Mild problems of kidney function that are only detected by laboratory tests (changes in creatinine and phosphate in the blood that do not cause you to feel different in any way)
- Lack of energy/general body weakness
- Upset stomach, vomiting, soft or liquid stools
- Abdominal pain
- More intestinal gas than normal
- Dizziness

**Rare adverse effects (expected to occur in less than 1% of the participants in this study)**

These adverse effects have been rarely observed in persons with HIV infection who are receiving tenofovir or Truvada®, plus other medications. It is not known whether these adverse effects will also occur in people like you, who do not have HIV infection and who are not taking other drugs for the treatment of HIV.

- Rash
- Liver function problems
- Serious kidney damage or failure
- Low phosphate levels (which is a chemical in the blood) or protein or sugar in the urine
- Inflammation or swelling and possible damage to the pancreas. The pancreas is an organ located in the abdomen that produces insulin and substances that aid in digestion.
Allergic reaction

Small changes in the mineral density of bones were observed in studies of HIV-infected people who were given tenofovir or Truvada®, plus other drugs used for HIV treatment. The changes in the mineral density of the bones did not cause any fractures, or other problems that bothered the patients. It is unknown if tenofovir or Truvada® can decrease the strength of bones in HIV-uninfected persons like you.

Lactic acidosis has occurred in HIV-infected persons taking tenofovir or Truvada®, in combination with other drugs. Lactic acidosis is a condition that can produce shortness of breath, nausea, and liver failure. This is a serious adverse effect of some treatments used for HIV infection.

You should call or come to the study clinic if you have unexplained urination, weight loss, cramps, muscle pain, dizziness, excessive fatigue, nausea, vomiting, or shortness of breath. If you have these symptoms, or any other symptoms that concern you, the study staff will evaluate your symptoms and determine whether you should stop your study pills.

Tenofovir and Truvada® have been studied in many people so the possible adverse effects are well known. Still, it is possible that tenofovir or Truvada® may have rare adverse effects that are not yet recognized. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. You should notify the study doctors if you feel that the study medication is causing you to have any symptoms.

Other medications

Many medications can be taken in parallel with the study medication used in this research study. However, some medications should not be taken while you are taking the study medication. If you take other medications during your participation in the study, there is a chance that we will need to obtain additional blood, and you may need to undergo medical evaluations and laboratory tests. While taking some medications, you will need to temporarily stop taking the study medication. If so, you would continue to participate in the study visits in order to monitor your health. In addition, you should tell the team of researchers if you plan to enroll in any other clinical trial while you are participating in this study. When you visit the study clinic, we will provide you with a list of medications that you should not take while you are participating in this study, and if you authorize us to, we will send this information to any doctor that you consider necessary to be informed. Please ask your study doctor about these medications if you have any questions.

Unknown risks

The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about continuing to participate in the study.

Risk of acquiring HIV infection and drug resistance

You may become infected with HIV during this study from your HIV-infected partner or from other sexual partners you may have. It is very important to use all the known risk reduction strategies to prevent the acquisition of HIV, like using condoms for all sexual relations and keeping your number of sexual partners low.
You will be receiving tenofovir or Truvada® and if you become infected with HIV during the study, you could become infected with a strain of the HIV virus that could be resistant to tenofovir, emtricitabine (one of the components of Truvada®), or lamivudine (a medication similar to emtricitabine). These three medications are used for HIV treatment. Resistance to antiretroviral medications may make effective HIV treatment more difficult and may limit your treatment options. Resistance to antiretroviral medications can affect the response of the virus in such a way that the virus may become resistant to tenofovir, emtricitabine, or to both. You will be able to discuss treatment and the generation of resistance to medications with the study doctor.

For more information about risks of this study, ask your study doctor.

**BENEFITS**

You may get no direct benefit from being in this study but you will be receiving either tenofovir or Truvada®, which we now know help keep HIV-uninfected individuals who have HIV-infected partners from getting HIV. Study staff will remind you of the importance of using condoms to protect against HIV.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV.

You will get counseling and testing for HIV. You will get free condoms. If you or your partner have health problems that may be due to infections passed during sex, you will get medicine to treat them, if needed. For other health problems, the study staff will give you care and treatment that is available at the clinic. For care and treatment that is not available at the clinic, study staff will tell you about other places where care and treatment may be available.

Your partner will receive care and support related to his/her HIV infection while this study is ongoing. This care will be either be provided through a referral clinic or, if not otherwise available, will be paid for by the study and will be provided [by the study staff or by the xxx organization]. Medications used to treat HIV will be given per national guidelines.

If you become infected with HIV while in this study, you will be offered counseling and clinical services for HIV while the study is ongoing. After the study is over, the study staff will no longer be able to provide this care to you or your partner. You and your partner will be referred to other HIV care programs that are available to you.

**NEW FINDINGS**

You will be told any new information learned during this study that is important for your health or might cause you to change your mind about staying in the study. You will be told when the results of the study may be available, and how to learn about them.

**COSTS TO YOU**

There is no cost to you for being in this study. Treatments available to you from the study will be given free of charge.
REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY

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

- The study is stopped or canceled.
- The study staff feel that staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.

ALTERNATIVES TO PARTICIPATION

[Sites to include/amend the following if applicable: There may be other studies going on here or in the community that you or your partner 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.]

REIMBURSEMENT

[Sites to insert information about local incentives:] You will receive money for your transportation costs, time and effort at each scheduled study visit. You also will receive payment for the costs of travel due to your visits.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any sample from you or information about you will be identified only by code. The link between your name and code will be kept in a secure location at the clinic only. We will not discuss any information about you with your partner unless you give written permission, and will encourage you to be present during the discussion. Any publication of this study will not use your name or identify you personally.

Your study records may be reviewed by study staff and representatives of:

- the University of Washington, including study monitors
- the Bill and Melinda Gates Foundation
- the United States Food and Drug Administration
- [insert applicable local authorities, e.g., Ministry of Health]
- [insert names of applicable IRBs/ECs]

A description of this clinical trial will be available on http://www.clinical.trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will
include a summary of the results. You can search this Web site at any time

RESEARCH-RELATED INJURY

[Sites to amend this sample text as needed, and/or specify institutional policy]

The study staff will monitor your health and the health of your partner while you are in this study.

You will have a study visit every month. Your partner will have a visit every 3 months. If you or your partner have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions].

If you are injured from participating in this study, you will be offered care at the study clinic, free of charge. It is important that you tell the members of the team of researchers at this clinic if you feel that you have been injured because of taking part in this study.

There is not a program of monetary compensation through this institution. If you require medical care that the study clinic cannot provide, the study doctors will refer you to the appropriate services or organizations that can provide care for the injury. If the study doctors determine that the injury is a consequence of your participation in the study, study funds will be used to pay for the medical care that you need.

You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

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

STATEMENT OF CONSENT AND SIGNATURES

I have read this form or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the study is voluntary. I understand that if I decide to join the study I may withdraw at any time. By signing this form I do not give up any rights that I have as a research participant.

[Insert signature blocks as required by the local IRB/EC:]

<table>
<thead>
<tr>
<th>Participant Name</th>
<th>Participant Signature/Thumbprint</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP Protocol</td>
<td>Page 21 of 36</td>
<td>Protocol Addendum #8</td>
</tr>
<tr>
<td>Version 3.0, 12 October 2007</td>
<td></td>
<td>28 July 2011</td>
</tr>
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</table>
CONSENT FOR OFF-SITE VISITS

It may be necessary for the members of the team of researchers of this clinic to visit you at your home or another location or to contact you via telephone as part of the study. Some of the scheduled study visits may take place at your home. In addition, if you have missed visits, study staff may visit you at your home. The study personnel will explain in greater detail the requirements to do these visits (like the conditions of the place, the type of visit and the duration of it) and the procedures to maintain your information in a confidential manner. However it is important that you know that home visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

To do this we will need you to authorize us to do so, please read carefully the following statement and initial and date one option. Choosing not to be visited outside of the study clinic will not affect your participation in this study.

__________        I DO agree to be contacted or visited at a site other than the study clinic

__________        I DO NOT agree to be contacted or visited at a site other than the study clinic

[Insert signature blocks as required by the local IRB/EC:]

Participant Name    Participant Signature/Thumbprint    Date
(print)

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

Witness Name    Witness Signature    Date
(print)
SPECIMEN STORAGE AND USE OF YOUR DATA AND SAMPLES FOR FUTURE STUDIES:

Please initial and date one option:

___________    I DO agree to store my data and samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

___________    I DO NOT agree to store my data and samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

[Insert signature blocks as required by the local IRB/EC:]

<table>
<thead>
<tr>
<th>Participant Name (print)</th>
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<tbody>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature</td>
<td>Date</td>
</tr>
<tr>
<td>Witness Name (print)</td>
<td>Witness Signature</td>
<td>Date</td>
</tr>
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</table>
## Study Visits and Procedures for Index (HIV-1 Infected) Participants in the Placebo Conversion Phase to Active PrEP

### ADMINISTRATIVE, BEHAVIORAL AND REGULATORY PROCEDURES

<table>
<thead>
<tr>
<th>Procedure</th>
<th>E</th>
<th>M3</th>
<th>M6</th>
<th>M9</th>
<th>M12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apply eligibility criteria</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Update locator information</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Collect behavioral information</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Provide HIV-1 pre and post-test counseling, including couples counseling</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Contraception counseling and provision/referral</td>
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### CLINICAL PROCEDURES

<table>
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<tr>
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<th>M9</th>
<th>M12</th>
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</thead>
<tbody>
<tr>
<td>Administer medical history</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Perform physical exam, including genital exam for STI assessment at 12 months or when clinically indicated&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Provide STI treatment</td>
<td>[X]</td>
<td>[X]</td>
<td>[X]</td>
<td>[X]</td>
<td>[X]</td>
</tr>
<tr>
<td>Collect urine specimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Collect genital swab specimens (women only)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collect blood specimen</td>
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<tr>
<td>Provide test results</td>
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<tr>
<td>Provide counseling about not sharing study drug</td>
<td>X</td>
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### LABORATORY PROCEDURES

#### Local Lab

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<thead>
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<th>M6</th>
<th>M9</th>
<th>M12</th>
</tr>
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<tr>
<td>Syphilis serology</td>
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<tr>
<td>Endocervical pap smear&lt;sup&gt;b&lt;/sup&gt; (women only)</td>
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<tr>
<td>CD4+ cell count&lt;sup&gt;c&lt;/sup&gt;</td>
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#### Central Lab / Specimen Repository<sup>d</sup>

<table>
<thead>
<tr>
<th>Procedure</th>
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<td>Plasma archive</td>
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<tr>
<td>Whole blood &amp; blood spot archives</td>
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<td>Urine archive</td>
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<td>Endocervical swab archive (women only), for HIV-1 PCR</td>
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<td>Endocervical swab for gonorrhea, chlamydia &amp; trichomonas PCR (women only)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Vaginal swab and slide for bacterial vaginosis evaluation (women only)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Urine archive for gonorrhea, Chlamydia and trichomonas PCR (men only)&lt;sup&gt;a&lt;/sup&gt;</td>
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### BLOOD VOLUME (mL)<sup>e</sup>

| E | 21 | 0  | 21 | 0  | 29.5 |
At 12 months, STI screening (syphilis serology and for women, an endocervical swab and a Pap smear and for men, a urine sample) will be performed, in addition to usual procedures. If clinically indicated, STI screening will be performed at any study visit.

Pap smears will be performed at sites where Pap smears are the standard of care and where cytopathology and referral for dysplasia management are available.

Every 6 months, CD4 determination will be completed.

Archived samples for the Central Lab will include:

1) Serum and plasma for eligibility and endpoint confirmation, and for secondary and tertiary study objectives (including study drug levels and HIV-1 genotypic and phenotypic resistance testing among a subset of participants).

2) Samples for STI and BV (for women) testing will be performed from at 12 months to assess the prevalence of genital tract infections in participants.

3) Endocervical swabs from HIV-1 infected female participants will be obtained at 12 months.

4) Whole blood and blood spot samples for secondary and tertiary study objectives. As detailed in the protocol, participants will consent to storage of samples for future research and IRB approval will be obtained prior to additional testing.

Blood volumes are maximums.

[] = if clinically indicated, based on participant history
Appendix XIX TEMPLATE CONSENT: Enrollment Consent for Index (HIV-1 Infected) Participants in the Placebo Conversion Phase to Active PrEP

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples
Version 3.0
12 October 2007

Consent for 12 months of active PrEP for the placebo arm

PRINCIPAL INVESTIGATOR: [insert name]
[insert physical address and relevant contact info]

INFORMED CONSENT

We are asking you to volunteer to continue in this research study. This study is for partners in which one person has HIV and the other does not. HIV is the virus that causes AIDS. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, and what would be expected of you if you agree to be in the study. This study is sponsored by the Bill and Melinda Gates Foundation and the University of Washington, which are located in Seattle, Washington, USA.

If you decide to participate in the research study, you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

PURPOSE OF THE STUDY

This research is studying two medications that suppress the HIV virus. One medication is called tenofovir. The second medication is a combination of tenofovir and another medication called emtricitabine. This combination is known as Truvada®. Recently, the research study you participated in showed that tenofovir and Truvada® can reduce the chances for HIV-uninfected men and women to get the HIV virus from their partner. This is called pre-exposure prophylaxis. The study also learned that tenofovir and Truvada® are safe (meaning that they do not produce significant health problems in persons who take them) when taken by HIV-uninfected men and women. In that study, your partner did not receive tenofovir or Truvada® but instead received placebo medication. Because your partner received placebo, you are now being offered to enter a new phase of the study in which your partner will receive 12 months of tenofovir or Truvada®. The purpose of this new phase of the study is to find out more information about tenofovir or Truvada® when used every day by HIV-uninfected men and women. All couples who received placebo, approximately 1600 in total, are being offered this new phase of the study.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that we will discuss with you. Once you understand the study, and if you agree to take part, we will ask you to sign your name or make your mark on this form. We will offer you a copy to keep.
Before you learn about the study procedures, it is important that you know the following:

- You do not have to be in this study if you do not want to join.
- You may decide not to take part in the study, or to withdraw from the study at any time, without losing the benefits of your or your partner’s routine medical care.
- If you decide not to take part in the study, you can still join another research study later, if one is available and you qualify.

STUDY GROUPS

In this research study, your partner will be assigned to one of two study groups – one group will receive tenofovir and one group will receive Truvada. No one in this phase of the study will receive placebo. Your partner will take two pills of study medication each day.

A computer program will randomly decide which type of study medication your partner receives. Your partner will have an equal chance of being assigned to tenofovir or Truvada. Neither you, your partner, nor any of the research staff in this clinic will know if your partner is taking tenofovir or Truvada.

Both groups are very important to this study. Couples in both groups will have the same study visits. All couples will get condoms and counseling on how to avoid HIV and other infections passed during sex.

The only known way to protect your partner against getting HIV during sex is to use a condom every time you and your partner have sex.

IMPORTANCE OF NOT SHARING THE STUDY MEDICATION

In this research study, your partner will take study medication each day. You will not take any study medication. At your visits to the research clinic, the study staff will ask you questions about your health and your sexual practices and will collect samples of your blood and genital secretions. These samples will be used to investigate whether there are factors that either increase or decrease the chances that HIV is transmitted from one person to another. They will also be used to determine whether some factors increase or decrease the chance that the study medication your partner is taking works to prevent your partner from acquiring HIV infection.

It is very important that you do not share your partner’s study medication. Although tenofovir and Truvada are used to treat HIV infection, they are only effective for treating HIV infection if they are used in combination with other medications used for treating HIV infection. If you take your partner’s study medication, you may be exposed to tenofovir or Truvada. If you are exposed to tenofovir or Truvada, your HIV could become resistant to tenofovir, emtricitabine (one of the components of Truvada), or lamivudine (a medication similar to emtricitabine). Resistance to these antiretroviral medications may reduce how well future HIV treatment will work for you.

During this study, we will test your blood every 6 months to monitor your immune function. If
those tests show that you require HIV treatment during the course of this research study, we will either provide treatment at the research clinic or refer you for appropriate treatment.

STUDY PROCEDURES

If you decide to take part in the study, your first visit will continue today, after you read, discuss, and sign or make your mark on this form. At today’s visit, several things will happen:

- The study staff will ask you questions about your medical history and your sexual practices
- You will undergo a physical exam.
- We will ask your permission to obtain a blood sample [up to 21 ml / less than 2 tablespoons]. We will obtain the sample using a sterile instrument (needle) inserted into a vein in your arm. The blood sample will be used for tests at the clinic and by study researchers at the University of Washington.
  - Some of the blood will be used by researchers at the University of Washington to confirm the results of the HIV tests that we do here, to measure the levels of HIV in your blood, and to look for other genetic, infectious, and immune factors that affect the chances of transmitting HIV to your partner.

After today’s visit, you will have scheduled study follow-up every 3 months. Your partner will have scheduled follow-up every month. During the months when you and your partner both have a visit, you should come to the clinic together, for your convenience and so you can have counseling together as a couple. If that is not possible, you can come for your visits by yourself if you wish. Each visit will take about 60 minutes. You are also encouraged to come to your partner’s monthly visits with your partner.

At each of your 3-monthly visits you will:

- Be asked questions about your health and medical history.
- Be asked questions about your sexual practices.
- Talk with study staff about ways to avoid HIV and other infections passed during sex. We encourage you to have this counseling with your partner, but you can have it by yourself if you wish.
- Get condoms.
- Get medical care or referrals for medical care and other services if you need them.
- Give updated information on where you live and how to keep in contact with you. The study staff 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]. 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.

**Every 3 months:**

- You will undergo a physical exam.

**Every 6 months:**

- We will ask your permission to obtain a blood sample [up to 29.5 ml / less than 2 tablespoons]. We will obtain the sample using a sterile instrument (needle) inserted into a vein in your arm. The blood sample will be used for tests at the clinic and by study researchers at the University of Washington.
  
  o Some of the blood sample will be used for a test called a CD4 cell count. The CD4 count is a measure of how well your immune system is functioning. The lower the CD4 count in persons who are HIV-infected, the more at risk they are for having problems from AIDS.
  
  o Some of the blood will be used by researchers at the University of Washington to confirm the results of the HIV tests that we do here, to measure the levels of HIV in your blood, and to look for other genetic, infectious, and immune factors that affect the chances of transmitting HIV to your partner.

**At 12 months:**

- You will undergo testing to look for sexually transmitted infections.
  
  o This will include a blood test for syphilis.
  
  o For women, the study staff will collect swab samples during a genital exam from your genital area to test for sexually transmitted infections. These will be collected using soft-tipped, sterile swabs. A Pap smear may also be performed.
  
  o For women, an additional swab will be obtained from your genital area. This will be sent to study researchers at the University of Washington to test for HIV in the genital area.
  
  o For men, you will be asked to provide a urine sample that will be used by researchers at the University of Washington to test for sexually transmitted infections.

**At any time in the study:**

- If you or the study staff think you may be pregnant, you will give urine for a pregnancy test (for women only).
• If you become pregnant, you can still participate in the study. You will be counseled about HIV and pregnancy. You will receive, or be referred for antenatal care for pregnant women with HIV (for women only).

• If you or the study staff think you may be having any health problems, the study staff can perform a physical examination and may offer additional testing and treatment, or referral for testing and treatment.

• If you are having health problems that may be due to a sexually transmitted infection, you will have a genital exam and receive medicine to treat the infections as needed.

• You can have extra counseling about HIV if needed between scheduled visits, either with your partner or by yourself.

• If you and your partner end your relationship before your last scheduled study visit, we will ask you to stay in the study as originally scheduled.

• If you decide to leave the study before your last scheduled study visit, we will ask you to have a final study visit with all the exams and tests listed above.

IF YOUR PARTNER BECOMES HIV INFECTED

During the course of the study we will provide you with condoms and other materials to help prevent transmission of HIV to your partner. However it is possible that your partner can become HIV infected.

If your partner has a positive HIV test during the study, the study staff will talk with your partner, and with you, about this test result. We will ask that you provide one set of blood and genital samples to help us understand HIV transmission from one person to another. If your partner has a positive HIV test on a day at which you are not attending the research clinic, we will ask you, either directly or via your partner, to come back to the clinic within a couple of weeks to provide these samples. The samples will include:

• A blood sample [up to 21 ml / less than 2 tablespoons]. We will obtain the sample using a sterile instrument (needle) inserted into a vein in your arm. The blood sample will be used for tests at the clinic and by study researchers at the University of Washington.
  
  o Some of the blood sample will be used for a CD4 cell count test.
  
  o Some of the blood will be used by researchers at the University of Washington to measure the levels of HIV in your blood and to look for other genetic, infectious, and immune factors that affect the chances of transmitting HIV from one person to another.

• For women, you will undergo a genital exam, during which a swab will be obtained from your genital area. This will be sent to study researchers at the University of Washington to test for HIV in the genital area.

• For men, you will be asked to give a semen sample that will be sent to the University of Washington for tests of the HIV that may be in the semen.
After you provide these samples, you will then resume your usual follow-up. Your partner will be asked to continue follow-up every three months, for at least one year, after his/her HIV infection is detected. You are welcome to come to those visits with your partner.

SPECIMEN STORAGE AND USE OF SAMPLES AND DATA FOR FUTURE STUDIES

We would like to save data from this study and samples of your blood, urine, and genital secretions at [local site] and at the University of Washington for future research by us and by other researchers. We will use these samples only for research related to HIV, HIV-related diseases, and sexually-transmitted infections. This will include testing for genes which may affect whether a person is more or less likely to get these infections, have more severe infection, or how people respond to the medications used in this study. Gene studies may test for a specific gene to understand these effects or help researchers find new genes that may have these effects. This research is experimental and these tests are not useful for your clinical care. Before your samples leave the clinic, they will be assigned a code and your name will not be on them. Your name will be linked to the code only at this clinic and only for five years after the study is completed. After that time, the link between your name and the code on your data and samples will be destroyed. An Institutional Review Board or Independent Ethics Committee, which watches over the safety and rights of research participants, must approve any future research studies using your data and samples. If you agree to store your samples, we will keep them for as long as sample remains that can be used for future research. If you do not want to have your samples saved for future research, you can still be in this study and your samples will be destroyed once testing for this study is completed. If you agree to store your samples now, but change your mind before the end of the study, let the study staff know and we will make sure that your samples do not get stored for future research. We will not sell your data or samples. Tests done on your samples may lead to a new invention or discovery. We have no plans to share any money or other benefits resulting from this invention or discovery with you.

RISKS AND/OR DISCOMFORTS

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise where the needle goes into your arm. You may feel discomfort during genital exams.

You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against HIV and other infections passed during sex, and your HIV test results. You may become worried or anxious while waiting for your test results. If you have HIV, knowing this could make you worried or anxious. Talking about HIV and finding out your test results could cause problems between you and your partner. Trained counselors will help you and your partner deal with any feelings or questions you may have.

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

Your partner will receive study medication during this research study. It is important that you do not share that study medication.
**BENEFITS**

You may get no direct benefit from being in this study. Study staff will remind you of the importance of using condoms to protect against HIV.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV.

You will get counseling and testing for HIV. You will get free condoms. If you or your partner have health problems that may be due to infections passed during sex, you will get medicine to treat them, if needed. For other health problems, the study staff will give you care and treatment that is available at the clinic. For care and treatment that is not available at the clinic, study staff will tell you about other places where care and treatment may be available.

You will receive care and support related to your HIV infection while this study is ongoing. This care will be either be provided through a referral clinic or, if not otherwise available, will be paid for by the study and will be provided [by the study staff or by the xxx organization].

**NEW FINDINGS**

You will be told any new information learned during this study that is important for your health or might cause you to change your mind about staying in the study. You will be told when the results of the study may be available, and how to learn about them.

**COSTS TO YOU**

There is no cost to you for being in this study. Treatments available to you from the study will be given free of charge.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY**

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

- The study is stopped or canceled.
- The study staff feel that staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.

**ALTERNATIVES TO PARTICIPATION**
[Sites to include/amend the following if applicable: There may be other studies going on here or in the community that you or your partner 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.]

REIMBURSEMENT

[Sites to insert information about local incentives:] You will receive money for your transportation costs, time and effort at each scheduled study visit. You also will receive payment for the costs of travel due to your visits.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any sample from you or information about you will be identified only by code. The link between your name and code will be kept in a secure location at the clinic only. We will not discuss any information about you with your partner unless you give written permission, and will encourage you to be present during the discussion. Any publication of this study will not use your name or identify you personally.

A description of this clinical trial will be available on http://www.clinical.trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your study records may be reviewed by study staff and representatives of:

- the University of Washington, including study monitors
- the Bill and Melinda Gates Foundation
- the United States Food and Drug Administration
- [insert applicable local authorities, e.g., Ministry of Health]
- [insert names of applicable IRBs/ECs]

RESEARCH-RELATED INJURY

[Sites to amend this sample text as needed, and/or specify institutional policy]

The study staff will monitor your health and the health of your partner while you are in this study.

You will have a study visit every 3 months. Your partner will have a visit every month. If you or your partner have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions].
If you are injured from participating in this study, you will be offered care at the study clinic, free of charge. It is important that you tell the members of team of researchers at this clinic if you feel that you have been injured because of taking part in this study.

There is not a program of monetary compensation through this institution. If you require medical care that the study clinic cannot provide, the study doctors will refer you to the appropriate services or organizations that can provide care for the injury. If the study doctors determine that the injury is a consequence of your participation in the study, study funds will be used to pay for the medical care that you need.

You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

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

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

STATEMENT OF CONSENT AND SIGNATURES

I have read this form or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the study is voluntary. I understand that if I decide to join the study I may withdraw at any time. By signing this form I do not give up any rights that I have as a research participant.

[Insert signature blocks as required by the local IRB/EC:]

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<th>Participant Name (print)</th>
<th>Participant Signature/Thumbprint</th>
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<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature</td>
<td>Date</td>
</tr>
<tr>
<td>Witness Name (print)</td>
<td>Witness Signature</td>
<td>Date</td>
</tr>
</tbody>
</table>

CONSENT FOR OFF-SITE VISITS

It may be necessary for the members of the team of researchers of this clinic to visit you at your home or another location or to contact you via telephone as part of the study. Some of
the scheduled study visits may take place at your home. In addition, if you have missed visits, study staff may visit you at your home. The study personnel will explain in greater detail the requirements to do these visits (like the conditions of the place, the type of visit and the duration of it) and the procedures to maintain your information in a confidential manner. However it is important that you know that this procedure may eventually affect your confidentiality.

To do this we will need you to authorize us to do so, please read carefully the following statement and initial and date one option. Choosing not to be visited outside of the study clinic will not affect your participation in this study.

___________  I DO agree to be contacted or visited at a site other than the study clinic

___________  I DO NOT agree to be contacted or visited at a site other than the study clinic

[Insert signature blocks as required by the local IRB/EC:]

Participant Name (print)  Participant Signature/Thumbprint  Date

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

Witness Name (print)  Witness Signature  Date

SPECIMEN STORAGE AND USE OF YOUR SAMPLES FOR FUTURE STUDIES:

Please initial and date one option:

___________  I DO agree to store my data and samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

___________  I DO NOT agree to store data and my samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

[Insert signature blocks as required by the local IRB/EC:]

Participant Name (print)  Participant Signature/Thumbprint  Date

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

PARTNERS PrEP Protocol
Version 3.0, 12 October 2007

PROTOCOL ADDENDUM

#9

3 November 2011

For study:

Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

IND # 75, 365
Version 3.0
12 October 2007

Purpose of the addendum: Modification of Protocol Team Roster to update personnel and titles at the University of Washington Coordinating Center.

Section 1.1 Coordinating Center

Add:

Mira Emmanuel-Ogier
Research Operations Coordinator
University of Washington

Jennifer Revall
International Research Coordinator
University of Washington

Harald Haugen, MS
Laboratory Manager
University of Washington

Katherine Thomas, MS
Biostatistician
University of Washington

Ting Hong, PhD
Biostatistician
University of Washington

Lara Beshaw, MPH
Clinical Data Manager
University of Washington

Justin Brantley
Data Manager
University of Washington

Downloaded From:  by a Non-Human Traffic (NHT) User  on 01/17/2019
Remove:

Amalia Magaret, PhD  
Co-Investigator, Study Statistician  
University of Washington

Linda Barnes, MHA, RAC  
Program Director  
University of Washington

Margaret Warner-Lubin, CCRA  
Clinical Operations Manager  
University of Washington

Jeanne Conley, RN  
Clinical Trials Manager  
University of Washington

Heena Shah, MPH  
Clinical Trials Coordinator  
University of Washington

Khris Kline  
Laboratory Manager  
University of Washington

Richard Wang, MS  
Statistician  
University of Washington

Replace (title change only):

Jared Baeten, MD, PhD  
Co-Investigator and Medical Director  
University of Washington

With:
Jared Baeten, MD, PhD  
Protocol Co-Chair, Co-Investigator and Medical Director  
University of Washington

Meighan Krows  
Clinical Trials Coordinator  
University of Washington

With:
Meighan Krows  
International Research Coordinator  
University of Washington
Dana Panteleeff  
Laboratory Quality Manager  
University of Washington  

With:  
Dana Panteleeff  
Manager of Research Operations  
University of Washington

*An updated delegation of authority log is kept within International Clinical Research Center at the University of Washington to reflect ongoing changes to the Coordinating Center protocol team. Any future changes to the protocol team roster at the Coordinating Center relevant to protocol Section 1.1 will be updated in that delegation of authority log in lieu of protocol addenda.
Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Statistical Analysis Plan

Deborah Donnell, PhD
Fred Hutchinson Cancer Research Center

Jared Baeten, MD, PhD
University of Washington

Version 2.0
3 February 2011
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Study Objectives and Summary

Protocol title: Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples

Design: Phase III, multi-site, randomized, double-blind, placebo-controlled, three-arm trial.

Population: Heterosexual HIV-1 discordant couples. The HIV-1 uninfected partners may be either male or female, and must not be infected with hepatitis B. At the time of study screening, the HIV-1 infected partner must have a CD4 count ≥250 cells/mm³ and must not otherwise meet national guidelines for initiation of antiretroviral therapy.

Study Size: 4700 HIV-1 seronegative partners within HIV-1 discordant couples (1566 in each treatment arm) are estimated to be needed for this endpoint-driven trial. This number of subjects is intended to achieve 147 events per pairwise comparison.

Study agents: Tenofovir disoproxil fumarate (or TDF, 9-[(R)-2-[[bis[[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate) and emtricitabine (or FTC, 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxatholan-5-yl]cytosine) are reverse transcriptase inhibitors that have been approved for the treatment of HIV-1 infection in humans by the U.S. Food and Drug Administration (FDA). TDF and a fixed-dose co-formulation of FTC/TDF will be used in this study.

Treatment Regimen: The HIV-1 uninfected partner will be assigned at random in a 1:1:1 ratio to one of three study arms: TDF, FTC/TDF, or placebo. Because similarly-appearing placebo tablets are not available for TDF and FTC/TDF, participants will take two tablets daily.

All study medication will be taken orally once daily as follows:
TDF arm: active TDF 300 mg orally once daily + placebo FTC/TDF orally once daily.
FTC/TDF arm: placebo TDF orally once daily + active FTC/TDF 200 mg / 300 mg orally
Placebo arm: placebo TDF orally once daily + placebo FTC/TDF orally once daily.

Active and placebo TDF are indistinguishable, as are active and placebo FTC/TDF. Thus, participants and study staff will be blinded to each participant’s randomization group assignment throughout the study. The TDF and FTC/TDF dosages to be used in this study are in accordance with approved dosages of these medications.

Study Duration: Accrual is estimated to take 30 months, and follow-up will continue for a total of approximately 52 months, with approximately 12 additional months of follow-up to complete follow-up procedures for infants and seroconverters. As an endpoint-driven trial, we estimate that we will need a minimum of 24 months of follow-up per participant to
accumulate sufficient study endpoints. Anticipating this, we will continue study follow-up for each participant up to a maximum of 36 months.

**Primary Objectives:**

1. To determine if once-daily, oral PrEP with TDF or FTC/TDF provides additional protective benefit in preventing HIV-1 acquisition among HIV-1 uninfected persons within heterosexual HIV-1 discordant couples who are also receiving standard prevention interventions.
2. To assess the safety of daily PrEP using TDF or FTC/TDF by comparing rates of adverse events (AEs) among HIV-1 uninfected individuals randomized to TDF or FTC/TDF PrEP to those randomized to placebo.

**Secondary Objectives:**

**Factors influencing efficacy**

1. To evaluate the efficacy of PrEP by the level of HIV-1 exposure for HIV-1 uninfected partners within HIV-1 discordant couples, defined by the frequency of sexual activity and the HIV-1 viral load in the HIV-1 infected partner.
2. To assess efficacy of PrEP by gender of the HIV-1 uninfected partner.
3. To measure the effect on efficacy of other potential co-factors implicated in transmission of HIV, including CD4 count of the HIV-1 infected partner and, for both partners, herpes simplex virus type 2 (HSV-2) serostatus, sexually transmitted infections (STIs), and male circumcision.

**Adherence:**

4. To assess adherence to once daily TDF or FTC/TDF PrEP among HIV-1 uninfected persons within HIV-1 discordant couples, and the effect of adherence on efficacy of PrEP to prevent HIV-1 acquisition.
5. To evaluate the frequency of PrEP drug sharing between the HIV-1 uninfected and HIV-1 infected partners within HIV-1 discordant couples, as measured by drug assays in HIV-1 infected and uninfected partners.

**Risk Compensation**

6. To characterize the association of once daily TDF or FTC/TDF PrEP with sexual behavior change of HIV-1 uninfected individuals within HIV-1 discordant partnerships.
7. To compare risk behaviors among HIV-1 discordant couples previously enrolled in the partners in Prevention HSV/HIV Transmission Trial (which evaluated the efficacy of HSV-2 suppressive therapy when given to the HIV-1 infected partner for preventing HIV-1 transmission), by examining changes in sexual behaviors when the HIV-1 infected versus HIV-1 uninfected partner is receiving a study drug.

**Safety**

8. To assess the effect of TDF and FTC/TDF chemoprophylaxis on the rate of congenital abnormalities and growth among infants born to HIV-1 uninfected female participants who become pregnant during the study (and in whom study drug is stopped at the time pregnancy is detected, using monthly pregnancy testing).
Effect of PrEP on early HIV-1 disease

9. Among those initially HIV-1 uninfected individuals in the trial who seroconvert to HIV-1, to assess the effect of PrEP on
   • Plasma HIV-1 viral load and CD4 cell counts during at least 12 months after HIV-1 seroconversion.
   • Frequency of genotypic and phenotypic antiretroviral drug resistance.
   • Other clinical, immunologic, and virologic parameters of HIV-1 disease.
A Final Analysis Plan

This describes the main statistical analyses that will be conducted on enrolled and randomized men and women at the end of the study. A subset of these will be presented to the DSMB at each meeting. No tables will be presented by arm in the Open Report during the conduct of the study. All tables and analyses presented by arm will be only in the Closed DSMB Report, available only to the members of the DSMB. When results are presented by study arm, the arms will be labeled Arm A, Arm B, and Arm C. A separate document will reveal the study product (i.e., Placebo, TDF or FTC/TDF) for each arm.

In the following analysis description, index refers to the HIV infected person in the discordant couple, and partner refers to the HIV uninfected person.

A.1 Analysis Datasets

In the definitions below, cohort refers to the people included in a dataset; datasets further specify which visits from the specified cohort are included.

**Intent to Treat Cohort:** The intent to treat cohort is all eligible randomized partner participants. The primary safety analysis will be conducted on the Intent to Treat Cohort, using an as-treated definition for inclusion of safety events.

- **Intent to Treat Safety Dataset:** The analysis of safety outcomes will be conducted on the safety dataset which includes all adverse and lab events occurring in partner participants in the ITT cohort.

- **Primary Safety Dataset** will include adverse and lab events occurring in the ITT cohort while participants are receiving study drug and within four weeks after stopping study drug. An exception to this is made for pregnancy losses and congenital abnormalities for pregnancies that were detected while a participant was taking study medication, which will be reported irrespective of whether they occur within 4 weeks of stopping study drug.

**Primary Efficacy Cohort:** The primary efficacy analyses will be conducted on the primary efficacy cohort, a modified intent to treat cohort that differs from the ITT cohort only in the exclusion of partner participants determined to be HIV RNA positive at the time of randomization.

- **Primary Efficacy Dataset** includes all post randomization follow-up time from the primary efficacy cohort until HIV seroconversion or end of study follow-up, whichever occurs first.

- **As-treated Efficacy Dataset** differs from primary efficacy dataset only in the exclusion of time intervals when the participant received no study drug (drug not dispensed).

Refer to Figures 1-4, which illustrate the exclusions.

**Index Participant Cohort:** The analysis of index participant will include the index partners of all eligible randomized partner participants in the ITT Cohort. Characteristics of the index participants provide correlates of efficacy, drug sharing and transmitted resistance.
All randomized participants are continued in follow-up unless one or more of the following criteria for termination are met:

1. The participant has violations of eligibility criteria judged to have significant safety risk by the study medical director and which resulted in termination of the couple from the study. These individuals are excluded from all efficacy analyses.
2. The participant’s informed consent is determined to be not valid.
3. The participant has been double enrolled. In that case, the participant’s data will be excluded from analysis altogether.
4. After enrollment, the HIV uninfected participant has an HIV positive determination based on site EIA testing. Presumed seroconverters are taken off study drug and continued in follow-up in the seroconverter cohort. These individuals are censored at the time of seroconversion in efficacy analysis. Adverse events data will continue to be reported in the safety data from the seroconverter cohort follow-up.

A detailed explanation of each participant excluded will be given.

A.2 Baseline Tables

In all Tables, summary statistics appropriate to the measurement scale and the data collected will be used to describe the data. Where specific categories are defined in the analysis plan (e.g. 0%-75%, 75%-90%, 90%-100%) they reflect expectations for reasonable summaries based on current experience. Depending on the final distributions actually observed, and providing it does not meaningfully modify the intent of the analysis, the categories used in the final analysis may be modified to allow better characterization of the distributions.

A.2.1 Study Accrual

The number of couples screened, enrolled and randomized per study month will be presented in a table overall and (1) by site and (2) by study arm. No formal statistical testing will be performed. All randomized participants will be included, including those who were later determined to have not met study inclusion criteria and are subsequently referred to as ‘ineligible’.

A.2.2 Baseline Demographic Characteristics

A table of baseline demographic characteristics describing partner and index participants will be presented. For partner and index separately:

- Age
- Education
- Participant in Partners in Prevention HSV/HIV Transmission Study
- Employment
- Income
- Number of children
- CD4 count (index only)
- HIV plasma viral load (index only)
- WHO HIV Stage (index only)
- Circumcision (males only)
- Gender
- Marital status
- Length of living together
Summary statistics appropriate for the measurement scale will be used to describe the distribution of these variables. These summary statistics will be presented in tables overall and (1) by site (2) by study arm. No formal statistical testing will be performed.

Tables

1. Partner demographics
   a. By site
   b. By study arm
2. Index demographics
   a. By site
   b. By study arm

A.2.3 Baseline Behavioral Characteristics
A table which includes the following baseline behavioral characteristics for partner and index participants will be presented:
   • With the study partner: number of times sexual intercourse, number of times unprotected sex in the past month.
   • With individuals besides the study partner: number of non-index partners in the last month, number of times sexual intercourse, number of times unprotected sex in the past month.
   • Contraceptive use (female only)

Summary statistics appropriate for the measurement scale will be used to describe the distribution of these variables. These summary statistics will be presented in tables separately for index and partners. For each of index and partner, tables will be presented (1) by site and (2) by study arm and (3) by gender. No formal statistical testing will be performed.

Tables

3. Index behavior
   a. By site
   b. By gender
   c. By study arm
4. Partner behavior
   a. By site
   b. By gender
   c. By study arm

A.3 Partner Adherence
The terms adherence and coverage are used to differentiate between participant behaviors and dispensing patterns. Adherence describes “When pills are dispensed, what proportion are taken?”, and this measure is conditional on pills being dispensed and returned. Coverage is “How many days do we estimate participant was exposed to study drug?” and this measure uses both dispensing records and pill counts to estimate the number of days drug was taken between study visits.

A.3.1 Descriptive Summaries of Adherence
For each month at each site, amongst those who complete a visit, we will compute the proportion of participants eligible to receive drug and the proportion dispensed treatment. For participants not eligible to receive drug, the reasons study drug was withheld will be reported.

For each month at each site, amongst those who complete a visit, pill count data will be used to assess adherence. We will report the proportion of dispensed bottles that should have been
returned. Amongst those who return bottles, we will tabulate the percent of doses taken, by site
and by study arm.

Self reported adherence data on missed doses and use of study drug by other people will be
tabulated.

Tables
5. Proportion of study drug dispensed
   a. By site
   b. By study arm
6. Self-reported adherence
   a. By site
   b. By study arm
7. Adherence by pill count
   a. By site
   b. By study arm

A.3.2 Drug Coverage
The proportion of days when drug was taken may affect the potential efficacy of the
active PrEP drugs for prevention of HIV infection. For each visit with an HIV test result,
drug coverage will be computed from the previous HIV uninfected test result to the
current HIV test result based on study drug holds (e.g. due to pregnancy and suspected
seroconversion) and pill count data from the same time period. For each month, at each
site, bottle dispensing and pill count data will be used to assess coverage between HIV
tests. We will report the proportion of person years where coverage cannot be assessed
due to missing pill count data, and the proportion of HIV testing visits with estimated
coverage of 0%, 1-79%, 80-90% and ≥90%.

Tables
8. Proportion of days covered by drug at each visit and overall:
   a. By site
   b. By study arm

A.3.3 Drug Sharing and ART initiation in Index Participants
HIV disease progression in index participants, and the initiation of ART, may have an impact on
drug sharing. Drug sharing will be assessed by self report (see ancillary adherence protocol for
additional data on assessment of drug sharing). We will describe the self-reported drug sharing
from the partner data. We will also report participants meeting national criteria for ART eligibility
and ART initiation by site and by study arm.

Tables
9. Self reported drug sharing
   a. By site
   b. By study arm
10. Index participants meeting national criteria for ART eligibility and initiating ART prior to
the visit
    a. By site
    b. By study arm
A.4 Retention

The proportion of index, and partner study participants retained at each study visit (i.e. monthly) will be computed. The CRF field used to assess retention in partner participants is testing completed at the visit. The CRF field used to assess retention in index participants is WHO staging in the visit. Any early terminations are assessed as expected but not retained at all subsequent visits. Following death, participants are assessed as not expected at all subsequent visits. These monthly retention rates will be presented overall, by study arm and by study site.

In addition, HIV end point retention tables will report the completeness of end point capture in the study for partner participants. These tables differ from visit-specific retention in that all (missed) visits before a subsequent HIV test are counted as retained for end point determination.

Finally, a table describing the reasons for early termination will be presented.

The retention statistics reported at each visit will include:

- Total enrolled
- # inappropriately enrolled (see section B1 above)
- # active in study
- # died
- Expected number at this visit (those who have completed the visit or are past the visit window)
- # Completed the visit or reached endpoint (retained)
- # No show or lost to follow-up
- Window not yet closed (not expected)
- Proportion retained at this visit (among expected)

Tables

11. For each site:
   a. Index: visit specific retention
   b. Partner: visit specific and end point retention

A.5 Safety Analysis

All safety tables will be performed on both the complete safety dataset and the as-treated safety dataset. Nominal p-values will be computed to guide assessment of imbalance between arms.

A.5.1 Clinical Adverse Events

Safety event analysis will occur primarily for partner participants. The analysis cohort for safety tables will be the safety analysis cohort. Tables and listings of serious adverse events (SAE) and expedited adverse events (EAE) will be presented for partners only (1) by site and (2) by study arm; and (3) by site and grade, and (4) by arm and grade. Serious adverse events are defined by the Federal Code of Regulations as:

- Death
- Life-threatening, or otherwise Grade 4
- Hospitalization or prolongation of hospitalization
- Persistent, significant disability or incapacity (captured, for the purposes of this study, as Grade 4 events)
- Congenital anomaly / birth defect
As defined in the protocol, among partner (HIV-1 uninfected participants); EAES are SAEs plus the addition of:

- All Grade 3 AEs
- Fetal loss
- Any medical event requiring treatment to prevent any of the above
- Grade 2 creatinine elevation
- All bone fractures

Tables reporting the number and percent of partner participants reporting any EAE and any AE within a category will be ordered by (1) Preferred Term within MedDRA body system overall, (2) Frequency of Preferred Term.

A separate listing of deaths will be given for partners, indexes and infants born of partner participants.

Tables and Listings

12. EAEs
   a. By grade, ordered by Body System and Preferred Term
   b. By arm ordered by Body System and Preferred Term
   c. By grade, ordered by Frequency of Preferred Term
   d. By arm, ordered by Frequency of Preferred Term
   e. By arm and grade, ordered by Body System and Preferred Term
   f. By arm and grade, ordered by Frequency of Preferred Term

13. SAE
   a. Listing by site, ordered by severity. This includes congenital anomalies and partner participant deaths.
   b. By arm ordered by Body System and Preferred Term

14. Clinical AEs
   a. By grade, ordered by Body System and Preferred Term
   b. By arm, ordered by Body System and Preferred Term
   c. By grade, ordered by Frequency of Preferred Term
   d. By arm, ordered by Frequency of Preferred Term
   e. Proportion of AEs by severity and site reported relationship to drug

15. EAE for indexes and Infants
   a. Listing of index EAEs (including deaths)
   b. Listing of infant EAEs (including deaths)

A.5.2 Laboratory Adverse Events
The following laboratory assessments are performed quarterly and at Month 1 on partner participants:

- Creatinine
- Phosphate
- Total leukocyte count
- Absolute neutrophil count
- Total hemoglobin
- Platelet count
- Bicarbonate
• Total bilirubin
• AST
• ALT
• Urine Dipstick (Protein, Glucose), performed per protocol specifications

Labs are graded using the DAIDS toxicity tables. Abnormal labs are actively retested for confirmation. Abnormal results that are confirmed (i.e. have not resolved) at a subsequent visit will be reported at the highest observed grade by arm and by grade.

Tables
16. Lab AEs
   a. Confirmed renal AEs in partner by severity
   b. Confirmed other laboratory AEs by severity
   c. Confirmed renal AEs in partners by severity and arm
   d. Confirmed other laboratory AEs by severity and arm

A.6 Efficacy Analyses for HIV Infection

A.6.1 Primary Analysis

Objective: Does once-daily oral PrEP provide a benefit that exceeds 30% effectiveness in preventing HIV transmission within heterosexual HIV-1 discordant couples?

Endpoint: HIV infection
Cohort: Primary Efficacy cohort
Visits: On-study follow-up time in primary efficacy cohort participants

HIV infection as measured by seroconversion will be assessed monthly and will be used as the primary endpoint for the treatment effect. The event time for HIV infection, if it occurs, is the time of the first positive HIV antibody test. Consistent with an intent-to-treat analysis and to preserve the integrity of randomization, women who are taken off drug because of pregnancy and breastfeeding, individuals who miss follow-up visits, and non-adherent individuals will be included in the analysis in their original randomization group if endpoint information is available within the protocol specified timeframe of follow-up. Participants who are infected prior to randomization, that is, are positive for HIV RNA at screening or enrollment visit, will be excluded from the ITT set in this primary (modified ITT) efficacy analysis. Individuals who drop out of the study, are terminated, refuse further testing prior to completion of follow-up or die prior to completion of follow-up will be treated as uninformatively censored as of their last HIV test. Participants who do not seroconvert and remain on study will be censored at their last on-drug on-study visit. The additional post-study follow-up after the final on-drug visit (i.e. at 4 and 8 weeks after cessation of study drug) will not be included in on-study follow-up time: test results from this period will be excluded from the primary analysis. Any HIV seroconversions that occur in the 8 weeks post-study follow-up period will be reported separately.
Details:

Definitions: Suspected HIV seroconversions, as determined by HIV EIA tests conducted at the study site, must be confirmed as HIV infected seroconversions by testing conducted at the central laboratory in Seattle. The end point committee is responsible for final determination of HIV infection endpoints and for determination of whether a participant was HIV infected at study enrollment. All determinations will be made by the committee while blinded to study arm. If confirmed, the time of the event for the primary efficacy analysis is the date of first HIV positive EIA at the site, unless otherwise determined by the end point committee. Suspected HIV infections that are not confirmed by central testing are censored at the time of last HIV negative visit.

All participants with suspected HIV seroconversions in the first three months after study enrollment will have their enrollment samples tested for HIV RNA. Those testing positive for HIV RNA at enrollment will be excluded from the primary efficacy analysis.

Statistical Analysis: Cox's proportional hazards model will be used for the primary analysis (SAS proc PHREG). Confirmed HIV-1 infection, as defined by the end point committee, will be the endpoint. The analysis will be stratified by site. The only covariate included in the model will be randomization arm. Follow-up time for participants who seroconvert will be measured from randomization to first positive test in participants with confirmed infection. If multiple positive tests are available for an individual, the first positive confirmed test will be used as the time of seroconversion, unless the endpoints review committee determines another visit should be used. Follow-up time for participants who never seroconvert to HIV-1 will be measured from randomization to last on-study negative HIV test. Incidence rates of HIV-1 (defined as the total number of HIV-1 seroconversions by the total number of person-years of follow-up at risk) will be presented in tables by (1) study arm and (2) by study arm by site. Two formal statistical comparisons between each active arm and the placebo arm will be performed. One will consider the hypothesis of any efficacy, and compute statistical significance against a null of 0% efficacy. The other will consider the hypothesis ruling out less than 30% efficacy, corresponding to the premise for which the study was powered.

The primary scientific question that will be reported in the scientific literature is the statistical significance of each active arm compared to efficacy of 0%. This p-value will be based on a log rank test comparing the distributions of infections times between treatment groups, stratified by site. The significance level for rejection will be set at (two-sided) p = 0.05.

The study has been designed with sufficient power to rule out efficacy lower than 30%. The formal computation of statistical significance compared to efficacy of 30% will use a Wald test of the hypothesis:

\[ H_0: HR = 0.7 \]
\[ H_a: HR < 0.7 \]

A one-sided test with \( \alpha = 0.025 \) will be used for each comparison of active arm with the placebo, i.e., there will be no adjustment for multiple comparisons. Efron's method for handling tied event times will be used. The estimated hazard ratio (HR), a 95% confidence interval, and a p-value for the hypothesis shown above will be given. Interim monitoring stopping boundaries for proven efficacy are based on ruling out efficacy lower than 30%.
A.7 Analyses supportive of the primary efficacy analysis

A.7.1 Supportive efficacy analyses

**Objective:** Does once-daily oral PrEP provide a benefit that exceeds 30% effectiveness in preventing HIV transmission within heterosexual HIV-1 discordant couples after excluding time off study drug due to pregnancy and breast feeding from the risk set?

Endpoint: HIV infection
Cohort: Primary efficacy cohort
Visits: All on-study follow-up time from all primary efficacy cohort participants, excluding time off drug in women due to pregnancy and breastfeeding.

This secondary analysis will be performed to approximate, under the assumption of uninformative censoring of pregnancy time, the on-drug efficacy of PrEP for prevention of HIV-1 acquisition. This analysis will be similar to the primary analysis described above except that women will be removed from the risk set (“censored”) when they discontinue study drug due to pregnancy and breastfeeding, as is specified in the study protocol (individuals that are non-adherent for other reasons will be included in the analysis in an ITT fashion). Women will be removed from the risk set when they discontinue study drug due to pregnancy (technically, women will be censored following the last HIV test just prior to discontinuing study drug due to pregnancy). Women will be added back into the risk set if they resume taking study drug following pregnancy and/or breastfeeding (technically, women will be added back to the risk set following the first HIV-negative test after resumption of study drug).

Statistical Analysis: Parallels the primary efficacy analysis.

**Objective:** Does once-daily oral PrEP provide a benefit that exceeds 30% effectiveness in preventing HIV transmission within heterosexual HIV-1 discordant couples after excluding time off study drug for any reason from the risk set?

Endpoint: HIV infection
Cohort: Primary efficacy cohort
Visits: All on-study follow-up time from all primary efficacy cohort participants, excluding known time off drug for any reason

This exploratory analysis will be performed to compute the observed difference in HIV-1 acquisition amongst those who had enough drug dispensed to achieve daily dosing in a given interval, based on study drug dispensing records. This analysis will be similar to the secondary analysis described above except that all visits will be removed from the risk set (“censored”) when study drug is discontinued for any reason or participants do not have drug dispensed for at least one study month (individuals that are non-adherent for other reasons will be included in the analysis in an ITT fashion). For participants who do not have drug dispensed (e.g. miss a study visit), it is assumed they discontinue drug 28 days after the day drug was dispensed. Participants will be removed from the risk set when they discontinue study drug (technically, will be censored following the last HIV test just prior to discontinuing study drug). Participants will be added back into the risk set if they resume taking study drug (technically, will be added back to the risk set following the first HIV-negative test after resumption of study drug).

Statistical Analysis: Parallels the primary efficacy analysis.
Objective: Does HIV risk differ by treatment group in an analysis stratified by coverage?

Endpoint: HIV infection
Cohort: Primary efficacy cohort
Visits: Primary efficacy dataset where coverage of study drug can be calculated.

If PrEP reduces risk of HIV infection then we expect that, all other factors being equal, the estimated RR due to treatment should vary inversely with days covered by drug (i.e. PrEP provides greater protection as coverage increases). This analysis of effect modification due to coverage will address that question as an exploratory analysis, in a “per protocol” analysis. HIV infection at each monthly visit will be the outcome in a time to event analysis. Coverage (as defined below) averaged over the previous 2 months will be a time-dependent predictor and we will examine how coverage modifies the effect of treatment. Coverage is averaged over two months to assess drug coverage prior to the time of HIV infection, recognizing a period of time between HIV acquisition and detection of antibodies and between development of a positive HIV serology and measurement of that positive serology at a study visit.

Individuals will be included in the analysis in their original treatment group. Women who become pregnant have zero coverage when therapy is withheld during pregnant and breastfeeding. The same approach will be used for persons who moved out of the area, missed a visit, and did not have access to the study drug as documented by the dispensing record. Individuals who drop out of the study and refuse further testing prior to completion of follow-up and individuals who die prior to completion of follow-up will be treated as uninformatively censored as of their last valid HIV test.

Although treatment is randomized, coverage is not, so adjustment for factors that confound or modify the coverage-treatment-risk relationship may be required. For instance, if coverage is related to sexual behavior then it is possible that increased coverage will lead to a decrease or no change in the treatment effect (if, for instance, highly adherent individuals have very low risk behavior) so the relationship between coverage and sexual behavior will be examined. In addition, although the strength of the relationship between adherence as measured by pill-count and actual adherence is unknown we will look at the relationship between self-reported adherence (<90% vs. >90%) and pill count adherence (<90% vs. >90%) as a measure of consistency of our adherence measures.

If the adjusted and unadjusted analyses give substantially different results or if the relationship between drug coverage, treatment and risk is different from our expectations, then further analyses will be conducted to explore and explain the reasons for the differences.

Details:
Estimation of days covered by dosing: For the supportive analysis of treatment effect by drug coverage, an estimate of days between HIV tests covered by drug will be computed, as follows.

- If no drug was dispensed during the period, drug coverage is 0%.
- If drug was dispensed but no pill count is available, drug coverage is unknown.
- If drug was dispensed and pill count is available, drug coverage is calculated as the proportion number of pills not returned out of number of doses expected to fully cover daily dosing in the period.
A proportional hazards model with HIV infection as the endpoint will be fit. Treatment group, percent coverage (proportion of days covered by pills taken since the last month’s HIV test based on dispensing records and pill counts; categorized as 0, 1–75%, 76–89%, ≥90% and missing), and their interaction will be included as covariates. Coverage will be treated as a time-dependent covariate and will be evaluated to coincide with the timing of the HIV measurements. Based on this model we will compute the estimated HR for HIV infection comparing TDF versus placebo and FTC/TDF versus placebo as a function of level of coverage.

Sensitivity analyses of observed differences will be conducted by adjusting for additional covariates including gender, age at enrollment, site, STI at enrollment, sexual behavior at enrollment (any non-study sexual partner), sexual behavior as a time dependent covariate (unprotected sex with study partner or non-study partner in the past month), male circumcision, HSV-2 status, index partner’s PVL and CD4. An (adjusted) estimated HR and 95% CI will be computed for each level of adherence and for additional covariates that predict risk of HIV acquisition.

A.7.2 Sub-Group Analyses

Sub-group analyses defined by baseline covariates will be performed in order to explore the uniformity of any treatment effects found in the overall analysis. The incidence rate of HIV-1 will be presented by study arm within each subgroup. Treatment effects for arm using the models described above will be estimated in each subgroup independently in order to informally evaluate the homogeneity of treatment effects. The primary subgroups where treatment effect will be evaluated are:

- Gender of HIV uninfected partner
- For male partner participants, circumcision.
- High vs. Low Viral Load in the index Participant

Secondary subgroups of interest are:

- Region: Kenya vs. Uganda
- For female partner participants, circumcision of the male index participant.
- Sexual activity
  - Any non-primary partner
  - Any/none unprotected sex
  - >= Median total sex acts
  - <= Median unprotected sex acts
- Age of HIV uninfected partner
- High vs. low baseline CD4
- HSV-2 status:
  - Partner
  - Index
- Any/None baseline STI
- Contraceptive use
A.7.3 Analyses of cofactors
Cofactor analyses of baseline covariates will be performed in order to explore the effect of any cofactor on the probability of HIV infection, and compute the treatment effects found in the overall analysis adjusted for significant cofactors. Univariate assessment of each term will be assessed by adding each cofactor separately to the models described above in order to test the significance of that cofactor. Multivariate models incorporating all significant terms will also be fitted.

- Gender of partner
- Circumcision of male partner
- Sexual activity
  - Any non-primary partner
  - Any/none unprotected sex
  - $\leq$ Median total unprotected sex acts
- Above/Below median baseline CD4, and continuous CD4
- Above/Below median baseline Viral Load, and continuous VL
- HSV-2 status
  - Partner
  - Index
- Any/None baseline STI
- Contraceptive use

A.8 Safety Analyses

A.8.1 Primary safety analysis
Objective: Are rates of adverse events in participants using once-daily oral PrEP using TDF or FTC/TDF greater than rates in the placebo arm?

Cohort: As treated safety cohort
Visits: All visits reporting safety events that occur within 4 weeks of taking study drug and any events occurring during pregnancy and breastfeeding.

Outcome:
- All serious adverse events
- All expedited adverse events
- All Grade 3 and 4 lab safety events (total and confirmed)

Details: All visits are included in the safety analysis, including visits after seroconversion and post stop visits. Events are included if the onset date is within 56 days of the last time study drug was dispensed (28 days of pill dosing and 28 days following last dose). All pregnancy losses and congenital abnormalities for pregnancies that were detected while a participant was taking study medication are reported irrespective of whether they occur within 4 weeks of stopping study drug.

Statistical analysis: Nominal p values will be used to guide comparison when excess safety events are observed on active compared to placebo arms.
A.8.2 Secondary safety analysis

Objective: Are rates of adverse events in participants exposed to once-daily oral PrEP using TDF or FTC/TDF greater than rates in the placebo arm?

Cohort: Safety cohort
Visits: All safety events reported in the study.

Outcome:
- All serious adverse events
- All expedited adverse events
- All Grade 3 and 4 lab safety events (total and confirmed)

Details: All visits are included in the safety analysis, including visits after seroconversion and post stop visits.

A.9 Secondary Analyses

A.9.1 Analyses of Adherence

Question: Does adherence differ by treatment group, time on study or behavior?

Cohort: Primary efficacy cohort
Visits: All visits where pill count data are reported (excludes visits where study drug withheld, not dispensed or bottles not returned).

Outcome:
- Primary
  - proportion of pills taken each month based on dispensing records, pill counts
- Secondary
  - proportion of pills taken based on self report
  - missed multiple doses
  - any sharing of study drug

Details: A logistic regression with proportion of tablets taken each month as the (primary) outcome will be used. Two regression models will be fit. The first will use only treatment group and time on study as predictors since these are never missing. The second will use treatment group, time on study and markers of risky sexual behavior (e.g., any unprotected sex in the last month, any non-study/new/multiple partner in the last month, unprotected sex with a non-study partner in the last month) as predictors. Since these analyses involve repeated observations on individuals, robust variance estimates (e.g. generalized estimating equations with independence working correlation), will be used to evaluate statistical significance and compute confidence intervals. Standard methods for model checking will be used to check the assumption of a linear trend over time in adherence.

Similar models will be fit using the secondary measures of adherence.

In addition to the above, rates of drug dispensing by month and by site will be computed (see section on adherence)
A.9.2 Change in sexual risk behavior over time
The reported levels of sexual risk in the HIV uninfected partner over time in study will be presented. Graphical and tabular displays will be used to illustrate the change in frequency of reported behavior during study participation by arm.

The following four behaviors will be reported:
1. Any non-primary partner
2. Any/none unprotected sex
3. $\leq$ Median total sex acts
4. $\leq$ Median unprotected sex acts

A.9.3 Effect of PrEP on early HIV-1 Disease
These analyses will be restricted to participants who become HIV infected during the trial, and participants with detectable HIV-RNA at baseline. This group of participants will be referred to as the infected cohort. The analysis period considered for these participants will extend beyond the study treatment period. Because this is a post-randomization subset observations are intrinsically biased, thus analyses restricted to this group are observational in nature.

Objective: Does set point viral load of the seroconverters differ by treatment arm?
Cohort: All seroconverters in the infected cohort
Visits: All visits between 4 and 24 month after estimated date of seroconversion with viral load determination.

The estimated date of infection is based on the first evidence of infection. For participants with first evidence of infection occurring with detectable RNA and undetectable HIV antibody, date of seroconversion is estimated as 17 days prior to that visit. For those with first evidence of infection occurring with HIV antibody, estimated date of seroconversion is the midpoint between last HIV negative and first HIV positive visit.

Viral load observations included in set point analyses are those measured at least 4 months after estimated seroconversion until 24 months past estimated time of infection, consistent with an assessment of steady state or set point viral load (visits beyond 24 months may be included, depending if there is evidence of deviation from set point). VL observed after beginning ART are not used in estimation of set point VL.

Difference in set point VL compared between arms using a linear mixed effect model with treatment arm as the primary covariate, adjusted for baseline and time dependent covariates as necessary.

The analysis will be conducted on 1) seroconverters uninfected at baseline and 2) all seroconverters.

Objective: Does CD4 count trajectory of the seroconverters differ by treatment arm?
Cohort: All seroconverter in the infected cohort
Visits: All visits with CD4 measures post seroconversion.

CD4 measures in seroconverters after initiation of ART will be excluded from the analysis. CD4 trajectories will be compared using LME models assuming random intercept, common slope. Transformations may be necessary to achieve normal distribution. Adjustment by
baseline and time dependent covariates will be included as necessary. Nonlinear modeling of trajectories will be considered if there is evidence that specifying linearity leads to a poor fit.

The analysis will be conducted on 1) seroconverters uninfected at baseline and 2) all seroconverters.

**Objective: Is resistance to TDF and TDF/FTC observed amongst participants on active study drug who seroconvert?**

Cohort: All seroconverter in the infected cohort
Visits: All visits with resistance measures post seroconversion.

We will assess the proportion of volunteers in each arm with the following mutations (which relate to TDF and FTC resistance) in the ITT population:

- K65R
- K70E
- M184V or I
- Any of the above or none.

Resistance findings will be stratified by subgroup of those with and without detectable HIV-RNA at enrollment.

**A.9.4 Other Secondary Analyses**

Other secondary analyses listed in the protocol are considered largely descriptive and exploratory and are thus not described in greater detail in this analysis plan.

**B Interim Analysis Plan**

The DSMB will meet approximately every 6 months to review study progress and emerging safety and efficacy trends as described in the DSMB charter document. In the proposed 52 month study, it is expected that the DSMB will meet 4 times for assessment of efficacy.

At each formal meeting of the DSMB, an open and closed report will present data current to approximately two months before the day of the meeting.

Details of the interim monitoring plan are described in a separate Interim Monitoring Plan document.
C Figures

Partners PrEP Transmission Endpoints

Figure 1: EVENTS in EFFICACY ANALYSES
Breakdown of study seroconversions

- Site-reported seroconversions, x F x M
- Confirmed seroconversions, x F x M
  - Events in the Intent to Treat Analysis
- Confirmed post-randomization seroconversions, x F x M
  - Events in the Primary Efficacy Analysis (Primary mITT)
- Confirmed nonpregnancy seroconversions, x F x M
  - Events in the Exclusion Pregnancy Efficacy Analysis (Secondary mITT)
- Confirmed on drug seroconversions, x F x M
  - Events in the As Treated Efficacy Analysis

- Unconfirmed by central lab testing, x F x M
- Seroconversions post stop 4 wk, x F x M
- Seroconversions post stop 8 wk, x F x M

- Excluded because HIV+ by PCR at enrollment*, x F x M
- Excluded because not on drug due to pregnancy and breastfeeding, x F x M
- Excluded because drug not dispensed due to other reason besides pregnancy, x F x M
Table 1 (ITT) cohort

### Primary Efficacy Analysis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Retention</th>
<th>Reason 1</th>
<th>Reason 2</th>
</tr>
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<tbody>
<tr>
<td>X All randomized couples</td>
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<td></td>
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<tr>
<td>X randomized to FTC</td>
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<tr>
<td>X eligible randomized to FTC</td>
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<tr>
<td>X randomized to TDF/FTC</td>
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<tr>
<td>X randomized to Placebo</td>
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<td></td>
<td></td>
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<tr>
<td>X eligible but not enrolled</td>
<td></td>
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</tbody>
</table>

### Retention for endpoints

- **6m**: X had no follow-up visits
- **12m**: X had no follow-up visits
- **18m**: X had no follow-up visits
- **24m**: X had no follow-up visits
- **30m**: X had no follow-up visits
- **36m**: X had no follow-up visits

- **X HIV+ at enrollment**: X in analysis
- **X HIV+ at enrollment**: X in analysis
- **X HIV+ at enrollment**: X in analysis

---

**Figure 2: Consort diagram for Primary Efficacy Analysis**

- X Screened
- X Not eligible
- X Eligible but not enrolled
- X All randomized couples
- X randomized to FTC
- X randomized to TDF/FTC
- X randomized to Placebo

---

**Primary Efficacy (mITT)**
Figure 3: Selection of visits for analyses using the ITT cohort

Intent to treat cohort

All follow-up visits
including post study and post seroconversion visits

Exclude visits after seroconversion and after end of study

ITT efficacy dataset

Safety dataset

Exclude events 4 weeks after stopping drug
Retain all pregnancy losses and congenital abnormalities.

As treated safety data
Primary Efficacy cohort

All follow-up visits

Exclude visits after seroconversion and end of study

Exclude visits with no drug due to pregnancy and breastfeeding

Excluded pregnancy dataset

Primary efficacy dataset

Coverage dataset

Exclude visits where adherence/coverage unknown

As treated efficacy dataset

Figure 4: Selection of visits for analyses using the Primary Efficacy cohort