HPTN 067
The ADAPT study:
A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP)

A Study of the HIV Prevention Trials Network

Sponsored by:

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LIST OF ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABV	Abacavir
ADAPT	Alternative Dosing to Augment PrEP pill Taking (study)
AE	Adverse event
ALT	Alanine transaminase
APTIMA	Amplified Probe by Transcription Mediated Amplification
ART	Antiretroviral Therapy
AST	Aspartate transaminase
AIDS	Acquired immunodeficiency syndrome
AZT	Zidovudine
CASI	Computer Assisted Self Interview
CBC	Complete blood count
CDC	US Centers for Disease Control and Prevention
CORE	(HPTN) Coordinating and Operations Center
CPQA	Clinical Pharmacology Quality Assurance Committee
CRF	Case report form
CRPMC	(NIAID) Clinical Research Products Management Center
CV	Coefficient of variation
DAIDS	Division of AIDS
DAERS	DAIDS Adverse Event Reporting System
DBS	Dried blood spots
DDI	Didanosine
DNA	Deoxyribonucleic acid
DOT	Directly observed therapy
EAE	Expedited adverse event
EC	Ethics Committee
EDM	Electronic drug monitoring
EFV	Efavirenz
EQA	External quality assurance
FDA	(United States) Food and Drug Administration
FTC	Emtricitabine
FTC/TDF	Emtricitabine / Tenofovir Disoproxil Fumarate
FTC-TP	Emtricitabine Triphospate
GEE	General Estimating Equation
GLP	Good Laboratory Practice
HBsAg	Hepatitis B Surface Antigen
HBCoreAb	Hepatitis B Core Antibody

HBsAb	Hepatitis B Surface Antibody
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
IoR	Investigator of Record
IMB	Information Motivational Behavior
IND	Investigational New Drug
IQA	Immunology quality assurance
IRB	Institutional Review Board
IUD	Intrauterine device
LDMS	Laboratory Data Management System
LL	Local laboratory
LLN	Lower limit of normal
LV	Laboratory verified (adherence)
MSM	Men who have sex with men
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NIMH	National Institutes of Mental Health
NL	(HPTN) Network Laboratory
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
OHRP	Office of Human Research Protection
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PEP	Post-Exposure Prophylaxis
PK	Pharmacokinetic
PrEP	Pre-Exposure Prophylaxis
PRO	(DAIDS) Protocol Registration Office
pSMILE	Patient Safety Monitoring and International Laboratory Evaluation
PSRT	Protocol Safety Review Team
QA/QC	Quality assurance/Quality control
RE	Regulatory entity
RNA	Ribonucleic acid
RSC	(DAIDS) Regulatory Support Center
SAE	Serious Adverse Event
SD	Standard deviation
SDMC	(HPTN) Statistical and Data Management Center
SIV	Simian immunodeficiency virus
SMC	Study Monitoring Committee
SOP	Standard Operating Procedure
SRC	Scientific Review Committee
SR	Self reported (adherence)
SSP	Study Specific Procedure
STI	Sexually transmitted infection
TDF	Tenofovir Disoproxil Fumarate

TFV	Tenofovir
TFV-DP	Tenofovir Diphosphate
TLFB	Timeline follow-back
TUC	Thailand Ministry of Public Health–United States (U.S.) Centers for Disease Control (CDC)
UCSF	University of California at San Francisco
ULN	Upper limit of normal
USAID	United States Agency for International Development
U.S.	United States
VQA	Virology quality assurance
WIHS	Women's Interagency HIV Study
WSM	Women who have sex with men
ZDV	Zidovudine

TERMINOLOGY FOR TENOFOVIR, EMTRICITABINE, AND THEIR DERIVATIVES

Abbreviation	Compound name	Comments
TDF	Tenofovir disoproxil fumarate	This is the inactive, oral formulation of tenofovir (TFV, trade name: Viread). The ester form enhances oral absorption and bioavailability. TDF is rapidly metabolized after dosing to the de-esterified pro-drug, which is also inactive.
TFV	Tenofovir	This is the inactive, de-esterified form of TDF. This is the form of the drug that is measured in serum, blood, other body fluids, and non-cellular tissue samples.
TFV-DP	Tenofovir diphosphate	This is the active, phosphorylated form of TFV that is generated in cells. This is the form of the drug that is measured in cells (*e.g.*, peripheral blood mononuclear cells, PBMCs). It is rapidly dephosphorylated to the inactive form outside of cells, and has a very short half-life outside of cells in tissue.
FTC	Emtricitabine	FTC is an inactive pro-drug that is activated in cells by phosphorylation. This is the form of the drug that is measured in serum, blood, other body fluids, and non-cellular tissue samples.
FTC-TP	Emtricitabine triphosphate	This is the active form of FTC that is generated in cells. This is the form measured in cells (*e.g.*, PBMCs).
Truvada®	FTC/TDF	This is the trade name of a co-formulated drug produced by Gilead Sciences, Inc. Each pill contains 300 mg of TDF and 200 mg of FTC.

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U.S. National Institute of Mental Health
U.S. National Institutes of Health

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

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

_____
Name of Site Principal Investigator

_____ _____
Signature of Site Principal Investigator Date

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SCHEMA

Purpose:
This is a behavioral study to evaluate the feasibility of intermittent dosing of a pre-exposure prophylaxis (PrEP) regimen. Recommendations for intermittent usage, compared with daily usage, may provide comparable coverage of possible exposures with pre- and post-exposure dosing, decreased pill requirements, and decreased symptoms. This study is designed to optimize and facilitate future efficacy research, to be proposed separately. The study aims to identify dosing regimens that foster healthy sexual practices and pill-taking behavior in people at high risk of human immunodeficiency virus (HIV) infection. The word ADAPT in the study title is an acronym for Alternative Dosing to Augment PrEP pill-Taking.

Design:
A Phase II randomized open-label clinical trial of oral Truvada® [tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC)] PrEP among HIV-uninfected men who have sex with men (MSM) and women who have sex with men (WSM), at high risk of acquiring HIV infection. The study includes a six week lead-in period which includes directly observed therapy (DOT) at Enrollment and Weeks 1 through 4, followed by one week without dosing to determine individual steady state pharmacokinetics (PK). This will provide the opportunity to create a pharmacokinetic analysis of drug levels to be expected at given rates of intake (adherence). Participants will then be randomly assigned to one of three dosage groups in a 1:1:1 ratio: daily dosing, time-driven dosing, and event-driven dosing. After randomization, participants will then complete a 24-week period of self-administered dosing (Weeks 6 through 30), with one visit four weeks after the completion of dosing (34 weeks total). Participants who acquire HIV infection during the study discontinue dosing and will be followed until study closure and referred for post-trial care as per local regulations. A subset of participants in each of the study arms will also participate in a qualitative evaluation of the social and behavioral aspects of differing dosing strategies utilizing focus groups after Week 34. A subset of clinic staff who directly interact with participants regarding pill-taking and sexual risk behavior, as well as a subset of participants identified as particularly informative will participate in key-informant interviews after Week 34.

Study Population:
HIV-uninfected MSM, WSM at high risk of acquiring HIV infection

Study Size:
360 evaluable participants, including 180 MSM and 180 WSM

Treatment Regimen:
Oral FTC/TDF in three dosage groups: daily dosing, time-driven dosing, and event-driven dosing. The time-driven dosing group will be asked to take FTC/TDF twice weekly with a post-exposure boost. The event-driven dosing group will be asked to take FTC/TDF before and after a potential exposure to HIV infection. In all three dosing groups, dosing will not exceed two doses per day or seven doses per week.

Study Duration:
The total duration of the study will be less than two years. Enrollment is planned over 8 months. Follow-up will include a 30-week dosing period, with a single (final) visit four weeks after completion of dosing. The 30-week dosing period includes a 6-week lead-in period which includes once-a-week DOT administered at Enrollment and Weeks 1 through 4, followed by one week without dosing. The lead-in phase will be followed by 24 weeks of self-administered use, a 4 week off-drug period, and a final clinic visit at Week 34.

Primary Objective:

- To test the hypothesis that recommending intermittent (non-daily) usage of oral FTC/TDF chemoprophylaxis, compared with recommending daily usage, will be associated with:
    - Equivalent coverage of sex events with pre- and post-exposure dosing
    - Lower number of pills needed for coverage and fewer pills used
    - Decreased self-reported symptoms/side effects (both severity and frequency) during 24 weeks of self-administered use

Secondary Objectives:

- Develop objective measures of drug exposure by obtaining steady state pre-dose "trough" drug concentration in several biological matrices for participants during a lead-in period of weekly DOT
- To describe safety outcomes among PrEP users including adverse events among all participants and drug resistance and plasma HIV ribonucleic acid (RNA) levels among participants who seroconvert
- Assess differences between arms in the acceptability of different PrEP regimens and in perceptions of advantages and disadvantages of different regimens
- Assess differences by arm in adherence
- Evaluate the potential influence of PrEP usage on changes in sexual behavior, planning for sex, prediction of risky situations, and recognition of possible HIV exposure from baseline to final on-drug assessment in relation to PrEP optimism

Study Sites:
The Thailand Ministry of Public Health–United States (U.S.) Centers for Disease Control (CDC) collaboration (TUC) Silom Community Clinic in Bangkok, Thailand for MSM, and Emavundleni Centre, The Desmond Tutu HIV Foundation in Cape Town, South Africa for WSM.

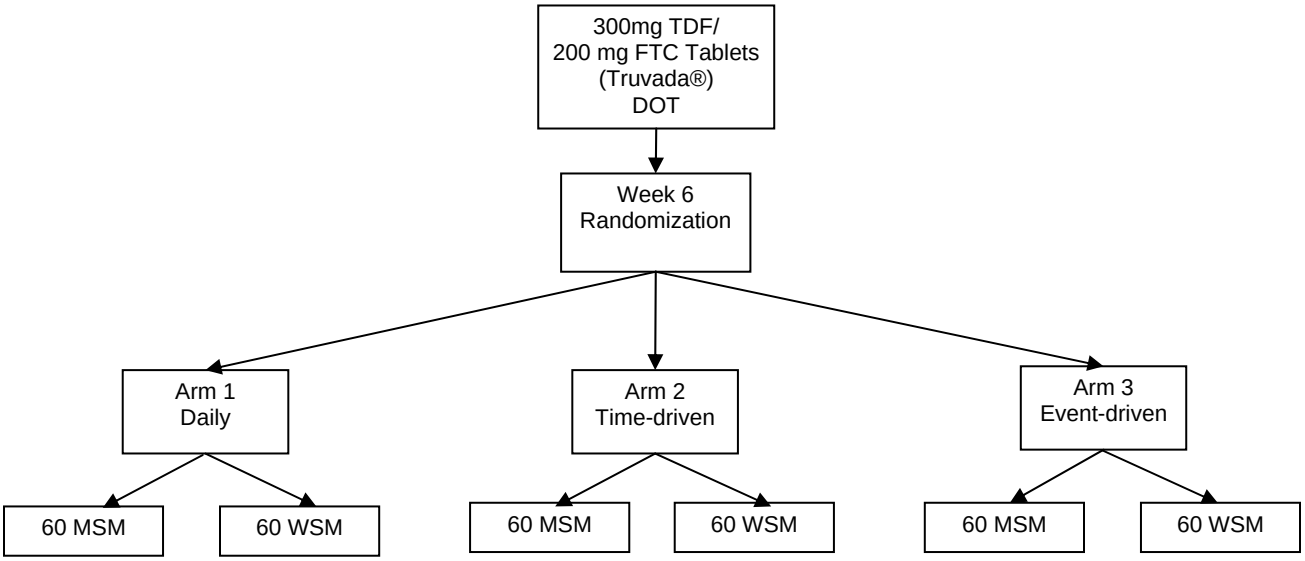
HPTN 067

The ADAPT study:

A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP)

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME

A) Randomization Scheme



B) Study Design

Week	**-10**		**0**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**34**
Screening											
Day -70 to -1											
Directly Observed Therapy											
Day 0 (Enrollment) up to Week 6/Randomization											
Self Administered Therapy											
Week 6/Randomization up to Week 30											
Final Visit											
Week 34											

1.0 INTRODUCTION

1.1 Background and prior research

The HIV epidemic is continuing to grow worldwide. Because no single prevention intervention is a panacea, multiple prevention strategies must be evaluated and made available as "combination intervention" as rapidly as possible for both men and women. The "tool box" for prevention of HIV infection should include different strategies such as condom usage and male circumcision, as well as behavioral, biomedical and structural interventions for HIV-uninfected and HIV-infected individuals. Daily PrEP with oral antiretroviral drugs is currently being evaluated in clinical trials in diverse populations and settings. However, for the majority of the "at-risk" populations, the prevention method of daily PrEP dosing may not match patterns of HIV risk-taking, which is unlikely to occur on a daily basis. Furthermore, daily dosing of PrEP was selected for on-going prevention trials based on dosing intervals that are approved for treatment of HIV infection.

Less frequent dosing of PrEP may be sufficient for prevention purposes as well as result in decreased drug costs and potentially lower risk of toxicity which may increase acceptability and improve utilization. Studying intermittent dosing can contribute critical information regarding behavioral effects, adherence reporting and counseling content. In addition, this study will be useful even in the setting of negative daily dosing trials if it identifies ways to foster pill use reporting and active study participation.

Therefore, strategies using intermittent PrEP regimens should be evaluated as an alternative tool for HIV prevention. Establishing the potential benefits and feasibility of intermittent regimens in terms of coverage, acceptability, resistance, and uptake, as well as potential influence on other risk-management strategies (*e.g.*, condom use) is critical in the portfolio of research that will advise the real-world dissemination and implementation of combination interventions.

The data from this study will provide an excellent opportunity to understand either a negative or positive outcome. Equipoise is the ethical basis for all randomized studies and maintaining equipoise is the responsibility of investigators and is taken very seriously by this investigative team. Maintaining equipoise is an active process, requiring first that the virtues of the "new approach" be highlighted to justify considering alterations to the standard of care. There is the potential for both negative and positive findings in this study. Intermittent dosing may lead to poor coverage of exposure, costs may increase because pills are wasted in ineffective attempts and resistance may occur in those who seroconvert.

The primary measure of pill-taking in this study will be based on the adjusted Electronic Drug Monitoring (EDM) device. The EDM data is transmitted

electronically to a database system and this data is used by interviewers to improve the accuracy of self-reported pill-taking via brief weekly interviews. EDM has received considerable support within the antiretroviral drug adherence literature as an objective measure of adherence,[1-4] although EDM has also been noted as potentially underestimating adherence.[5] Accuracy of EDM is dependent on case-openings being indicative of (a proxy for) pill consumption. The appropriateness of this assumption is increasingly suspect if participants do not use the EDM case for pill dispensation, or dispense pills without actually consuming them. The weekly interviews were developed to address these possibilities and to increase the accuracy of EDM data with appropriate adjustments. Please see further information on the use of EDM data in this trial in Sections 2 and 5.

1.2 Animal studies of chemoprophylaxis

The most encouraging data suggesting that intermittent PrEP may be a plausible prevention strategy comes from a recent study in which monkeys were well-protected from simian immunodeficiency virus (SIV) infection after receiving one dose of TDF plus FTC at either 7 days, 3 days, or 2 hours pre-SIV exposure followed by a second dose 2 hours post-exposure.[6] While encouraging, these data cannot be directly extrapolated to humans due to the differences in simian anatomy and pharmacokinetics, as well as differences between HIV and the SIV challenge strain.

The coformulation of FTC/TDF is selected for this trial because it was the most active in pre-clinical studies of non-human primates. While TDF or FTC alone had some protective activity in animal studies, the combination of both agents was associated with higher levels of protection. The combination has been co-formulated as a single pill, and is available from Gilead Sciences, Inc. under the trade name "Truvada®".

1.3 Human FTC/TDF trials

The nucleotide reverse transcriptase inhibitors (NRTIs) TDF and FTC were licensed by the U.S. Food and Drug Administration (FDA) for treatment of HIV-l infection in 2001 [7] and 2003 [8], respectively. In August 2004, the FDA licensed a fixed dose co-formulated drug containing 300 mg TDF and 200 mg FTC (trade name: Truvada®).[9] TDF and FTC have demonstrated outstanding safety and efficacy in human clinical trials.[10, 11] TDF has characteristics that make it suitable for evaluation as a chemoprophylaxis agent. These characteristics include: prolonged intracellular half-life that allows once-a-day dosing, high levels of tolerability, potent antiviral effects, and selection of drug-resistant variants that have mutations associated with diminished viral replication capacity.

Several clinical trials evaluating the efficacy of FTC/TDF (administered daily) for PrEP are ongoing. These multi-site trials are being conducted in many countries and in different populations including young women (CDC-funded study in Botswana,[12] USAID-funded FemPrEP,[13] NIH-funded VOICE[14]), MSM (NIH and

Gates funded I-PrEX[15]), intravenous drug users (CDC funded study in Thailand[12]), and discordant heterosexual partners (Gates funded Partners study[16]). The earliest results from some of these studies are expected in the fall of 2010.

1.4 Significance of Determining Pharmacology of Intermittent PrEP

Assuming dose proportionality is found, this model will be used to estimate extracellular and intracellular drug exposure in multiple compartments for any dose and dosing interval combination. This model will be critical to the following three areas: 1) developing an optimal pharmacology-based adherence intervention for future PrEP studies, 2) assessing adherence in ongoing studies with currently stored samples, and 3) developing a pharmacokinetic-pharmacodynamic (PK/PD) model to determine target intracellular drug exposures that prevent HIV infection.

1.5 Drug Concentration as an Adherence Measure

In clinical trials, measurement of drug concentrations has been proposed as a potential quantitative measure of medication adherence. In this protocol, we plan to use drug concentration of tenofovir in different biological matrices as a measure of adherence. We propose the following model to quantitatively estimate the percent adherence to the prescribed regimen:

% Adherence = 100 ● (observed concentration / expected concentration) + σ + ε

where σ represents the sources of measurable variability (inter- and intra-individual variability and drug assay variability) and ε is the random unmeasured error.

Pre-dose "trough" samples will be collected at Weeks 18 and 30 following unwitnessed doses to be used to represent the "observed" drug concentrations and taken to reflect two examples of concentration to assess adherence. This will enable estimation of adherence at two times during the study. (More frequent assessments were not planned due to financial and site specific logistical constraints.) The "expected" drug concentrations are based on steady-state pre-dose drug concentrations after, so-called, "directly observe therapy" or DOT which is the subject specific reference for 100% adherence. The ratio of drug concentrations (observed/expected) is taken as a rough estimate of the proportion of prescribed doses that were actually taken plus other known and unknown variability. Any differences between the observed and expected values are attributed primarily to adherence, since the expected value estimates (described

below) control for adherence, and since other significant sources of variation (*e.g.*, assay variability and environmental variables) are reasonably assumed to be stable over time.

Biological matrices and analytes to be sampled include serum tenofovir (TFVs), serum emtricitabine (FTCs), intracellular tenofovir diphosphate (TFV-DP), intracellular emtricitabine triphosphate (FTC-TP), hair tenofovir (TFVh), and hair emtricitabine (FTCh). Each of these has different assay variability and analyte half-life. Tenofovir half-lives are generally longer than emtricitabine. Serum analytes are less than a day, intracellular analytes half-life can be several days to one week, and the half-life of the analyte in hair can be more than a month. It should be noted that these half-life estimates are not well established for intracellular phosphates and analytes in the hair. These characteristics are mentioned because they may relate directly to the limitations of drug concentration as a method of adherence. For example, all things being equal, increasing variability diminishes the ability to discriminate between different degrees of adherence. Due to a larger accumulation index, a longer drug half-life allows both greater ability to discriminate among adherence levels and less susceptibility to the "white coat effect" wherein a subject may appear to be 100% adherent after taking only one dose of medication immediately prior to a study visit without having taken any prior doses. The long half-life can also require delays until steady-state is achieved (five times the drug half-life in the biological matrix) and limit the ability to detect poor adherence "holidays" in time frames much shorter than the half-life. For example, the two long half-life measures (cells and hair) can be insensitive to a holiday (no drug taking for a week or a few days, respectively) when most of an observation period may be associated with very high adherence. It is anticipated that a combination of adherence measures (*e.g.*, microelectromechanical systems (MEMS) devices) can help improve sensitivity to this type of adherence issue. The impact of half-life, accumulation index, and inter- and intra-subject variability are described further below. Finally, hair color and hair treatments (*e.g.*, dye and perms) can alter assessment of drug concentration in hair. A sexual event dependent drug schedule is a challenge for drug concentration as adherence measure, because the standard "expected" value is not related to DOT steady-state directly, though steady-state DOT data can be used to estimate single dose drug kinetics which can, in combination with sexual event reporting, be used to estimate expected drug concentrations. However, this introduces an undesired subjective variable (sexual activity reporting) that could be as inaccurate as pill-taking diaries.

1.6 Development and Validation of Tenofovir Hair Assay

Methods for the detecting tenofovir (TFV) in hair have been developed and validated by Dr. Yong Huang's laboratory at University of California at San Francisco (UCSF) and a Women's Interagency HIV Study (WIHS) investigator group at UCSF.[17] This method using liquid chromatography/mass spectroscopy/mass spectroscopy (LC/MS/MS) has been validated for the range of 0.01 to 0.4 ng/mg hair. Subsequently, the feasibility of hair collection and ability to detect TFV in hair were evaluated among HIV-uninfected MSM participating in a CDC-sponsored PrEP study in San Francisco. Single samples of hair were collected and tested in a blinded fashion in this placebo-controlled trial. Overall, hair collection was found to be feasible and acceptable among men enrolled in a PrEP trial, and hair analysis was highly sensitive and specific for TFV exposure in these participants. Correlative studies between peripheral blood mononuclear cells (PBMC) and hair levels and between different directly-observed dosing patterns and TFV hair levels are currently in progress.

1.7 Drug Concentration Simulation Models

In computer simulation models, the "expected" drug concentration is based on the PK characteristics of the drug and the prescribed dosing regimen of the study. To facilitate these simulations, PK data are available from several reports in which TDF (Viread®) has been administered to human research participants. From these studies, one can make some estimates of the effective intracellular half-life for tenofovir diphosphate (TFV-DP), the active moiety of the drug, which appears to be approximately ~150 hours.[18-20] From these studies, however, the inter-individual variability for half-life and peak concentration (C_{max}) for TFV-DP is relatively large (coefficient of variation around 50% to 65%). Accordingly, the best parameter estimates for such a simulation come from individual study participants. To avoid intensive, frequent PK sampling, which would be cumbersome in a clinical trial, one can employ a combination of (1) population-based estimates from the studies like those cited above, and (2) data from a few samples from each individual in a prospective study. This approach substantially reduces inter-individual variation, while reducing logistical complexity of the study. To remove the variable of adherence in estimation of individual PK parameter estimates, samples collected from the individuals tested should follow an observed dose. With an observed dose, the possibility of variable adherence affecting subsequent drug concentrations is removed. This leaves the following variables to consider: inter-individual PK variability, assay variability, and unknown sources of noise that may vary with time in the environment. Examples of simulations of the dosing strategy of TFV-DP in PBMCs and TFV in blood serum (Figure 1-1) are shown below.

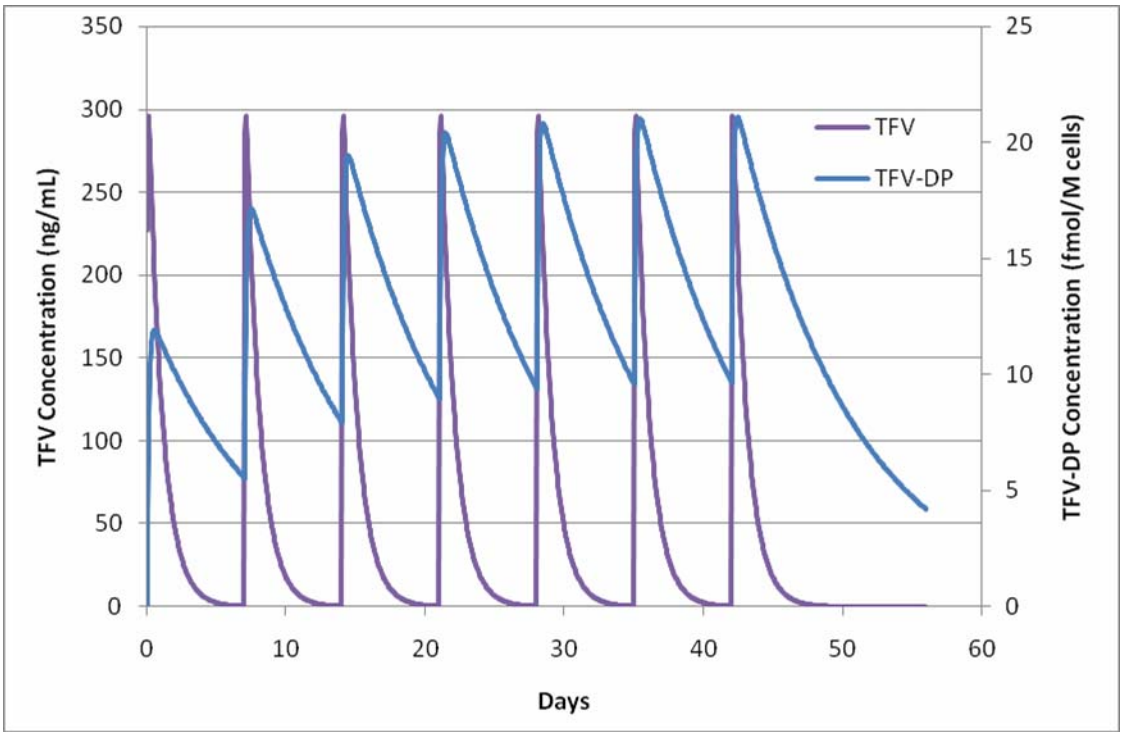


Figure 1-1.
Simulation of TFV-DP concentration in PBMCs (y-axis-1) and in blood serum (y-axis-2) versus time (x-axis) anticipated with the weekly regimen planned for this study: TDF 300 mg weekly; note the regimen is administered as Truvada® (FTC/TDF). Note the minor increase in C_{tau} and C_{max} between Day 28 and Day 35 in PBMCs where intra-individual variability will be estimated. Simulation parameters are based on data from previous studies.[18-20] Simulations assume dose-proportionality and do not include intra-individual or inter-individual variation. Note the wide swings in concentration in blood serum over the dosing interval indicating that the concentration is very sensitive to changes in time of the preceding dose or missing the preceding dose. However, the concentration is insensitive to missed doses several days prior to the sampling time.

To use the computer modeling methods described above, two key facts must be determined with regard to the interaction of drug, participant, and regimen: intra-individual variability and dose-proportionality. Knowledge of these variables is essential for planning future studies that use estimated PK parameters based on individual drug concentrations to evaluate adherence.

1.8 Dose-proportionality and Drug Accumulation

In order for drug concentration to be used as an adherence measure, the dose-proportionality must be stable at concentrations throughout the adherence range of

interest: from concentrations associated with 100% adherence down to concentrations associated with lower levels of adherence. While dose-proportionality is closely related to first order PK, there are other conditions that will cause disproportionate kinetics, even for a first order drug. Very few drugs exhibit mixed or zero order PK in the clinically relevant concentration range (*e.g.*, aspirin, phenytoin, and fluoxetine). For these drugs, a proportional increase in dose results in a disproportionately large increase in concentration. For other drugs, a proportional increase in dose may result in a disproportionately small increase in concentration. This can be seen in drugs with saturable absorption, and with drugs that are anabolized to phosphorylated forms within cells, such as TFV, FTC, and zidovudine (ZDV). For example, because phosphorylation of zidovudine (AZT)-monophosphate within cells is the rate-limiting step in AZT-triphosphate anabolism, increasing the AZT dose can result in disproportionately small or no increase in AZT-triphosphate. For either cause of disproportionate PK, the assumption of proportionate change in adherence (as with expected and observed drug concentrations) becomes more complex.

While the dose-proportionality for both TDF and FTC are well-established [21, 22] this proportionality has not been determined for the phosphorylated moieties of these drugs and must be established for one to use TFV-DP or FTC-triphosphate (FTC-TP) as measures of adherence to a Truvada® (FTC/TDF) regimen.

Other proportionality factors are dose frequency and the accumulation of drug concentration with time – characteristics that are unique to each drug and dosing regimen. Drugs that are dosed at intervals more frequent than their half-life accumulate over time and achieve concentrations that are higher at steady-state than following a single dose. This accumulation – the so-called "accumulation index" or R_{ac} – varies with the ratio of the drug half-life to dose frequency as follows:

> $R_{ac} = 1/(1 - e^{-k\tau})$, where k is the elimination rate constant [Ln(2)/half-life] and τ is the dosing interval.

The greater the drug half-life is, the greater the accumulation index. The higher the accumulation index, the greater the magnitude by which drug accumulation will exceed sources of noise in drug concentration assessment (*e.g.*, dosing time variation, assay variability, assay sensitivity, and inter- and intra-individual variability). When measuring adherence with drug concentration, one is assessing the magnitude of difference between (1) the expected concentrations of drug at prescribed dosing intervals assuming 100% adherence, and (2) the actual drug concentrations from an unobserved dosing period. The difference is attributed to

less than 100% adherence. A reduction in adherence has the equivalent effect on concentration as a reduction in the frequency of dosing (*i.e.*, the concentration falls). Drugs with a large accumulation index provide a greater degree of detectable difference between 100% adherence and lesser adherence. For drugs with little accumulation (dose frequency less than their half-life), it may be very difficult to discriminate the concentration associated with a single dose (without any prior doses) from perfect adherence. Therefore, a participant with poor adherence can appear to a have high level of adherence with a low accumulation index drug and drug regimen combination. In contrast, large accumulation index drug and drug regimen combination is very resistant to "white-coat adherence", in which a participant takes one or several doses within the day prior to a scheduled research clinic visit.

Table 1-1. **Accumulation index for parent and phosphorylated moieties of TDF and FTC dosed either weekly (168 hours) or daily (24 hours).** Drug moieties and regimens are ranked by accumulation index. An index of 2 indicates a doubling of concentration at steady-state compared to a single dose. An index of 1 indicates no accumulation at steady-state. For example, the concentration observed with 100% adherence can look the same as no adherence if the non-adherent participant takes a single dose prior to the observed blood collection when TFV, FTC or FTC/TDF are used with prescribed weekly dosing regimens. By contrast, the concentration expected with 100% adherence to FTC/TDF will be 9.6 (TFV-DP) or 2.7 (FTC-TP) times the concentration observed if a participant has taken only a single dose prior to the scheduled observation.

Table 1-1. Accumulation index for parent and phosphorylated moieties of TDF and FTC dosed either weekly (168 hours) or daily (24 hours).				
Drug moiety	**Half-life (hours)**	**Dosing interval (hours, tau)**	**Dosing interval / half-life (tau/HL)**	**Accumulation index (R_{ac})**
TFV-DP	150	24	0.2	9.5
FTC-TP	36	24	0.7	2.7
TFV-DP	150	168	1.1	1.9
TFV	17	24	1.4	1.6
FTC	10	24	2.4	1.2
FTC-TP	36	168	4.7	1.0
TFV	17	168	9.9	1.0
FTC	10	168	16.8	1.0

For this reason, TFV-DP (the intracellular form of TFV) is an excellent candidate for drug adherence monitoring, especially with daily dosing (Table 1-1). With an intracellular half-life of ~150 hours, daily to weekly dosing of TDF has a TFV-DP accumulation index ranging from of 9.5 to 1.9, offering a great range of sensitivity for determining reduced adherence over a large range of dose frequencies. In contrast, TFV concentration (measured in blood serum), when TDF is dosed daily, would be expected to perform much less well, with a small difference in drug accumulation at steady-state during daily dosing when compared to a single dose (*e.g.*, taken on the day of observation). When using TDF on a weekly dosing regimen, there is no anticipated difference between drug concentrations of serum TFV compared to taking a single dose of TDF without any prior doses. Contrasting the two lines in Figure 1-1 illustrates this point graphically. The different dose regimens are easily distinguishable in Figure 1-1 where intracellular TFV-DP is measured. In contrast, the TFV serum levels are largely overlapping with daily and weekly dosing at least one day per week.

1.9 TDF and FTC drug resistance

If HIV infection occurs during the trial, the participant may be exposed to both TDF and FTC before HIV infection is diagnosed.

Participants will be tested for HIV infection at Screening, Enrollment, and Weeks 4, 6, 10, 14, 18, 22, 26, 30, and 34. HIV RNA testing will be used in addition to serologic testing for HIV infection if a participant has signs or symptoms consistent with acute (pre-seroconversion) HIV infection, or expresses a concern about recent HIV acquisition. Frequent testing for HIV acquisition during the study period will allow prompt cessation of study drug in an HIV-infected

participant, minimizing the risk that resistant virus will emerge. Recent results of a trial of topical Tenofovir gel were encouraging in that there was no indication of resistance.[23]

1.9.1 Patterns of drug resistance associated with TDF and FTC

HIV mutations associated with TDF resistance are well-defined. TDF resistance usually results from selection of HIV with the K65R mutation, or with a combination of three or more mutations associated with resistance to thymidine analogue NRTIs. Rare insertion mutations near codon 69 can also affect TDF susceptibility.[7] Even in the presence of the K65R mutation, HIV isolates are partially susceptible to TDF. The K70E mutation is also associated with TDF resistance.

High-level resistance to FTC can develop with a single mutation, M184V or I, within weeks with monotherapy.[8] The M184V/I mutations also confer high-level resistance to lamivudine (3TC), and low-level resistance to abacavir (ABV) and didanosine (DDI), but increase susceptibility to ZDV and TDF.[9] No clinical studies have evaluated the timing for emergence of resistance mutations when TDF and FTC are used in combination.

1.9.2 Substantial barrier to HIV resistance to TDF and FTC

The accumulation of antiretroviral drug resistance mutations is usually associated with decreased fitness of HIV. Viruses that only have the K65R mutation have a replication capacity of ~53% compared to wild-type virus; replication capacity is further decreased to ~24% when the K65R and M184V mutations are both present [7].

Among HIV-infected individuals treated with TDF/3TC/efavirenz (EFV) combinations for up to three years,[24] the K65R mutation occurred in 2.7% (8/299) of patients and the M184V mutation occurred in 6% (18/299) of patients. In a study of treatment-naïve patients,[25] patients received either TDF/FTC/EFV (n=257) or Combivir® (ZDV+3TC)/EFV (n=254) for 48 weeks. Among the 34 patients with virologic failure at 48 weeks, 17% (2/12) in the TDF/FTC/EFV group and 32% (7/22) in the Combivir/EFV group had M184V mutations. No patients developed K65R mutations through 48 weeks of the study. In a Phase III trial that involved adding TDF to a failing regimen, the K65R mutation occurred in 3% (n=183) of the patients receiving TDF, and the M184V mutation occurred in 1% of all patients on antiretroviral therapy including 3TC (n=274) by Week 24.[26] Taken together, these data indicate a substantial barrier to TDF resistance. Combined use of FTC/TDF may further increase the barrier to drug resistance.

1.10 Rationale

1.10.1 Justification for Intermittent PrEP

All current PrEP trials are evaluating daily dosing of antiretroviral drugs for HIV prevention. The daily dosing strategy was selected for prevention trials based on dosing intervals that are approved for treatment of HIV infection. The hypothesis for this trial is that daily dosing of FTC/TDF for prevention may be excessive. The rationale for this hypothesis is the following: (a) the intracellular half-lives of the TDF and FTC are ~150 hours and ~48 hours respectively, which provides substantial drug concentrations to be present for several days after each dose [27], (b) non-human primate models indicate that dosing once a week may be sufficient for protection if post-exposure dosing is also used,[6, 28] (c) the majority (>80%) of individuals at high risk of HIV infection are exposed to HIV less often than daily, typically only once or twice a week,[29] and (d) the amount of virus exposing uninfected users of PrEP is substantially less than the amount of virus present in individuals with established HIV infection who require treatment. Importantly, the dosing interval for treatment has never been optimized; although daily dosing was found to be effective for treatment of HIV infection in clinical trials, less frequent dosing has not been evaluated for HIV treatment or prevention. Doses of TDF higher than 300 mg per day appear to be less active in treatment studies than the 300 mg dose,[21] which may reflect tolerance issues.

Intermittent PrEP has several potential advantages over daily dosing. First, less frequent dosing is expected to decrease side-effects related to drug exposure. Lower doses of PrEP agents may diminish mild side effects, such as cramping, diarrhea, flatulence, headache, and dizziness, which could interfere with adherence. Even if these side effects are rarely severe enough to require stopping HIV treatment for infected individuals, they may interfere with adherence when taken for prophylaxis. While current PrEP trials will assess overall rates of adverse events (AE), little or no information is being obtained regarding interactions between drug dose, non-specific grade 1 symptoms, adherence, or actual patterns of pill-use, and drug exposure. This gap in knowledge will persist even after the current generation of trials is completed, and therefore is directly addressed in this project.

Cost reduction is another important advantage of intermittent dosing in intermittently exposed persons. Exploratory analysis for PrEP in the U.S. indicates that cost-effective implementation would be challenging.[29] Cost concerns suggest that interventions would have to be targeted to the highest incidence subgroups of the population, many of whom are difficult to identify because of social stigma and other factors. Similarly, cost effectiveness of PrEP is expected to be marginal in Africa and Asia,[30, 31] where the majority of HIV infections occur and where the U.S. government is providing most of the funding for HIV treatment and HIV prevention programs. Intermittent dosing, if shown to be effective, would greatly facilitate cost-effective implementation of PrEP. The cost of the drug (Truvada®) is a major component of the total program cost of

PrEP. In HPTN 067, we will follow the number of pills required and used very closely. In addition, we realize that PrEP programs involve a variety of additional costs (*i.e.* HIV counseling and testing) in addition to pill-use. Outside of the aims of this study, we will collaborate with experts in this field to inform fully developed cost effectiveness modeling to evaluate the cost effectiveness of the intervention. We will work with staff and investigators to identify differences in resources associated with different usage groups in all elements including counseling, communications, community education, drug importation, drug storage, drug dispensation, drug labeling, medical evaluation, and laboratory testing.

Further, in relation to self-administration of PrEP, there is reason to believe that intermittent regimens may foster higher rates of adherence if these regimens are perceived as being more acceptable, feasible, and responsive to one's specific risk reduction needs. These critical aspects of uptake and acceptability of PrEP are essential in preparing for the wide-scale availability of these prevention strategies and best supporting their dissemination and implementation, if found efficacious in ongoing studies.

The decision about whether a larger efficacy trial of intermittent PrEP should go forward is, of course, speculative at this point and will involve results from the HPTN 067 trial, ongoing studies of daily oral and topical PrEP, and potentially other sources as well. In the context of HPTN 067, the conditions that would favor for moving either intermittent PrEP arm forward are:

- Equivalency of coverage between daily PrEP and intermittent PrEP. If coverage is significantly lower in the intermittent PrEP arm relative to the daily arm then this would suggest that intermittent PrEP might have lower efficacy for HIV prevention and should move forward only if additional information becomes available that the missing coverage may not be essential for efficacy. If coverage in the intermittent PrEP arm is equal to or better than the daily arm, then this would suggest that intermittent PrEP might have equivalent (or better) efficacy for HIV prevention;
- Significantly decreased drug usage in the intermittent PrEP arm. If fewer pills are used in the intermittent PrEP arm relative to the daily arm then intermittent PrEP will be less expensive to implement.
- Significantly decreased side effects in the intermittent PrEP arm relative to the daily arm. A major reason for interest in intermittent PrEP is the hypothesis that fewer drug doses will result in fewer side effects.
- An efficacy trial of intermittent PrEP versus daily PrEP will be warranted if current trials show that daily PrEP is sufficiently effective to be considered as a viable HIV prevention tool. An efficacy trial of intermittent PrEP versus placebo would be warranted if daily oral PrEP fails to demonstrate efficacy relative to placebo, and the failure of daily recommendations is found to be attributable to low levels of drug exposure that may be improved with intermittent dosing recommendations.

Although the results of a recent trial of intermittent topical dosing of Tenofovir were encouraging, the converse to all of the conditions above may also occur.[23] It may prove challenging for participants to forecast and recognize sexual risk resulting in lower adherence and coverage. Recommendations for intermittent dosing may complicate use such that participants elect not to use PrEP at all. Further, intermittent dosing may not foster daily habits that may be important for use. Finally, anxiety associated with thinking about HIV exposure may form a barrier to PrEP use. Although drug resistance was not observed in non-human primate studies of intermittent PrEP, drug resistance risk in people may be more, or less, likely during intermittent use of PrEP in people.

1.10.2 Justification for comparing event-driven dosing and time-driven dosing to daily dosing

Post-exposure prophylaxis (PEP) frequently fails on an intent-to-treat basis because individuals fail to recognize significant exposures to HIV, or fail to timely initiate prophylaxis after being exposed.[32] Anxiety, denial, imperfect communication with partners, lack of information, and substance use all contribute to failure to initiate PEP regimens. These factors may or may not bear on use of intermittent PrEP regimens. Barriers and facilitators will be fully characterized and are anticipated to include unintentional factors (periodic forgetting, challenges in prospective memory, or planning) and more internally driven factors (such as stigma, intentional avoidance, beliefs in negative outcomes from pill-use, inaccurate information about pill content or use) which will be generally organized by a theory-based approach to predicting actual patterns of pill-use across and within the different arms (daily, time-driven, or event-driven).

Event-driven dosing will require specific communication between study counselors and participants to promote skills in identifying antecedents of sexual risk in order to prepare participants for the conditionality of taking a tablet prior to sexual events. Thus, it is anticipated that participation in the event-driven arm may foster planning for sexual activity, and more explicit recognition of the risks of HIV exposure associated with sexual activity. Such planning and recognition may ultimately affect partner choice, the amount and types of sexual activity, the patterns of PrEP use, and overall exposure to HIV. For example, planning for sexual activity may include plans for using condoms, disclosure, strategic positioning, and other risk reduction strategies. Pill-use is anticipated to be an integral part of this planning and thus across arms it is assumed that those in the event-driven arm will demonstrate a pattern of pill-use most consistent with recommendations. Further, little is presently known about actual preferences from a participant or clinic staff perspective for intermittent versus daily dosing. End of study questionnaire items will provide information about overall preferences for regimens of varying kinds, and focus group data will inform overall perceptions of feasibility of each regimen with qualitative data. A subset of study participants and clinic staff will participate in post-study focus groups and key-informant interviews to understand the extent and reasons for the development of preferences for certain regimens over others. These multiple

sources of data will provide much needed characterization of how intermittent versus daily PrEP is viewed by those assigned to different arms.

1.10.3 Theoretical basis for postulating behavioral effects of intermittent dosing

This research provides a unique opportunity for hypothesis driven, theory-based research on PrEP use, and risk behavior in the context of PrEP trials. An adapted Information, Motivation, Behavioral skills (IMB) model of risk reduction and health behavior adoption is applied as an organizing explanatory framework for the assessment and characterization of core factors influencing both condom-use and PrEP use. The IMB model was originally formulated primarily as a theory of risk reduction [33] and has since been articulated to a host of health promotion behaviors, including HIV prevention,[34-39] self breast examinations,[40] and antiretroviral medication adherence.[34, 35]

Essentially, the IMB model proposes that a health behavior is a function of one's fund of accurate information about the behavior, one's personal and social motivation towards the behavior, and one's set of behavioral skills for implementing the behavior across various conditions and one's associated self-efficacy for doing so. We position exploration of important aspects of self-perception social roles and their impact on PrEP use and sexual and PrEP use behavior in the context of PrEP as one of the factors that contribute to one's overall motivation towards desired behaviors. The core constructs and the structural relations among these constructs are specified such that information and motivation can co-vary but are not determinants of each other; information and motivation both relate to behavioral skills in positive directions so that the more informed one is about a health behavior or the greater one's personal and social motivation towards the health behavior, the greater one's set of behavioral skills for implementing that behavior; one's set of behavioral skills for implementing a health behavior relates directly to the implementation of the health behavior in question. For behaviors that have not become overly automated, this is a mediated model where the direct relations between information and behavior and between motivation and behavior are largely mediated by behavioral skills. Essentially, this mediation suggests that when behaviors are difficult or complex, being well informed or highly motivated is insufficient to impact on behavior if one's skills in implementing that behavior over diverse situations and over time are not also well developed.

The utility of the identified core constructs, as well as their structural relations, has been supported by numerous studies with diverse populations[34] and is the basis for a number of risk reduction (condom use) intervention approaches, including prevention protocols for HIV-positive persons in care[41] and ART adherence interventions.[42] The model has also been used in other PrEP trials to organize barriers and facilitators to pill-taking, to providing accurate reports of pill-taking, and intervention approaches to support pill-taking efforts.

Articulated to the behaviors of interest in the present study, an adapted IMB-model to address condom-use and PrEP use specifically in the context of the proposed intermittent PrEP trial was developed (Figure 1-2). Drawing from previous research, as well as an interest in providing greater specificity in indentifying and characterizing important aspects of risk reduction behavior in relation to PrEP use, each of the core constructs of the IMB-model were elaborated to the kinds of facilitators and barriers that are anticipated to be most influential to the adoption of PrEP across the study arms (thus resulting in risk event coverage via PrEP) and the kinds of information, motivation, and behavioral skills for condom use in the context of PrEP that would be expected to predict potential changes in participants' condom use over the course of their participation in the PrEP trial.

Behavior-relevant information includes funds of accurate information, and also the extent to which participants believe common pieces of misinformation to be true or factual. As indicated in Figure 1-2, where basic information about condoms or about PrEP, PrEP trials, and one's assigned regimen is important, of equal importance is the extent to which participants believe inaccurate "facts" to be true (such as, 'condoms contain HIV or other diseases,' 'PrEP drugs cause HIV,' 'participants are asked to leave the trial if they are not consistently adherent to PrEP'). Specific to this construct, it is likely that without appropriate counseling support, participants in the more complex dosing arms (intermittent) may have greater difficulty in reaching requisite informational levels about the specific requirements of their regimen. However, given the comprehensive counseling approach adopted in this study, significant differences in accurate information for condom use or PrEP use are not anticipated. Because of concerns that intermittent doses may be "too complicated" for individuals to negotiate over time, establishing a null difference in knowledge of regimen and regimen requirements is very important. Also, differences in misinformation between arms are of interest.

Behavior-relevant motivation houses a number of core subconstructs (Figure 1-2). Within this construct, personal and social beliefs and attitudes towards the adoption and non-adoption of the behavior are housed. To the extent that one has strong positive attitudes and beliefs that adoption of the behavior will bring positive consequences (personal and social), and non-adoption is not viewed as positive, participants are expected to be in a better position to adopt the behavior consistently (providing requisite skills are in place). Individuals experiencing personal and social barriers to behavior adoption will be less apt to develop requisite skills or, subsequently, practice the behavior consistently.

There is an emphasis on specific variables to the traditional conceptualization of motivation within the IMB-model to allow for better representation of the kinds of attitudes and beliefs that are critical in elucidating what has been identified as risk compensation. The theory of risk compensation [43] postulates that biomedical prevention interventions, like PrEP, could decrease perceived risk of HIV infection and increase risk behavior. Positive associations between optimistic

attitudes regarding treatment or prevention interventions and sexual behavior may reflect risk compensation. Because attitudes towards PrEP and condom use are an essential aspect of the IMB-model, adapting the model to expand on the motivation construct to include detailed assessment of perceived positive consequences of PrEP use and of condom use (particularly in terms of potential changes in condom optimism that may occur as a result of PrEP trial involvement) and perceived vulnerability to positive consequences of PrEP and condom use and negative consequences of non-use (most specifically, to HIV infection in unprotected events), the current study will offer an examination of mechanisms by which risk behavior may change in participants. Further, because of the comprehensive conceptualization of motivation adopted in the model, this study will be positioned to be able to speak to risk compensation (where perceived risk in the context of non-condom use would diminish through adoption of an alternative [PrEP use] strategy). It is important to note, however, that the current study's counseling protocol developed to support pill-taking and condom use will not allow for a 'naturalistic' characterization of either of these phenomenon. However, this work would build to the growing literature evaluating changes in risk-behavior in the context of PrEP when appropriate counseling is provided.[44]

The model has also been adapted to provide for better representation of core features of social theories of sexual conduct. Social theories of decision making have demonstrated explanatory and predictive power in the field of behavioral economics,[45 46 47] particularly in the context of decision-making under conditions of uncertainty. Presently, little is known about the role participants develop in the context of PrEP trials or the relation between these roles and risk-prevention behaviors. The exploration of these important aspects of the "PrEP participant role" and their impact on PrEP use and sexual behavior in the context of PrEP is positioned as one of the factors that contribute to one's overall motivation towards these behaviors. Like other aspects of motivation, we anticipate that positive self-beliefs - positive attributes one would use to describe oneself in their role in the trial and as a active contributor to it (prevention activist) - will contribute to higher motivation towards PrEP use and condom use and that this will be more characteristic of participants in the intermittent than the daily PrEP arm.

The behavioral skills construct (Figure 1-2) includes objective and perceived skills in the implementation of the targeted behavior, across diverse and challenging circumstances, as well as one's perceived efficacy in being able to implement an attained skill. As the most proximal construct to behavior, and in the context of the structural relations identified by the IMB-model, skills carry the direct relation between lead-in (exogenous) constructs (information and motivation) and the behavior itself (condom use, PrEP use). Essentially, the IMB-model proposes that even the highly motivated and well informed will have difficulty adopting a behavior if they do not develop or feel comfortable using requisite skills to actually perform the behavior in the situations that typify behavioral execution in their daily lives. For example, a woman who is well informed about condom use and is highly motivated to use condoms may be

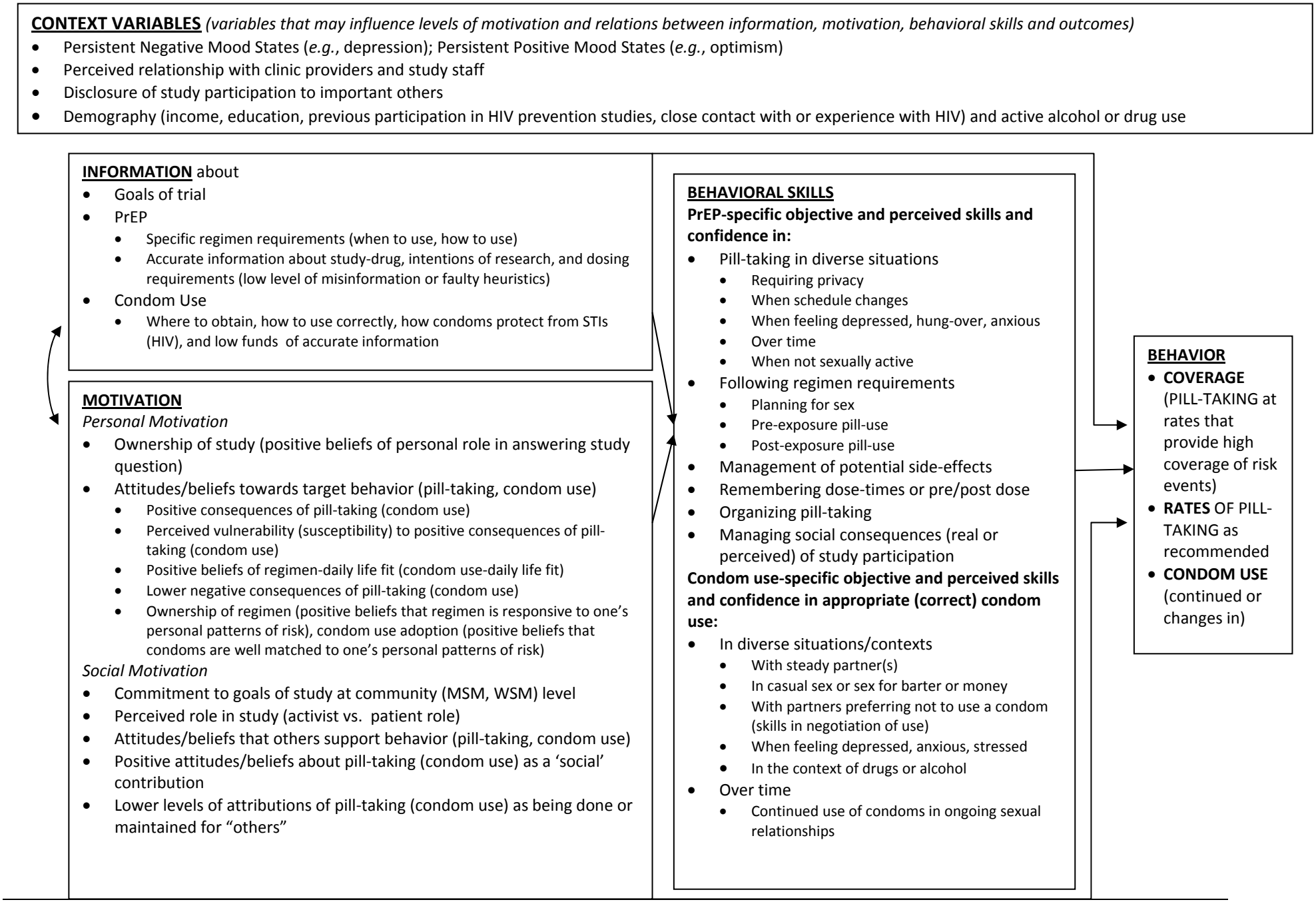
unable to consistently adopt the behavior if she does not have the negotiation skills needed to convince her partner to use a condom. A participant who requires privacy when taking his PrEP dose may be informed and motivated, but may lack the skills needed to take PrEP in privacy (*e.g.*, planning, use of hiding strategies). To the extent that the targeted behavior becomes increasing difficult in the context of one's life, skills play an increasingly large role in mediating the relation between the lead-in constructs and the outcome behavior.

Because assigned PrEP arm likely will require differing sets of requisite skills for consistent and regimen-accurate pill-taking, the effects of being in the intermittent PrEP arm on the development of and changes in certain skill-sets is of a particular interest. Those assigned to the event-driven arm are asked to take a pre-exposure dose prior to and following a sex event. The unique requirement of pre-exposure dose taking is addressed in counseling support for individuals in this arm through guidance in the development of sexual 'forecasting' skills - skill sets for predicting when a potential event may occur. Part of this prediction will involve exploration of one's personal patterns of sexual behavior and risk exposures. As such, it is possible that those assigned to this arm will increase their sexual planning skills, as well as their abilities to clearly identify important factors in sexual (and prevention-related) decision making. While all arms participating in risk reduction and condom adoption counseling, the repeated cumulative exposures to forecasting risk may produce unique skills acquisition and efficacy in the event-driven arm.

Outside of the core constructs of the adapted IMB-model, an additional set of 'moderating' variables are typically defined in IMB-models [34]which include variables that are believed to alter, and at times attenuate IMB-model proposed relations. Severe depression, active substance use, or homelessness were identified in the IMB-model of antiretroviral medication adherence as factors that limit IMB-model based interventions and would require resolution before changes in information, motivation, or behavioral skills could be promoted through intervention.[48] The 'moderator hypothesis' is not adopted in the adaptation of the IMB-model for PrEP use. Instead, these personal and situational variables are used to define the context in which PrEP use must be negotiated, and are incorporated in the adherence/PrEP use counseling approach. As indicated in Figure 1-2, context variables include persistent negative mood, persistent positive/optimistic mood, perceived relationship with study staff and providers, disclosure of study participation to important others, active drug/alcohol use, and personal history (education, participation in other trials) and are used to help to define the psychological and social context in which participation in the trial, experiences of negotiating trial participation, and one's PrEP-related information, motivation, and behavioral skills are developed, experienced, and modified. Context variables will be examined to assess for unique contributions in influencing PrEP adherence and PrEP related information, motivation, and behavioral skills areas.

A specific goal of this study is also to contrast the potential influence of persistent mood state on changes on risk behavior. If a pattern of reduced condom use is observed in the sample from baseline to final on-drug assessment, the data will be examined for a unique relation between PrEP optimism within the motivation construct and decreased condom use, while controlling for the influence of persistent optimism. Because the role of PrEP optimism is central in risk compensation models, to assess whether there is a relation between PrEP optimism and reduction of condom use when using PrEP in this sample and whether that relation is actually accounted for by not so much PrEP optimism but more a propensity to have overly optimistic expectations more generally. Moreover, the comprehensive representation of motivation in the adapted IMB-model will allow for the examination of how general and PrEP specific optimism co-exist with perceived susceptibility to HIV infection. The study team anticipates that general optimism will be associated not only with PrEP optimism, but also with condom optimism and decreased perceived susceptibility to HIV in the context of risk, condom, and PrEP use. Elucidating the relations between depression, pessimism, and perceptions of relationships and rapport with study team and risk behavior, as well as its core determinants, is a unique contribution of the present research. While depression and substance use have been well demonstrated in their relation to risk,[49-51] the manner in which these factors co-exist or contextualize core facilitators and barriers to one's funds of information, motivation, and behavioral skills is less well understood, but critical in the empirical guidance of support strategies for PrEP use.

Figure 1-2: Adapted IMB-model of PrEP and Condom Use



1.10.4 Rationale for drug level testing

Fostering adherence and minimizing social desirability bias in adherence reporting are challenges for prevention trials that are increasingly appreciated. For example, while reported adherence in the Carraguard microbicide trial was 96%, adherence utilizing an objective measure of applicator use was only 44%.[52] In HPTN 039, reported adherence to acyclovir was not associated with herpes virus isolation in regions where high levels of adherence were reported, suggesting substantial over-reporting of adherence.[53] All measures of adherence and pill-taking can be influenced by participants seeking to satisfy their roles, although electronic pill monitoring devices and pill counts may adjust for recall bias.

HPTN 067 will evaluate the use of drug levels in PBMCs as objective measures of drug exposure and pill-use. FTC-5'-triphosphate and tenofovir-5'-diphosphate have long intracellular half-lives (~48 and ~150 hours, respectively) such that measurements made using specimens collected at clinic visits will reflect pill-use over the previous days to weeks. Such measures of long term drug exposure are less influenced by "white coat" effects, where pills are utilized more in the day immediately prior to the clinic visit. The relationship between drug level and pill-use is complicated by individual factors that affect absorption, distribution, and clearance of drugs.

In this study, the relationships between drug exposure and pill-taking will be calibrated for each participant during a lead-in phase including DOT. In this manner, the study will have an objective measure of pill-use and over-reporting of pill-use for Weeks 10, 18 and 30 when plasma will be evaluated for drug levels. This objective measure will be used to more sensitively detect participants who have discontinued all pill-use despite reports to the contrary, and to identify the extent of over-reporting of pill-use in the three usage groups for the weeks prior to these evaluation periods. Recommendations for intermittent use may be associated with less over-reporting of pill-taking because intermittent regimens require more thoughtful behavior; therefore, social expectations for pill-use may be less. HPTN 067 may also provide important new information regarding the factors that explain variance between pill-taking and drug exposure in African and Asian populations. These factors may include sex, body size, age, and ethnic background, although this comparison may be confounded by near uniform and different genders in these two geographic regions.

1.10.5 Relevance to the goals of the HPTN

The goal of the HPTN is to identify effective methods to prevent HIV infection. While existing PrEP research may find that daily dosing is associated with some protection against HIV infection, there is little information available about how PrEP implementation and uptake can best be supported. Additional information that can identify core facilitators and barriers to PrEP use is needed to maximize the availability and effectiveness of PrEP. It is also possible that existing trials

may fail to demonstrate efficacy of daily PrEP, due to dose-related intolerance or insufficient adherence to regimens that may be poorly matched to risk behavior or sexual activity. HPTN 067 will test whether one dosing strategy is preferable to others for the purposes of future efficacy studies. In doing so, the IMB-model used to characterize PrEP use, risk, and changes in risk allows for a detailed examination of which factors appear most influential of PrEP use, across and within study arms, and to the use of condoms. HPTN 067 will test specific hypotheses regarding sexual and adherence behavior related information, motivation, and behavioral skills, with additional examination of the relative role of PrEP- and condom use-optimism, general optimism, depression, substance use, and social roles developed in regard to being part of this PrEP trial among participants. Across all arms, participants are supported by an IMB-model based, participant-centered counseling protocol to promote pill-taking and continued or increased condom use. The differences observed between the arms will reflect differences that would be anticipated to emerge in the context of PrEP when it is delivered with appropriate support. HPTN 067 has direct relevance to PrEP uptake, feasibility, adoption and it offers to provide a level of empirical guidance to better understanding and promoting these factors that have not been offered to date.

1.10.6 Design advantages

Chemoprophylaxis is a fast moving field with multiple studies in progress. It is impossible to predict with confidence the results of existing studies or when pivotal information will become available. HPTN 067 is designed to address questions that are significant regardless of the outcome of existing PrEP trials.

A key advantage of this protocol is that it brings together investigators and communities that are leading current pivotal studies in the PrEP field, including pre-clinical evaluation of dosing strategies in animal models and clinical trials of safety and efficacy of daily dosing in injection drug users, WSM, and MSM. This assures that there will be a benefit from insights gained during the current trials, including both published and unpublished findings.

This trial is designed to inform a larger efficacy study aimed at dose optimization. The efficacy study would have a non-inferiority design if daily oral TDF/FTV PrEP were found to be superior to standard interventions in current trials. Alternatively, if daily dosing is not found to be efficacious in current trials because of dose-related intolerance or poor adherence related to pill burden, the future efficacy study would have a superiority design versus standard of care, which would remain no use of PrEP.

Regardless of eventual design, a future efficacy study of intermittent PrEP requires guidance in terms of patterns of pill-taking adherence and a strong signal for acceptability and feasibility within the targeted participant groups. HPTN 067 will assess the feasibility of different intermittent dosing strategies, identify theory-based determinants of sexual and pill-taking behavior during PrEP use,

maintain cohorts of participants interested in intermittent PrEP, and build interagency infrastructure that is essential for efficacy evaluation, regardless of whether it utilizes superiority or non-inferiority designs. Because nearly 20,000 people are expected to finish PrEP trials in the next three years, there would be ample opportunity to fully power a non-inferiority study of daily versus intermittent PrEP. This study would develop the information, collaborative relationships, and infrastructure required to develop the next generation of PrEP research and program development.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective:

To test the hypothesis that recommending intermittent (non-daily) usage of oral FTC/TDF chemoprophylaxis, compared with recommending daily usage, will be associated with:

- Equivalent coverage of sex events with pre- and post-exposure dosing
- Lower number of pills needed for coverage and fewer pills used
- Decreased self-reported symptoms/side effects (both severity and frequency) during 24 weeks of self-administered use

2.2 Secondary Objectives:

- Develop objective measures of drug exposure by obtaining steady state pre-dose "trough" drug concentration in several biological matrices for participants during a lead-in period of weekly DOT
- To describe safety outcomes among PrEP users including adverse events among all participants and drug resistance and plasma HIV RNA levels among participants who seroconvert
- Assess differences between arms in the acceptability of different PrEP regimens and in perceptions of advantages and disadvantages of different regimens
- Assess differences by arm in adherence
- Evaluate the potential influence of PrEP usage on changes in sexual behavior, planning for sex, prediction of risky situations, and recognition of possible HIV exposure from baseline to final on-drug assessment in relation to PrEP optimism

2.3 Study Design

HPTN 067 is a Phase II randomized open-label clinical trial of oral FTC/TDF PrEP among HIV-uninfected men who have sex with men (MSM) and women who have sex with men (WSM) at high risk of acquiring HIV infection. The study includes a six weeks lead-in period including DOT at Enrollment and Weeks 1 through 4, followed by one week without dosing to determine individual steady state pharmacokinetics. This will provide the opportunity to create a pharmacokinetic analysis of drug levels to be expected at given rates of intake

(adherence) which will be analyzed as part of the secondary analysis to confirm self-reported data. Participants will then (at Week 6) be randomized to one of three dosage groups in a 1:1:1 ratio: daily dosing, time-driven dosing, and event-driven dosing. After randomization, participants will complete a 24-week period of self-administered dosing, with one visit four weeks after the completion of dosing (34 weeks total). Participants who acquire HIV infection during the study will discontinue dosing and will be followed until study closure and referred for post-trial care as per local regulations. A subset of study participants in each of the study arms (convenience sample) and clinic staff will also participate in a qualitative evaluation of the social and behavioral aspects of differing dosing strategies, to include focus groups and key informant interviews after Week 34.

2.4 Description of the intervention

2.4.1 Once-a-week directly observed dosing lead-in component

A six week lead period consisting of DOT at Enrollment and Weeks 1 through 4, followed by one week without dosing will be used to estimate steady-state drug levels and accumulation and decay constants for each individual. The purpose of obtaining these estimates is to interpret adherence measurements during the subsequent self-administered dosing phase of the study. During the DOT phase, all participants will begin the study by having weekly visits from Enrollment through Week 5. During this period, participants will begin learning how to use the EDM device prior to beginning the self-administered phase. At Enrollment through Week 4, participants will receive one directly observed dose per week of oral FTC/TDF (five doses total). No drug will be administered during Week 5. PBMC specimens will be collected for analyses of drug levels at Weeks 4 and 5. These values will be used to estimate the accumulation and decay constants and steady state levels of TFV-DP; FTC-TP may also be measured. Blood samples should be collected prior to dosing. Serum and hair samples will also be collected prior to dosing and stored at selected study visits, which may be used for comparison of PBMC drug levels to drug levels in those samples. These concentrations will be evaluated to test for steady-state and the "expected" pre-dose concentration for each individual. Week 4 and Week 5 data (Week 5 alone if steady-state has not been achieved) will provide a point estimate for the expected concentration at steady-state and an estimate of intra-individual variability in this pre-dose concentration. Decay will be monitored from drug dose concentration data collected at Week 6. Participants who miss any dose during this phase will not be randomized and will be replaced. The Study Specific Procedures (SSP) Manual will detail acceptable windows for the DOT phase.

2.4.2 Self-administered dosing component

After the 6-week lead-in period including DOT (Enrollment and Weeks 1 through 4 followed by no dose at Week 5), participants will be randomly assigned to one of three unblinded PrEP usage groups at Week 6: (1) daily usage, (2) time-driven usage, and (3) event-driven usage, as described in the Schema. Individuals will

participate in theory-based, participant-centered, individual, brief (10-15 minutes) counseling sessions optimized for each usage plan at study visits. This counseling approach will draw from well-established models (*e.g.*, motivational interviewing) and will be based on the IMB model adapted for this research. This counseling will also be informed by the current literature on effective strategies and approaches to promoting adherence to antiretroviral therapy (ART).[54, 55]

Essential content for the counseling approach will be derived from preliminary work with focus groups of individuals from eligible populations to be funded separately. This approach, entitled "Next Step Counseling", includes structural, cultural, and personal facilitators and barriers to daily, time-driven, and event-driven pill-use. This counseling approach seeks to target and address adherence-related information, motivation, and behavioral skills required to produce optimal rates of adherence. For different arms, the information and skills targeted differ slightly in content particularly in early sessions. All participants will receive regimen-specific information during their first counseling session, which will vary between but not within the study arms. Information regarding the mechanisms of FTC/TDF for potential HIV-prevention will be standardized across the arms, but the added messaging that focuses on how one's specific assigned regimen provides protection against infection will be arm (regimen) specific.

Additionally, messaging for preparatory skills needed for one's specific regimen schedule will be explored. For the daily arm, this exploration includes review of commonly used strategies for daily pill-taking (*e.g.*, dose timing, matching dose with daily event). For the time-driven arm, strategies to remember dose-taking twice weekly, ways to identify risk events requiring a post exposure dose, and 'rules of thumb' for when a post-exposure dose replaces a weekly dose or a weekly dose replaces a post-exposure dose will be discussed. For the event driven arm, strategies for sexual forecasting, those strategies discussed with the time driven arm for post-exposure and 'rules of thumb' for not exceeding recommended doses per week will be discussed. These issues will be re-visited as needed at subsequent sessions.

All remaining aspects of the semi-structured counseling approach to support PrEP use will be administered identically to participants through targeted discussions of pill-taking at each study visit. The exact content and strategies identified in each counseling session are individually targeted and tailored, thus the approach is intended to have the flexibility to identify and address specific strengths and weaknesses in integrating pill-taking into the ecology of one's daily life, which will vary at the level of the individual participant. While the content intentionally varies by participants, the discussion process of the pill-taking is standardized across participants and all arms. Exceptions, previously noted, are in first session in terms of information-delivery and the identification and exploration of regimen-specific skills.

Risk-reduction counseling for condom use will also be included, as is standard for PrEP trials, and will be enhanced to mobilize the participant-centered approaches

and skills developed with trainings and implementation of the Next Step Counseling protocol. All participants will be counseled about the known benefits, or lack thereof of PrEP, and that they should protect themselves in other ways, including using condoms during intercourse. All groups will be informed that missed doses should be taken when the person remembers, **but no more than two pills per 24-hour period, or seven pills per week should ever be taken**. Counseling at each study visit will target increasing the perceived ease of pill-taking and decreasing perceived burden of pill-taking, utilizing various client-centered, motivational interviewing and motivation enhancement strategies. All participants in each arm will receive identical counseling, although the informational content pertinent to pill-taking regimen will vary by arm, as will the relative weight of specific skills (***e.g.***, sexual planning skills development). All participants will receive a sufficient supply of study medication to last until the next scheduled visit, accompanied by an electronic pill monitoring system to track the timing and frequency of pill-use.

If individuals in the time- and event-driven arms are having sex frequently and taking the pills as recommended, they could end up taking the pills daily. Although preliminary research has indicated that this behavior is likely to be rare, the counseling and behavioral strategies that lead to daily use would remain distinct, as described above. As the participants in the time-driven arms will be encouraged to think about possible exposure to HIV in the context of pill taking, while the participant in daily arms will be encouraged to build pill taking into daily routines. Migration and preferences between arms will be monitored in this trial. In practice, there will undoubtedly be considerable variation in sexual frequency in the persons enrolled in this study and understanding the advantages and disadvantages of time-driven and event-driven usage strategies across the spectrum of sexual activity will be possible.

During this period of self-administered PrEP, participants will be asked to take pills only from the EDM device/case. The EDM cases electronically transmit the date and time of all case openings to a central server, which is then distributed to the interviewers conducting the weekly phone-based assessments of pill-taking and risk behavior. To assess pill-taking, the EDM-collected data will serve as a prompt for interviewers to query participants. For each case opening, the participant will be asked to describe what happened (number of pills loaded or dispensed (which could be zero if the case was opened with no release of tablets) and what happened with each dispensed tablet (taken or not taken; time/day of consumption if taken). After assessing the outcomes associated with each documented case-opening, participants will be asked if they had any additional pill-events that were not discussed to capture pills that were consumed but *not* dispensed from the EDM case. Pill-taking assessment will be followed by assessment of risk events (day/time and type of event) using a timeline follow-back approach, when needed or when time intervals assessed extend beyond one week.

Because the current assessment of adherence to PrEP regimens requires the collection of highly specific sexual and pill-taking behaviors (*e.g.*, time of sex events and times of pill-taking), retrospective recall of events and pill-taking in traditional one-month or three-month intervals is likely to prohibit the collection of the information needed with a reasonable degree of accuracy. Recent work suggests that shorter recall intervals produce more accurate reports of risk behavior,[56] while daily telephone based (as well as electronic diary and web-based diary) assessments have a well demonstrated history.[57-60] To balance potential sensitization with need for accurate recall, a weekly schedule of phone-based interviews will provide the main vehicle for collection of time and type of sexual events, as well as determination of outcomes for each EDM recorded device opening. Phone interviewers will be trained in neutral assessment approaches, with careful messaging to participants at each call providing permission statements and normalization of reporting "risk" events and missed pills to reduce self-presentation bias. Additionally, interviewers will be trained in timeline follow-back (TLFB) techniques for participants who have difficulty in recalling events and for use when the assessment interval has for whatever reason extended beyond approximately the past week. The TLFB approach is well supported in the literature for providing accurate reports of risk behavior.[61] To assist participants in recall, sexual behavior journals and small diary cards will be created for the purposes of the current research and offered to participants for use, although are not required. Participants opting to use these memory aids will be asked to use them when conversing with the interviewer on weekly calls. To minimize self-presentation bias, recording tools (journals or diary cards) are specific to risk behavior. We will also develop separate recording cards for recall of outcomes of opening the pill-container (*e.g.*, when more than one pill or no pills are dispensed, and approximate consumption times of pills dispensed at one time and taken at another time) that will similarly be made available, but are not required.

The data collected via these weekly interviews will be used to adjust the EDM-collected data to produce a continuous measurement of pill-taking throughout participation in this phase of the project. These data will also be used to produce the longitudinal assessment of risk (condom use or non-use). The adjusted EDM data and risk behavior data will be combined to calculate PrEP coverage of risk events.

2.4.2.1 Daily usage

Those randomized to the daily dosing group will receive recommendations to take FTC/TDF once a day regardless of sexual activity. Details regarding pill-taking counseling will be provided in the counseling manual.

2.4.2.2 Time-driven usage

Those randomized to the time-driven dosing group will be asked to take FTC/TDF twice weekly with a post-exposure boost. Specifically, they will

receive recommendations to take one pill two days per week, three to four days apart, regardless of sexual activity. In addition, they will be instructed to take a post-exposure booster dose within two hours after sexual intercourse, defined as any penile intromission, whether oral, vaginal, or anal, and whether or not condoms were used. The post-exposure dose should be taken after the first penile insertive sex and not repeated if there are multiple penile intromissions in a day. The post-exposure boost will also count as one of the twice-weekly doses if it occurs on the prescribed day. Pill-taking counseling in the time-driven arm will be the same as in the daily arm, with adjustments in education provided for the recommended regimen (*e.g.*, additional information pertaining to booster doses).

2.4.2.3 Event-driven usage

Those randomized to the event-driven dosing group will be asked to take one tablet of FTC/TDF, preferably between 24 to 48 hours prior to sexual intercourse and a post-exposure booster dose within two hours of sexual intercourse, defined as any penile intromission, whether oral, vaginal, or anal, and whether or not condoms were used. If the participant anticipates sexual intercourse, but did not take the dose 24 hours prior to the event, the participant should take the pre-exposure dose as soon as possible before the event. The post-exposure boost will also count as a pre-exposure dose for the next sex act that occurs up to 48 hours later. Pill-taking counseling in the event-driven arm will be the same as in the daily arm, with adjustments in education and skills-building provided for the recommended regimen (*e.g.,* additional information pertaining to booster doses and pre-exposure doses, and skills development in forecasting sexual exposures to facilitate appropriate pre-event dose taking).

3.0 STUDY POPULATION

The study will enroll 360 evaluable HIV-uninfected volunteers: 180 MSM at the CDC TUC Silom Community Clinic in Bangkok, Thailand, and 180 WSM at Emavundleni Centre, The Desmond Tutu HIV Foundation in Cape Town, South Africa.

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

3.1 Inclusion Criteria

- At least 18 years old
- Literacy in one of the study languages (Thai, Xhosa and/or English)
- Able to provide written informed consent
- Able to provide weekly telephonic updates
- Within 70 days of Enrollment:

- serum creatinine ≤ upper limit of normal (ULN) and calculated creatinine clearance of at least 70 mL/min by the Cockcroft-Gault formula where:
  - eCcr (female) in mL/min = [(140 – age in years) x (lean body weight in kg) x 0.85] / (72 x serum creatinine in mg/dL)
  - eCcr (male) in mL/min = [(140 – age in years) x (lean body weight in kg)] / (72 x serum creatinine in mg/dL)
- Serum phosphate ≥ the lower limit of normal (LLN)
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2 x ULN
- Hemoglobin ≥ 10 g/dL
- Hepatitis B virus (HBV) immunity, demonstrated as a negative test for hepatitis B surface antigen (HBsAg) and a positive test for either HBsAb or hepatitis B core antibody (HBsAb) test

- Willing and able to provide adequate locator information.

Note: Participants without HBV immunity at screening will be offered vaccination as indicated in Section 5.1.

3.1.1 MSM

- Male at birth
- Reporting anal intercourse with at least one man in the past six months
- One or more of the following risk factors for HIV acquisition in the past six months according to self report:
  - Sexual intercourse with more than one man
  - History of an acute sexually transmitted infection (STI)
  - Sex in exchange for money, goods or favors
  - Condomless intercourse (oral, anal or vaginal) with a partner known to be HIV-infected or of unknown HIV infection status according to self report

3.1.2 WSM

- Female at birth or self identify as female
- Not pregnant or breastfeeding
- Not able or intending to become pregnant during the next year
- If able to become pregnant, self reported use of an effective method of contraception at Enrollment, and intending to use an effective method for the next 34 weeks (refer to Section 4.6 for effective methods of contraception)
- One or more of the following risk factors for HIV acquisition in the past six months according to self report:
  - Sexual intercourse with more than one man
  - History of an acute STI
  - Sex in exchange for money, goods or favors
  - Condomless intercourse (oral, anal or vaginal) with a partner known to be HIV-infected or of unknown HIV infection status

3.2 Exclusion Criteria

- Proteinuria 2+ or greater at screening
- Glucosuria 2+ or greater at screening
- Serious and active medical or mental illness
- One or both HIV rapid tests is reactive at Screening or Enrollment, regardless of subsequent HIV diagnostic test results
- Signs or symptoms suggestive of acute HIV infection
- Use of hypoglycemic agents for diabetes or agents with known nephrotoxic potential
- Serum phosphate level below site laboratory LLN (lower limit of normal)
- Current participation (or participation within three months of screening) in any HIV prevention study.
- Previous or current participation in an HIV vaccine trial.
- Acute or chronic HBV infection
- Participant has a psychological or social condition or an addictive disorder that would preclude compliance with the protocol
- Any other reason or condition that in the opinion of the IoR would interfere with participation, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

3.3 Recruitment Process

Site Institutional Review Board (IRB)-approved media advertisements, telephone scripts, and fliers may be used by recruiters at venues of socialization, open houses, and public events.

MSM will be recruited from the Bangkok MSM Cohort study, an ongoing prospective study of HIV infection among 1,000 HIV negative MSM at the Silom Community Clinic.

The community education and recruitment team located at the Emavundleni Centre will use their extensive networks in the Nyanga District to recruit WSM to this study. They will also utilize the IRB-approved pre-screening protocol at the Emavundleni Centre to locate potential recruits who will be invited to participate.

3.4 Co-Enrollment Guidelines

Study participants may not enroll in other HIV vaccine or interventional prevention trials to reduce participant burden with study visits, to facilitate high levels of adherence and retention (including compliance with study medications), to avoid potential unblinding of HIV vaccine trials, and to avoid confounding in the interpretation of the primary and secondary endpoint data.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain him/her for 34 weeks of follow-up in order to minimize possible bias associated with loss-to-follow-up. For each lost participant who participated in all or part of the DOT phase but was not randomized, an additional participant will be enrolled. Optimally, participant retention procedures will be established to achieve at least 90% retention at Week 34 (from randomization). Study site staff are responsible for developing and implementing local standard operating procedures (SOPs) to target this goal. Components of such procedures will include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit
- Thorough explanation of the importance of all three study treatment groups to the overall success of the study
- Collection of detailed locator information at the Screening visit, and active review and updating of this information at each subsequent visit
- Use of mapping techniques to establish the location of participant residences and other locator venues
- Use of appropriate and timely visit reminder mechanisms
- Immediate and multifaceted follow-up on missed visits
- Mobilization of trained outreach workers or "tracers" to complete in-person contact with participants at their homes, other community locations, and friends and family
- Regular communication with the study community at large to increase awareness about HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits

3.6 Participant Withdrawal

Regardless of the participant retention methods described above, participants may voluntarily withdraw from the study for any reason at any time. The IoR 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, Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, and Coordinating and Operations Center (CORE) Protocol Specialist. Participants who withdraw prior to Randomization/Week 6, or who miss any dose during the DOT will not be randomized and will be replaced.

Desire to stop using the study medication or to use study medication in a manner that differs from the recommended usage is not a reason for participant withdrawal from the study. These participants should be encouraged to remain in the study and complete study procedures. Participants should continue to be provided study medication as long as they express interest in continuing. Participants who report intentional overdosage of drug (more than 1 tablet in 2

hours, more than 2 tablets in 24 hours, or more than 7 tablets in 7 days) should receive repeated counseling regarding pill-use and study medication should be withheld in consultation with the Protocol Safety Review Team (PSRT) if overdosage is deemed likely to occur again despite repeated counseling.

Participants may be withdrawn if the study sponsor, government or regulatory authorities, [including the Office of Human Research Protection (OHRP) and the US FDA] or site IRBs/Ethics Committees (ECs) terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (as described in Section 5.7) of participants who terminate from the study prior to Week 34, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4.0 STUDY DRUG/INTERVENTION

4.1 Study Drug/Intervention Formulation/Content

FTC/TDF is a fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF. It is available as Truvada®, a medication approved by the U.S. FDA [62] for treatment of HIV-1 infection. Further information on Truvada® is available in the current package insert.[62]

4.2 Study Drug/Intervention Regimen(s) and Administration

After the 6-week lead-in period including DOT, participants will be randomly assigned to one of three unblinded PrEP usage groups of oral therapy: (1) daily usage, (2) time-driven usage, and (3) event-driven usage. During this period of self-administered therapy, FTC/TDF tablets will be dispensed in an EDM device as outlined in the Study Specific Procedures.

Daily Dosing
Those randomized to the daily dosing group will receive recommendations to take one FTC/TDF tablet once a day with or without food regardless of sexual activity.

Time-Driven Dosing
Those randomized to the time-driven dosing group will be asked to take one FTC/TDF tablet twice weekly with or without food with a post-exposure boost. Specifically, they will receive recommendations to take one tablet two days per week, three to four days apart, regardless of sexual activity. In addition, they will be instructed to take a post-exposure booster dose of one tablet within two hours after sexual intercourse, defined as any penile intromission, whether oral, vaginal, or anal, and whether or not condoms were used. The post-exposure dose should be taken after the first penile insertive sex and not repeated if there are multiple penile intromissions in a day. The post-exposure boost will also count as one of the twice-weekly doses if it occurs on the prescribed day.

Event-Driven Dosing

Those randomized to the event-driven dosing group will be asked to take one tablet of FTC/TDF with or without food, preferably between 24 to 48 hours prior to sexual intercourse and a second post-exposure booster dose within two hours of sexual intercourse, defined as any penile insertive sex, whether oral, vaginal, or anal, and whether or not condoms were used. If the participant anticipates sexual intercourse, but did not take the dose 24 hours prior to the event, the participant should take the pre-exposure dose as soon as possible before the event. The post-exposure boost will also count as a pre-exposure dose for sex that occurs up to 48 hours later.

Note: For all arms, no more than two tablets per 24-hour period, or seven tablets per week should ever be taken.

4.3 Study Drug/Intervention Supply and Accountability

Study Product Supply, Distribution and Accountability

Emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg study product tablets are manufactured and provided by Gilead Sciences, Inc. under the trade name Truvada®. FTC/TDF tablets must be stored in the pharmacy in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity. Store at 25°C. Excursions permitted between 15° to 30°C.

Study Product Acquisition

Emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg study product will be supplied by the NIAID Clinical Research Products Management Center (CRPMC). The study site pharmacist can obtain FTC/TDF study products through the CRPMC by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks*, and instructions in the SSP Manual.

Study Product Accountability

The site pharmacist must maintain complete records of all study products received from the NIAID Clinical Research Products Management Center and subsequently dispensed to study participants. All study products must be stored in the pharmacy. All unused study products must be destroyed in accordance with the procedures outlined in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* and according to local procedures.

4.4 Toxicity Management

In general, the site investigator has the discretion to hold study drug at any time if she or he feels that continued study drug use would be harmful to the participant, or interfere with treatment deemed clinically necessary according to the judgment

of the investigator. Unless otherwise specified below, the investigator should immediately consult the PSRT for further guidance in restarting study drug or progressing to permanent discontinuation.

4.4.1 Grading System

The grading system is located in the Division of AIDS Table for Grading Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification August 2009), which can be found on the Regulatory Support Center (RSC) Web site: http://rsc.tech-res.com/safetyandpharmacovigilance/.

4.4.2 Discontinuation of Study Drug in the Presence of Toxicity

Grades 1 or 2
In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study drug, and that is not specifically addressed below, may continue use of the study drug per protocol.

Grade 3
Participants who develop a Grade 3 AE or toxicity that is not specifically addressed below and is judged to be related to study drug by the IoR/designee, study drug use should be temporarily discontinued in consultation with the PSRT. In general, and unless otherwise decided in consultation with the PSRT, the investigator should re-evaluate the participant at least weekly for up to 2 weeks (or for 2 weeks following the receipt of the results for lab toxicities) to document resolution of toxicity to less than Grade 2. The study drug should be permanently discontinued if improvement to severity ≤ Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study drug use is resumed and the same Grade 3 AE recurs at any time, the IoR/designee must consult the PSRT for further guidance on holding of study drug, frequency of reevaluation or progression to permanent discontinuation of the study drug.

Grade 4
Participants who develop a Grade 4 AE or toxicity that is not specifically addressed below (regardless of relationship to study drug) should have the study drug temporarily discontinued. The IoR/designee must consult the PSRT and continue the temporary study drug hold until a recommendation is obtained from the PSRT. In general, study drug use will not be resumed if the Grade 4 AE is considered related to study drug use. If, in consultation with the PSRT, study drug use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study drug must then be permanently discontinued.

4.4.3 General Criteria for Discontinuation of Study Drug

Participants may voluntarily discontinue the study drug for any reason at any time. Site IoRs will permanently discontinue participants from study drug per protocol for any of the specific criteria below, which may be further clarified in the SSP Manual. Site IoRs also may permanently discontinue participants for reasons not shown here or in the SSP Manual. In such cases, the Site IoRs should first query the PSRT for review. The PSRT will provide a written response to the site indicating their recommendation based on careful review of all relevant data.

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

- Participants who miss any dose during the DOT phase (Weeks 1-5) will not be randomized and therefore will not continue to the self-administered phase.
- HIV-1 infection. Such participants will not resume study drug use at any time. **Study drug will be held immediately upon recognition of the first reactive rapid HIV test or positive GenAptima HIV RNA assay.** The IoR/designee must permanently discontinue study drug if HIV infection is confirmed. A decision to resume study drug in participants who are subsequently confirmed to be HIV-uninfected requires approval of the Protocol Chair, PSRT and HPTN NL.
- Viral hepatitis. Such participants will not resume study drug use at any time.
- Pregnancy. A participant who becomes pregnant must not resume study drug use.
- Breastfeeding. Study drug use may not resume for participants who report breastfeeding at any time after enrollment.

Any participant who prematurely discontinues study drug should be followed according to the procedures in the Schedule of Evaluations in Appendix I, with the exception of study drug dispensation, counseling, and adherence measurements.

Study drug will be temporarily withheld from a participant for any of the following reasons:

- Report of use of prohibited concomitant medications described in Section 4.8. Study drug use may resume when the participant reports that s/he is no longer taking the prohibited medication, provided other reasons for temporary study drug hold/permanent discontinuation do not apply.
- The participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing study drug use, according to the judgment of the IoR/designee. The IoR/designee must consult the PSRT on all temporary study drug holds instituted for this reason for further guidance on resuming study drug use, continuing the temporary hold, or progressing to permanent discontinuation. If study drug use is temporarily held/permanently discontinued

for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume study drug use at that time.

Participants who temporarily or permanently discontinue study drug will be instructed to return all study drug as soon as possible.

4.5 Management of Specific Toxicities

Specific guidance related to product hold is also noted here, as it pertains to the clinical management of toxicities.

4.5.1 Nausea, Vomiting, and Diarrhea

Participants with Grade 1 or 2 nausea, vomiting, or diarrhea may be treated symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories at the discretion of the site investigator. The site investigator should order any clinically relevant laboratory analyses (per judgment of the IoR/designee). Participants should be reminded to take study drug with food.

Participants with Grade ≥ 3 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, must discontinue the study drug temporarily until grade 2 or lower and be treated symptomatically. Should condition(s) not improve to Grade ≤2 within 7 days, the IoR/designee should consult the PSRT for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug.

Repeat episodes of these events will be handled independently, and the instruction above will be followed for each event.

4.5.2 AST/ALT Elevations

Note that all study participants will either be immune to HBV at study entry, or will receive HBV vaccination. Therefore, HBV infection is not likely to be a cause of AST/ALT elevations.

Careful assessments should be done to rule out the use of alcohol, lactic acidosis syndrome, non-study medication-related drug toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST or ALT of any grade. The participant must be carefully assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain, or hepatomegaly. If the AST/ALT elevation is considered most likely to be due to concomitant illness or

medication, standard management, including discontinuation of the likely causative agent, if possible, should be undertaken. If symptoms or signs of clinical hepatitis are present, study drug must be held or discontinued (see below).

Grade 1

For study participants with less than Grade 1 AST and ALT at study entry, an increase to Grade 1 AST or ALT even in an asymptomatic participant may be of concern.

AST and ALT must be repeated as soon as possible (at most within 1 week of the receipt of the results). Study drug may be continued while repeating AST and ALT at the discretion of the investigator provided the participant is asymptomatic. Should the repeat AST and ALT testing indicate a continuation of Grade 1, the PSRT should be immediately consulted.

In the case of symptomatic participants, study drug will be held temporarily, and management (including resumption of study drug) should be arranged in consultation with the PSRT.

Grade 2

Participants should have AST/ALT re-checked as soon as possible (at most within 1 week of the receipt of the results) and then be followed weekly until levels are Grade $\leq$ 1. The frequency of follow up may be altered at the discretion of the site investigator following consultation with the PSRT. Study drug may continue at the discretion of the investigator provided the participant is asymptomatic.

In the case of symptomatic participants, study drug will be held temporarily, and management (including resumption of study drug) should be arranged in consultation with the PSRT.

Grade 3

Study drug should be temporarily held for any Grade 3 AST or ALT. Participants should have AST/ALT re-checked as soon as possible (at most within 1 week of the receipt of the results). Participants should then be followed weekly until levels are Grade $\leq$ 1. Resumption of study drug should be arranged in consultation with the PSRT. If improvement to Grade $\leq$1 cannot be documented within three weeks of receiving the Grade 3 results, study drug must be permanently discontinued.

If following a Grade $\geq$3 event(s) the participant is permitted to resume study drug, but has an additional event (AST and/or ALT) at a Grade 3 level, the

IoR/designee must temporarily hold the study drug, offer symptomatic treatment (if appropriate), and order any clinically relevant laboratory analyses (per judgment of the IoR/designee). The PSRT should be consulted for further guidance on continuing the temporary hold, clinical management of the participants, or progressing to permanent discontinuation of the study drug.

Grade 4
Study drug should be permanently discontinued for any Grade 4 AST or ALT and the PSRT should be immediately notified. Participants should have AST/ALT re-checked as soon as possible (at most within 1 week of the receipt of the results). Participants should then be followed weekly until levels are Grade ≤ 1 unless indicated by the PSRT.

Note for all Grades
If the investigator has determined in consultation with the PSRT that the case has stabilized, it may be possible to decrease the frequency of follow-up laboratory testing in addition to resumption of study drug.

4.5.3 Calculated Creatinine Clearance

If the calculated creatinine clearance is ≤50mL/min, it should be confirmed within 1 week of the receipt of the results, and the PSRT should be consulted. If the calculated creatinine clearance is confirmed to be ≤50mL/min, the study drug must be permanently discontinued. Participants who fail to have a confirmed test within 7 days of receiving the initial result, should be permanently discontinued from use of the study drug.

If re-testing yields a result >50mL/min, the IoR/designee must consult the PSRT for further guidance on resuming study drug use, continuing the hold temporarily, or progressing to permanent discontinuation.

By which the investigator in consultation with the PSRT has determined that the case has stabilized, it may be possible to decrease the frequency of follow-up laboratory testing in addition to resumption of study drug.

4.5.4 Hypophosphatemia

Grades 1 and 2
The phosphate should be repeated within 2 weeks of the receipt of any initially abnormal results. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution. Other causes of

phosphate loss should be evaluated. Unless other temporary study drug hold requirements apply, study drug need not be held.

Grade 3

The phosphate should be repeated within 1 week of receipt of any initially abnormal results, and should be accompanied by serum creatinine testing and urine dipstick for protein/glucose. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution, and other causes of low phosphate should be investigated. Participants with any of the following results (of tests accompanying the repeat phosphate test) will have study drug held:

- Proteinuria >3+
- Glycosuria >3+
- Creatinine ≥1.5 X ULN
- Creatinine clearance ≤50 mL/min

Participants may continue study drug provided that:

- Study drug hold is not otherwise indicated (*e.g.*, due to the results of creatinine, creatinine clearance, urine protein, and/or urine glucose)
- Phosphate levels will be retested approximately weekly until return to ≤Grade 2, unless other retesting schedule has been advised by the PSRT

Grade 4

The phosphate should be repeated within 1 week of the receipt of any initially abnormal results, and should be accompanied by serum creatinine testing and urine dipstick for protein/glucose. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution. Other causes of low phosphate should be investigated.

Participants will have study drug held, and the PSRT must be immediately contacted. Phosphate levels will be retested approximately weekly until return to ≤Grade 2, unless another retesting scheduled has been advised by the PSRT. Participants may resume study drug, provided that:

- Study drug hold is not otherwise indicated (*e.g.*, due to the results of serum creatinine, creatinine clearance, urine protein, and/or urine glucose)
- The phosphate level has returned to ≤Grade 2
- A request to resume study drug is approved by the PSRT

PSRT notification should occur for any result ≥Grade 2 for protein or glucose measured by urine dipstick performed at the time of confirmatory draw for a phosphate level.

4.5.5 Proteinuria

Proteinuria will be assessed by urine dipstick. A finding of 1+ proteinuria should be confirmed with a second urine dipstick performed no earlier than one week but no later than 2 weeks after detection of the first 1+ proteinuria. Proteinuria of 2+ or greater does not need to be confirmed at a separate visit.

The IoR/designee should temporarily hold study drug in the following circumstances:

- Detection of 3+ or greater proteinuria at any visit. Study drug should be held regardless of serum creatinine or phosphorus results obtained at the time of proteinuria detection. Urine dipstick testing and serum creatinine and phosphate should then be performed monthly for at least three months.

- Detection of 2+ proteinuria. Study drug should be held until results of serum creatinine and phosphorus results obtained at the time of proteinuria detection are available. Study drug hold should continue if hold criteria outlined for serum creatinine and/or phosphorus are met. If neither value meets criteria for study product hold, study drug should be resumed.

- Detection of 1+ proteinuria confirmed on two separate visits. Study drug should be held only if serum creatinine or phosphorus results obtained at the time of detection of proteinuria meet hold criteria (Sections 4.5.3 and 4.5.4).

4.5.6 Glycosuria

Glycosuria will be assessed by urine dipstick. A finding of 1+ glycosuria should be confirmed with a second urine dipstick performed no earlier than one week but no later than 2 weeks after detection of the first 1+ glycosuria. Glycosuria of 2+ or greater does not need to be confirmed at a separate visit.

The IoR/designee should temporarily hold study drug in the following circumstances:

- Detection of 3+ or greater glycosuria at any visit. Study drug should be held regardless of serum creatinine or phosphorus results obtained at the time of proteinuria detection. Urine dipstick testing and serum creatinine and phosphorus should then be performed monthly for at least three months.

- Detection of 2+ glycosuria. Study drug should be held until results of serum creatinine and phosphorus results obtained at the time of glycosuria detection are available. Study drug hold should continue if hold criteria outlined for

serum creatinine and/or phosphorus are met (Sections 4.5.3 and 4.5.4). If neither of these values meets criteria for study drug hold, study drug should be resumed.

- Detection of 1+ glycosuria confirmed on two separate visits. Study drug should be held only if serum creatinine or phosphorus results obtained at the time of detection of glycosuria meet hold criteria.

4.5.7 HIV Infection

Frequent testing for HIV acquisition during the study period will allow prompt cessation of study drug in an HIV-infected participant, minimizing the risk that resistant virus will emerge. Therefore, HIV testing will be performed at Screening, Enrollment, and Weeks 4, 6, 10, 14, 18, 22, 26, 30 and 34, and also (1) at any visit during which signs or symptoms of a viral syndrome are present, (2) at any visit where a participant expresses concerns about recent acquisition of HIV infection, or (3) at the discretion of the site investigator. If a recent infection is suspected, a GenAptima HIV RNA test for acute HIV infection will be performed. At the Screening and Enrollment visits, individuals will be deferred and referred for evaluation and care if they have any signs or symptoms consistent with acute (pre-seroconversion) HIV infection, or if they express a concern about recent HIV infection. Signs and symptoms consistent with acute HIV infection include fever (temperature > 38° C), pharyngitis, or a new rash. Evaluation of possible acute HIV infection prior to enrollment will be performed outside of the study, according to local testing guidelines. If an individual is confirmed to be HIV-uninfected after evaluation, they may resume the Screening and Enrollment process.

Any enrolled participants who acquire HIV infection during the study will permanently discontinue study product and will be followed after Enrollment at Weeks 4, 6, 10, 14, 18, 22, 26, 30 and then every 12 weeks after Week 30 until the last study participant completes follow-up at the study site. HIV-infected participants will be followed to contribute information regarding HIV outcomes after PrEP exposure, to maintain confidentiality, and to comply with expectations of communities. Participants who test positive for HIV during the DOT phase will be replaced, but will be continued to be followed.

4.6 Clinical Management of Pregnancy

Receipt of study medication by biologically female study participants requires use of an effective method of contraception, including an intrauterine device (IUD),

hormonal contraception, or sterilization. All participants should also use male or female condoms for prevention of HIV and other STIs. As needed, study staff will provide contraceptive counseling to enrolled participants throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery and/or active referrals to local service providers. Study staff also will provide participants with male and/or female condoms and counseling on use of condoms.

Pregnancy testing will be performed at Screening, Enrollment and at Weeks 4, 6, 10, 14, 18, 22, 26, and 30. Participants will be encouraged to report all signs or symptoms of pregnancy to study staff. Participants who are pregnant will stop study drug but will continue to be followed according to the schedule of visits. The site IoR or designee will counsel any participants who become pregnant regarding possible risks to the fetus according to site-specific SOPs. Participants may not enroll if they are currently breastfeeding and study drug should be discontinued if any participant identifies that she is breastfeeding after enrollment. The IoR or designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

Participants who are pregnant at the Week 30 visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant Case Report Forms (CRFs). Outcomes meeting criteria for expedited adverse event reporting also will be reported.

4.7 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. Site IoR may, with the approval of the PSRT, withdraw participants before their scheduled termination visit to protect their safety. Participants who withdraw prior to Randomization/Week 6, or who miss any dose during the DOT will not be randomized. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the OHRP or US FDA), or site IRBs/ECs terminate the study prior to its planned end date. Site investigators are required to consult the Protocol Chair and Protocol Biostatistician prior to the termination of any study participant. Study staff will record the reason(s) for all withdrawals in participants' study records.

Any participant who wishes to discontinue study participation prematurely for any reason should undergo the evaluations regularly scheduled for Weeks 30 prior to discontinuation and dismissal from the study, provided that the participant is willing to do this.

4.8 Concomitant Medications

With the exception of medications listed as prohibited (see below, this section), enrolled study participants may use concomitant medications during study participation. All concomitant medications, including prescribed and over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations reported within the 70 days prior to study enrollment and throughout the course of the study will be recorded on the Case Report Forms (CRF) designated for that purpose. Medications used for the treatment of AEs that occur during study participation also will be recorded on applicable study case report forms.

Should participants report use of any of the following medications, they will be required to discontinue use of study drug: interleukin therapy, medications with significant nephrotoxic potential (including but not limited to amphotericin B, aminoglycosides, cidofovir, foscarnet and systemic chemotherapy), and medications that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid).

5.0 STUDY PROCEDURES

An overview of the study visit and procedures schedule is presented in Appendix I. Study visits will occur at Screening, Enrollment, at Weeks 1, 2, 3, 4 and 5 during the DOT lead-in phase, at Week 6 (randomization), and at Weeks 10, 14, 18, 22, 26, and 30 during the self-administered PrEP phase; a final visit will be conducted four weeks after completion of the dosing phase (at Week 34). Presented below is additional information on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites will be provided in the SSP Manual.

5.1 Screening

Screening procedures may occur over one or more visits. All participants must provide written informed consent for screening before completing any other procedures. Participants who fail screening for any reason may rescreen one additional time.

The following procedures will occur as part of screening:

<u>Administrative, Behavioral, and Regulatory Procedures</u>

- Informed consent
- Assign participant ID

- Collection of locator information
- Demographics information
- Behavioral Assessment (Computer Assisted Self Interview [CASI])

Clinical/Counseling Procedures

- Medical history (including concomitant medications)
- HIV risk reduction counseling

Laboratory Procedures

- Urine specimen for pregnancy testing for women with reproductive potential
- Urine dipstick for protein and glucose
- Blood specimen for the following:
  - HIV rapid testing, with confirmatory testing if one or both tests is reactive
  - Complete blood count (CBC)
  - Serum creatinine
  - Serum phosphate
  - AST/ALT
  - HepBsAg
  - HepBsAb and HepBCore Ab testing (if HepBsAg is negative)
  - Plasma for storage

Participants who are susceptible to HBV infection will be offered HBV vaccination. They may be retested for evidence of HBV immunity after the second dose of HBV vaccine.

Screening may be discontinued at any time if a participant is found to be ineligible. HIV counseling and testing will be offered to everyone who consents to screening. Sites will follow the HIV testing algorithm for screening included in the SSP Manual. If a reactive result is obtained for one or both of the HIV rapid tests, the person is not eligible for the study. Additional testing to confirm HIV infection will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be referred for appropriate care.

If all laboratory tests and interview screening indicate that an individual is eligible for the study, s/he will be asked to return to the site to provide informed consent for enrollment after the study is thoroughly explained to him/her. Those who are not eligible will be informed that they do not meet the requirements of the study and, if necessary, will be referred for appropriate medical care. There must be no more than 70 days between Screening and Enrollment.

5.2 Enrollment

If all Inclusion/Exclusion Criteria are met, then the participant may enroll. Participants with one or more reactive HIV rapid test results will not be eligible

for the study. Final eligibility determination and enrollment must be completed within 70 days from the time of the first blood draw for the screening HIV test. The effective point of enrollment is the time of first directly observed weekly dosing. The effective point of randomization is the assignment of study arm at the Week 6 visit. Participants must be present at the study site for enrollment.

The following procedures will occur as part of enrollment:

Administrative, Behavioral, and Regulatory Procedures

- Confirm locator information
- Confirm eligibility

Clinical/Counseling Procedures

- Administer study drug (DOT)
- HIV risk reduction counseling
- Interim medical history including concomitant medications
- Full physical examination
- Orientation to the EDM device

Laboratory Procedures*

- Urine specimen for pregnancy testing for women with reproductive potential
- Blood specimen for the following:
  - HIV rapid testing, with confirmatory testing if one or both tests is reactive. Note: if one or both HIV rapid tests are reactive, the participant is ineligible to enroll in this study (should not receive study drug).
  - Plasma for storage

*All HIV rapid testing and specimen collection should be completed prior to administration of study medication.

5.3 Weeks 1-5

A period of DOT will be used to estimate steady-state drug levels and accumulation and decay constants for each individual. During the DOT phase, all participants will begin the study by having weekly visits from Enrollment through Week 5. At Enrollment through Week 4, participants will receive one directly observed dose per week of oral FTC/TDF (five doses total). No drug will be administered during Week 5. Participants who miss any dose during this period will not be randomized and will be replaced.

The following procedures will occur during Weeks 1 through 5:

Administrative, Behavioral, and Regulatory Procedures

- Confirm locator information
- Social Harms Assessment

Clinical/Counseling Procedures

- HIV risk reduction counseling (Week 4 only)
- Administer study drug (DOT) at Weeks 1 through 4
- Interim medical history including concomitant medications
- AE Assessment

Laboratory Procedures*

- Specimens collected at Week 4 only (not collected at Weeks 1, 2, 3, or 5):
  - Urine specimen for pregnancy testing for women with reproductive potential
  - Blood specimen for the following:
    - HIV rapid testing, with confirmatory testing if one or both tests is reactive
    - Dried blood spots (DBS) for storage**
    - AST/ALT
    - Serum Creatinine

- Specimens collected at Weeks 4 and 5 only (not collected at Weeks 1, 2, or 3):
  - Blood draw for the following:
    - Plasma for storage
    - PBMCs for storage
    - Serum for storage
  - Hair for storage
  - Urine for storage

No medication administered at Week 5.

*All HIV rapid testing and specimen collection should be completed prior to redosing of study medication.
**DBS are stored for genetic testing related to drug metabolism and/or HIV infection, provided that the participant provided consent for this testing. Consent for genetic testing is optional and will not affect study participation.

5.4 Week 6/Randomization

After the 6-week lead-in period including DOT, participants will be randomly assigned to one of three unblinded PrEP usage groups: (1) daily usage, (2) time-driven usage, and (3) event-driven usage. Participants will receive counseling optimized for each usage plan. Participants must be present at the study site for randomization.

The following procedures will occur during Week 6:

Administrative, Behavioral, and Regulatory Procedures

- Confirm locator information
- Randomization

- Social harms assessment
- Behavioral Assessment (CASI)

Clinical/Counseling Procedures

- Adherence orientation
- HIV risk reduction counseling
- AE assessment
- Study drug supply and associated counseling
- Symptom driven physical examination
- Interim medical history including concomitant medications

Laboratory Procedures*

- Urine specimen for pregnancy testing for women with reproductive potential
- Blood specimen for the following:
  - HIV rapid testing, with confirmation if one or both HIV rapid tests is reactive
  - Plasma for storage
  - PBMCs for storage
  - Serum for storage
- Hair for storage
- Urine for storage
- Urine dipstick for protein and glucose

*All rapid testing and specimen collection should be completed prior to redosing of study medication.

5.5 Weeks 7 through 29

The following procedures will occur during Weeks 7 through 29 (Visits conducted at Weeks 10, 14, 18, 22, and 26):

Administrative, Behavioral, and Regulatory Procedures

- Weekly telephone or personal contact
  - Review of EDM and sexual intercourse events
- Confirm locator information
- Social Harms Assessment

The following additional procedures will occur at Week 18:

- Behavioral Assessment (CASI)

Clinical/Counseling Procedures

- HIV risk reduction counseling
- AE assessment
- Study drug supply, pill counts and associated counseling
- Symptom driven physical examination

- Interim medical history including concomitant medications

Laboratory Procedures*
All Visits:
- Urine specimen for pregnancy testing for women with reproductive potential
- Blood specimen for the following:
  - HIV rapid testing, with confirmation if one or both tests is reactive
  - Plasma for storage

Weeks 10 and 18 only:
- Blood specimen for the following:
  - CBC
  - Serum creatinine
  - Serum phosphate
  - AST/ALT
  - PBMCs for storage
  - Serum for storage
- Hair for storage
- Urine for storage
- Urine dipstick for protein and glucose

*All HIV rapid testing and specimen collection should be completed prior to redosing of study medication.

5.6 Week 30

The following procedures will occur during Week 30:

Administrative, Behavioral, and Regulatory Procedures
- Confirm locator information
- Social harms assessment
- Behavioral Assessment (CASI)

Clinical/Counseling Procedures
- HIV risk reduction counseling
- AE assessment
- Return of EDM device and pill count
- Symptom driven physical examination
- Interim medical history including concomitant medications

Laboratory Procedures*
- Urine specimen for pregnancy testing for women with reproductive potential
- Blood specimen for the following:
  - HIV rapid testing, with confirmation if one or both tests is reactive
  - CBC

- Serum creatinine
- Serum phosphate
- AST/ALT
- Plasma for storage
- PBMCs for storage
- Serum for storage

- Hair for storage
- Urine for storage
- Urine dipstick for protein and glucose

5.7 Week 34

The following procedures will occur during or after Week 34 (post study follow-up visit):

Administrative, Behavioral, and Regulatory Procedures

- Social harms assessment
- Focus groups and key informant interviews with selected study participants and site staff are to be conducted after Week 34 *

Clinical/Counseling Procedures

- HIV risk reduction counseling

Laboratory Procedures

- HIV rapid testing, with confirmation if one or both tests is reactive
  - Plasma for storage if one or both HIV rapid tests is reactive
- Urine dipstick for protein and glucose

*Note: The focus groups and key informant interviews with selected participants and site staff may be done at any time within a 3 month window after Week 34.

5.8 Participants who have suspected or documented HIV infection during the study

The FDA-cleared Amplified Probe by Transcription Mediated Amplification (APTIMA) HIV-1 RNA Qualitative Assay (Gen-Probe, Inc, referred to as the GenAptima HIV RNA test) may be used to confirm HIV infection in enrolled participants who have one or more reactive HIV rapid tests. This assay will also be used at follow-up visits to resolve the HIV infection status of participants whose HIV status is not clear (*e.g.*, newly reactive HIV rapid test(s) with a negative or indeterminate Western blot) and to confirm or rule out acute HIV infection in participants who have signs or symptoms of acute HIV infection or express a concern that they might be newly HIV-infected. Rapid diagnosis of HIV infection in participants who become HIV-infected during the study will allow prompt cessation of study drug (to minimize the risk of resistance) and appropriate counseling.

If any enrolled participant has one or more reactive HIV rapid tests or a positive GenAptima HIV RNA test, study drug must be discontinued immediately and the Site IoR, Protocol Chair, and the HPTN NL must be notified. A decision to resume study drug in participants who are subsequently confirmed to be HIV-uninfected requires approval of the Protocol Chair, PSRT and HPTN NL.

Any participant who is found to have confirmed HIV infection after Enrollment will be followed at all scheduled visits and also every 12 weeks after the Week 30 visit, until the last participant at that study sites completes his or her final study visit. HIV-infected participants will be followed to contribute information regarding HIV outcomes after PrEP exposure (including viral set point), to maintain confidentiality, and to comply with expectations of communities. Participants with confirmed HIV infection will be referred for HIV counseling and treatment as appropriate.

5.9 Participants Who Become Pregnant

All protocol-specified study procedures will continue with the exception of administration of study product, instructions for study product use, and adherence counseling.

5.10 Behavioral Data Collection

There are five primary methods used in data collection for pill-taking, risk behavior, core and sub-construct areas, and perceptions of acceptability; (1) EDM data indicating the dates/times that the EDM case was opened (adjusted by self-report data as described below), (2) weekly incentivized phone-based brief interviews to record risk events, (3) CASI collected self-report measures, (4) qualitative focus group and key informant interviews with study participants and clinic staff who directly interact with participants regarding their pill-taking and sexual risk behavior; and (5) data collected on CRFs during regular visits.

5.10.1 Quantitative Behavioral Component

5.10.1.1 Coverage and Sexual Behavior

The primary measure of pill-taking will be based on the adjusted EDM data. The EDM data is transmitted electronically to a database system and this data is used by interviewers to improve the accuracy of self-reported pill-taking via brief weekly interviews, as in Section 2.4.2. Further, several steps will be taken to reinforce participant use of the EDM case. At Enrollment, all participants will be instructed to use the EDM case for each pill-taking event, provided with an explanation of why the EDM case is needed to achieve the scientific aims of the study, and trained on its use. Staff will also explore any difficulties with EDM case use. Finally, to minimize curiosity openings during the study, clinic staff will work to familiarize the participant with the EDM device, and will provide the

participant with an EDM device and a one month supply of multivitamin pills during the DOT phase.

Because the timing of sexual events is critical to establishing coverage in the intermittent arms, sexual behavior will be assessed during weekly interviews to minimize difficulties with recall. During weekly phone interviews, the interviewer will also ask the participant if a sex event occurred during this time period and the day(s) of the event(s) will be recorded. For each event-day, the general start and end time of the event/session/or round, event type(s), and number of partners involved, as well as if condoms were used during all insertions for that round/session, will be collected. This will be repeated until all days/events are characterized. Interviewers will be staff or contractors otherwise unknown to the participant, and trained in neutral assessment and timeline follow-back techniques to facilitate brevity and minimization of social-desirability (or self-presentation) bias. In the event that a participant is not contacted for a given assessment week, additional attempts will be made to contact the participant with the timeframe adjusted to reflect the entire interval since the last contact. Where no contact has been made and the participant comes to a monthly clinic visit, the telephone based interview data will be replaced with an in-person interview from a trained staff member. Alternative data collection method will be noted in the participant's data.

In addition to the weekly interview risk-data collected, a more general risk assessment will be included as a brief measure in the CASI assessments including safer sexual practices such as serosorting, sexual positioning, etc. that are not part of the event-based data collected during the weekly telephone interview. While it is improbable that participants will be able to recall the timing of events occurring during this longer time period, the assessment of risk behavior occurring over the last one to three months is not uncommon.[61, 63-66] These CASI delivered items will be constructed with sensitivity to keeping the full CASI assessment no more than 30 minutes in full.

Participants will complete CASI based surveys at Screening, and at Weeks 6, 18, and 30. CASI instruments have been selected to represent the core constructs of the adapted IMB-model, and the context variables identified in the present research. Measures for inclusion in a particular CASI assessment are varied to manage participant burden so not all measures will be repeated at every assessment. Some measures will need to be developed or refined to be culturally appropriate for the targeted groups of participants although all measures have versions that have been used in some manner in previous research within different communities. All questionnaires will be administered via CASI in the local language at the study site.

If a participant needs assistance with CASI, a study staff member will help him or her and this help will be noted in the CASI data. The administration of questionnaires will take approximately thirty minutes. Non-literate participants will not be eligible for this study.

5.10.2 Qualitative Behavioral Component

5.10.2.1 Focus groups and key informant interviews

We will explore differences between arms in the acceptability of different PrEP regimens using qualitative research methods, including focus groups and key informant interviews. Two focus groups will be performed per study arm at each site. Each focus group will include 6-8 study participants per study arm group per site per focus group. These groups will include a total of 72-96 participants. Two key informant interviews will be performed per study arm per site with selected study participants identified by study staff for a total of 12 participant key informants. In addition, a total of 6-8 key informant (site staff who interacted directly with participants during the study) interviews will be conducted of 3-4 staff members per site. Key informant interviews will be conducted after the on-drug period (after Week 34). Participants who discontinue study drug early for reasons not related to AEs or symptoms/side effects will be specifically targeted for the focus groups and key informant interviews, as their participation will provide information on why some high-risk individuals who have access to PrEP elect not to use it. Focus groups and key informant interview are each anticipated to last approximately 2 hours.

Focus groups: For participant focus groups, participants will be recruited from clinic through advertisement of the focus groups approximately 6 weeks prior to conducting the groups; participants not attending the clinic during this enrollment period will be contacted to be made aware of these groups. Convenience sampling will be used, where interested participants are enrolled until each focus group is "filled". Enrollment ends when all groups are filled. Note that results of focus groups will be interpreted and presented with this limitation in mind. Adequate reminders will be used to ensure participants attend the event at the appropriate date and time. Focus group participants will be encouraged to select a pseudonym or nickname to protect their confidentiality within the group. Focus groups will be held in a private space in the clinic or off-site in a space where responses cannot be overheard by clinic attendees or staff. All focus groups will be administered, recorded and transcribed in the native language of the site. Analysis will be completed at each site and then transcripts will be translated. General themes will be identified across sites. Recordings and transcripts will be maintained in a secure location and destroyed after analysis according to DAIDS guidelines for data retention.

A focus group guide will be developed that has queries posed to each group regarding;

- their perceptions of feasibility, acceptability and ease of uptake for their assigned regimen
- if they altered the regimen to better 'fit' their daily life or risk behavior
- whether they would switch to a different regimen if available
- what the ideal regimen would be

- common barriers and facilitators to following their regimen
- whether important others knew the participant was enrolled in the study
- feelings towards the project, project-staff, and how pill-taking and condom use was supported
- perceptions of the support provided for pill-taking and for condom use, how they would change it, and what frequency or type of support would be most acceptable to them if they were taking PrEP outside of the context of research.

Additionally, to further guide theory and intervention development, self-perceived attributes defining "PrEP participant", "consistent PrEP user" and "consistent condom user" will be qualitatively explored. Discussion from focus groups will be transcribed and coding will be approached with a two-phase analytic method (fully detailed in Section 7.5.6), including both theory-grounded and content analyses. Theory-grounded methods will be used to identify the emerging themes, primarily surrounding pill-taking and condom use in the context of PrEP. Content coding will focus on the adapted IMB model of pill-taking and condom use through focused identification of content within the core determinants of the IMB model and content related to barriers and facilitators of each behavior that cannot be coded with the model constructs. Data gathered from focus groups are intended to supplement and inform the quantitative results obtained regarding perceptions of dosing schedule, feelings about group assignment, perceptions of HIV risk, disclosure of study participation and pill-use to sexual partner(s), housemates and family, relationships with study staff, perceptions of social role, and factors influencing use of pills.

Key informant interviews: Direct-care clinic staff will have had extended cumulative interactions with participants in each of the study arms by the close of the on-drug phase. Therefore, each of these staff is considered to be a key informant with valuable knowledge of and experience with each of the regimens and how participants interacted with the study and the regimen demands. Selected study participants, such as those who crossed over study arms, discontinued study drug, or withdrew from the study, will also be considered key-informants. Semi-structured interview guides will be developed that query interviewees along similar themes listed above. Because of the structured nature of these interviews, content analysis will be the primary analytic strategy focused on coding main content of responses to queries. Data will supplement participant-based responses to quantitatively and qualitatively assess acceptability and feasibility and to refine the adapted model developed for the present research. Key informant interviews for participants will be completed by staff not directly involved in the study. Key informant interviews with staff will be completed by clinic staff who do not function in a supervisory role for the interviewee. All key informant interviews will be held in a private space in the clinic or off-site in a space where responses cannot be overheard by clinic attendees or staff.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

Close cooperation between the Protocol Chair(s), study site Investigator(s), NIAID Medical/Program Officer, CORE Protocol Coordinator, SDMC Biostatistician, HPTN NL, and other study team members will be necessary in order to monitor participant safety and to respond to occurrences of toxicity in a timely manner. The team will have regularly scheduled conference calls during the period of study implementation, and additional *ad hoc* calls will be convened if required.

The study site Investigators are responsible for continuous close monitoring of all AEs that occur among study participants after enrollment, and for alerting the PSRT if unexpected concerns arise.

A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, one or more site clinicians, and the SDMC Clinical Affairs Safety Associate will serve as the PSRT to be chaired by the Protocol Chair. The HPTN SDMC will prepare routine safety data reports for review by the PSRT, which will meet via conference call approximately once per month or as needed throughout the period of study implementation to review safety data, discuss product use management and address any potential safety concerns. The content, format and frequency of safety data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation.

6.2 Clinical Data Safety Review

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

HPTN SDMC Clinical Affairs staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer for review.

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

Recommendations regarding permanent discontinuation of study product may involve sponsor consultation with the U.S. FDA.

In the unlikely event that the protocol team or PSRT has serious safety concerns that lead to a decision to permanently discontinue the study product for all participants and stop accrual into the study, the protocol team or PSRT will request a review of the data by the HPTN SMC before recommending that the study be stopped. If at any time, a decision is made to discontinue the study product in all participants, DAIDS will notify the U.S. FDA and the site Investigators of Record will notify the responsible IRBs/ECs expeditiously.

6.3 Adverse Event definition and reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS Expedited Adverse Events (EAE) Manual, which is available on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com/safetyandpharmacovigilance/. This information is also available in Section 14.4 of the HPTN Manual of Operations at http://www.hptn.org/network_information/policy_procedure/HPTNMOP2010.htm.

6.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant who has been administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. The term “investigational product” for this study refers to the oral medication Truvada® (emtricitabine/ tenofovir disoproxil fumarate).

Study 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 where a study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained, and required data elements will be recorded on study CRFs. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents and the appropriate AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009).

6.3.2 Serious Adverse Events

Serious AEs (SAEs) will be defined per International Conference on Harmonisation (ICH) guidance, as specified in Version 2.0 of the Manual for Expedited Adverse Events to DAIDS, dated January 2010.

6.3.2.1 AE Reporting to DAIDS

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

According to the SAEs reporting category in the manual, all SAEs occurring during the study reporting period (defined below) will be reported to the DAIDS RSC Safety Office in an expedited manner, within three reporting days of site awareness of the events (see definition in Appendix D of the manual).

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

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

The study agent for which expedited reporting is required is Truvada® (emtricitabine/ tenofovir disoproxil fumarate). For each trial participant, the AE

reporting period begins at Enrollment and ends when the participant completes the Week 34 or early exit Visit.

After Week 34 or early exit, only suspected, unexpected, serious adverse drug reactions (SUSARs; defined in Version 2.0 of the DAIDS EAE Manual) that study staff become aware of on a passive basis (from publicly available information) will be reported to DAIDS in an expedited manner.

6.3.2.3 Grading severity of adverse events

The severity of all AEs will be graded according to the current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 (with Clarification dated August 2009), which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

6.3.3 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. The relationship of all AEs to study product will be assessed as specified in Version 2.0 of the DAIDS EAE Reporting Manual.

6.4 Pregnancy Outcomes

Pregnancy outcomes will be collected for all applicable study participants. After the participant's final study contact, any pregnancy outcomes that meet criteria for SAE reporting (*e.g.*, congenital anomalies) occurring among participants will continue to be expeditiously reported.

6.5 Regulatory Requirements

Information on all reported AEs will be recorded on CRFs and included in reports to the FDA and other applicable government and regulatory authorities. The site IoR/designee will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. The site IoR/designee also will submit AE information and any other relevant safety information to the IRB/Ethics Committee (EC) in accordance with IRB/EC requirements.

6.6 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (*i.e.*, because participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs/ECs at least annually, or according to their individual

requirements. Social harms will be collected and reported on CRFs during regular visits. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SSP Manual. While maintaining participant confidentiality, study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm, to minimize the potential occurrence of such harm.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is a Phase II randomized open-label clinical trial of oral Truvada® (FTC/TDF) PrEP among HIV-uninfected MSM and WSM at high risk for acquiring HIV infection.

The study will randomize 360 people, 180 MSM at the TUC Silom Community Clinic in Bangkok, Thailand and 180 WSM at Emavundleni Centre, The Desmond Tutu HIV Foundation in Cape Town, South Africa. The study includes a lead-in period of 6 weeks including DOT to determine individual steady state PK, and a 24-week self-administered PrEP phase to assess adherence, sexual behaviors, tolerance, and acceptability. At Week 6, participants will be randomized and assigned to one of three dosage groups in a 1:1:1 ratio: daily dosing, time-driven dosing, and event-driven dosing. During the self-administered PrEP phase, all participants will engage in PrEP adherence counseling during all study visits and once per week telephone contacts will be used to query each participant regarding sexual exposure and pill-use. If a participant cannot be reached for a given week or weeks of phone-based assessment, an interview based timeline follow-back approach administered at the next clinic visit will be used to complete missing information and will be denoted as having been collected via this alternative method. Focus groups (selected participants) and key informant interviews (selected participants and clinic staff) will occur within three months after Week 34.

7.2 Study Endpoints

7.2.1 Primary Endpoints

Consistent with the primary study objective to test the hypothesis that recommending intermittent (non-daily) use of oral FTC/TDF chemoprophylaxis, compared with recommending daily usage, will be associated with:

- Equivalent coverage of sex events with pre- and post-exposure dosing
- Lower number of pills needed for coverage and fewer pills used

- Decreased self-reported symptoms/side effects (both severity and frequency) during 24 weeks of self-administered use, the following endpoint(s) will be assessed:

- The proportion of sexual exposures covered by pre- and post-exposure dosing. Coverage will be determined based on the adjusted electronic and self-reported pill-use data. Specifically, a sex act will be considered "covered" if the following two conditions are met:
  i. At least one pill is taken during the 4 days (96 hours) before the act or prior to the act on the day of the act (*e.g.*, if a sex act occurs on Friday, that act would be covered if a pill was taken on Monday, Tuesday, Wednesday, Thursday, or Friday prior to the act) and:
  ii. At least one additional pill is taken within 24 hours of the act (*e.g.*, if a sex act occurs on Friday at 11 pm, that act would be covered if the second pill was taken between Thursday 11 pm and Saturday 11 pm).

  Note that the same pill can cover a pre-exposure dose and a post-exposure dose if events are closely spaced. At no time should a participant in the intermittent arm be taking more pills than the daily arm.
- The (minimum) total number of pills needed for 100% coverage over the follow-up period (based on randomization arm and self-reported sexual history in the weekly interviews) (after Week 6 up until the Week 30 visit).
- The total pills actually used over the follow-up period, based on the adjusted electronic and self-reported pill-use data (after Week 6 through Week 30)
- The self-reported symptom/side effect scores (to be developed) for common symptoms/side effects including headache, dizziness, cramping, abdominal pain, and flatulence. Collected during clinic visits.

7.2.2 Secondary Endpoints

Consistent with the secondary study objective to develop objective measures of drug exposure among PrEP users by obtaining pre-dose "trough" drug concentration in several biological matrices for participants enrolled during a lead-in period of weekly DOT, the following endpoint(s) will be assessed:

- Measurement of TFV-DP in PBMCs. Samples will also be collected and stored for possible future substudies comparing the level of TFV-DP in PBMCs to the levels of extracellular TFV in serum and of TDF-DP in hair. FTC and its phosphorylated derivative, FTC-TP, may also be measured.

Consistent with the secondary objective to describe safety outcomes among PrEP users, including AEs among all participants and drug resistance, and plasma HIV RNA levels among participants who seroconvert, the following will be provided:

- A listing of all AEs (see Sections 6.3.1 and 6.3.2) by grade, relationship to study product, and arm
- A listing, by arm, of drug resistance test results and plasma HIV RNA levels among all participants who seroconvert while on study

Consistent with the secondary study objective to assess the acceptability of different PrEP regimens and perceptions of advantages and disadvantages of different regimens, the following endpoint(s) will be assessed:

- The proportion of participants in each of the study arms who self-report acceptability of assigned study arm collected on CASI assessment
- Perceptions of advantages and disadvantages of different regimens as reported by participants and clinic personnel in focus groups and key informant interviews

Consistent with the secondary study objective to assess differences by arm in adherence, PrEP use, and related information, motivation and behavioral skills, the following endpoints will be assessed:

- The percentage adherence (number of pills taken/number of pills recommended based on regimen) and percentage of correctly timed adherence (number of pills taken within the recommended timeframe/number of pills recommended for intermittent arms) during 24 weeks of follow-up based on weekly interviews and adjusted EDM data
- The percentage adherence (number of pills taken/number of pills recommended based on regimen) during 24 weeks of follow-up based on pill counts
- The proportion of participants who discontinue all PrEP use based on self-report via CASI or weekly interviews
- Information related to PrEP use, motivation, and behavioral skills based on self-report via CASI

Consistent with the secondary study objective to evaluate the potential influence of PrEP usage on changes in sexual behavior, planning for sex, prediction of risky situations, and recognition of possible HIV exposure in relation to PrEP optimism, general optimism and other demographic variables, the following endpoints will be assessed:

- The frequency of unprotected sex acts via CASI
- Planning for sex assessed via CASI
- Safer sex planning survey assessed via CASI
- Perceived vulnerability assessed via CASI
- PrEP optimism assessed via CASI
- General optimism assessed via CASI
- Demographic measures assessed at enrollment

7.3 Accrual, Follow-up, and Sample Size

The study is mainly powered to assess and compare the proportion of HIV exposures covered by pill-use (coverage) in the different populations and usage

groups. The study will randomize 360 people, 180 MSM at the TUC Bangkok site and 180 WSM at Emavundleni Desmond Tutu site. In each site, 60 participants will be randomly assigned to each of three study arms. The total number of sex acts and the number of covered sex acts will be computed for each participant based on the adjusted EDM data and weekly telephone interviews. A covered sex act is defined as one with pre- and post- drug use in a time period defined in Section 7.2.1. Further details will be provided in the statistical analysis plan.

There are two hypotheses of interest for the coverage endpoint. First, we are interested in the non-inferiority hypothesis that the selected intermittent arm is not markedly inferior to the daily arm in the percentage of sex acts covered by pill-use:

(1)
Ho: $pd - pi > \delta$
Ha: $pd - pi < \delta$

Where pi is the average proportion of covered sex acts in the intermittent arm, pd is the corresponding quantity for the daily arm and δ represents an "indifference region" (*i.e.*, if the average proportion of covered sex acts for the intermittent arm is within at least δ of the daily arm we will consider them to be equivalent). The second hypothesis is that one intermittent arm has a higher proportion of covered sex acts compared to the other intermittent arm:

(2)
Ho: $pi_1 = pi_2$
Ha: $pi_1 \neq pi_2$

Where pi_1 is the proportion of covered sex acts in one intermittent arm and pi_2 is the proportion in the other intermittent arm.

The following are assumed in the sample size calculations: each person will report, on average, 50 sex acts over the 24 week self-administered follow-up period. This will vary from person to person and in the final analysis we will account for variable numbers of sex acts across participants. For simplicity, we ignore that variability here. It is assumed that 90% of sex acts in the daily arm will be covered (10% uncovered). Further, it is assumed that the proportion of uncovered acts will vary across participants with a coefficient of variation (CV) of 40% - 80% (a relatively large variance). The sample size calculations of Hayes and Bennett [67] are used directly to assess the power for the superiority hypothesis (2) and we adapt their approach for the non-inferiority hypothesis (1).

Table 7.1 Non-inferiority region (δ) for hypothesis (1) assuming 60 participants or 120 participants depending on whether risk-group specific analyses or overall analyses is considered, 50 acts per participant, α =0.05 (one-tailed). Power is computed against the alternative that coverage is exactly equal in the two arms (*i.e.* $\delta = 0$).

CV	Power	% ``uncovered'' sex in daily arm (1 – pd)	null δ	
			n=60	n=120
.4	.9	.1	0.031	0.022
.4	.95	.1	0.035	0.025
.6	.9	.1	0.040	0.028
.6	.95	.1	0.045	0.031
.8	.9	.1	0.049	0.034
.8	.95	.1	0.055	0.039

Table 7.2 Minimum detectable difference between the rate of covered sex acts in one intermittent treatment arm as compared to the other intermittent arm (hypothesis 2), assuming 60 participants or 120 participants depending on whether risk-group specific analyses or overall analyses is considered, 50 acts per participant, $\alpha = 0.05$ (two-tailed).

CV	Power	The rate of uncovered sex acts in intermittent arm 1 ($1 - pi_1$)	Minimum detectable rate of uncovered sex in intermittent arm 2 ($1 - pi_2$)	
			n=60	n=120
.4	.8	.1	0.134	0.123
.4	.9	.1	0.140	0.127
.6	.8	.1	0.145	0.130
.6	.9	.1	0.154	0.136
.8	.8	.1	0.160	0.139
.8	.9	.1	0.173	0.146

Table 7.1 shows the equivalence region for the non-inferiority test that the rate of ``uncovered'' sex acts in the intermittent arm is not different from that in the daily arm. The smaller the equivalence region is, the better power to test the non-inferiority hypothesis will be achieved. For a fairly large CV (0.4-0.6), Table 7.1 shows that the targeted sample size provides a rather small equivalence margin, around 0.03-0.04, when the daily arm has 10% sex not ``covered'' by pill-use. Table 7.2 shows the minimum detectable rate of covered sex in one intermittent arm when the other intermittent arm has 10% covered sex acts. The closer the minimum detectable rate is to 0.1, the better power to detect small differences. For a CV between 0.4-0.6, Table 7.2 suggests the targeted sample size provides good power to detect a 0.03-0.05 increase from the daily arm. This analysis

suggests that there is good power for comparing the rates of covered sex acts between the two intermittent arms. Tables 7.1 and 7.2 are relatively insensitive to the number of acts per participant so deviations from the expected 50 acts per person or small amounts of loss to follow-up will not significantly affect power for the coverage endpoint. Additional power calculations were conducted to examine the impact of varying rates of covered sex act (0.8~0.95) on the minimal detectable difference (see tables in Appendix II). Similar power performances were observed for the range of rates.

Table 7.3 The sample size needed to achieve a fixed power level (0.8 or 0.9) to a detect difference in tolerance scores (based on Vertigo symptom scale for dizziness) between the daily arm and one intermittent arm, given a range of CV, assuming tolerance scores are collected twice in the study, the average tolerance score in the daily arm is 15, the standard deviation within subject is 5, $\alpha = 0.05$ (two-tailed).

CV	Power	The average tolerance scores in the intermittent arm	Sample size needed per arm
.4	.8	10	26
.4	.9	10	34
.6	.8	10	46
.6	.9	10	61
.8	.8	10	75
.8	.9	10	99

The proposed sample size also provides good power to detect differences in the tolerance scores between the daily arm and one intermittent arm, corresponding to the hypotheses

(3)
Ho: ud= ui
Ha: ud≠ ui

where ud is the mean tolerance score in the daily arm and ui is the mean tolerance score in the intermittent arm.The Vertigo symptom scale for dizziness is used for illustration. This scale will be measured twice in this study. Based on literature on validation of this scale [68] the mean of this scale in the daily arm is assumed to be 15, the standard deviation among two measurements within a subject is assumed to be 5, the required sample sizes to detect 1/3 decrease in one intermittent arm for various sizes of CV and power, using a two sided test ($\alpha = 0.05$) are shown in Table 7.3. The sample size calculation is based on formula in Hayes and Bennett.[67] For a pooled analysis, the target sample size will provide good power to detect a decrease of at least 1/3 in dizziness scores (from an average of 15 to an average of 10) in the intermittent arm as compared to the daily arm, even after allowing for a small loss to follow-up. For within risk group analyses, the target sample size will provide adequate power to detect similar decrease provided the CV is 0.6 or less (which we believe is likely).

Table 7.4 shows the power to detect the difference of the number of pills used in the study between the daily arm and the intermittent arm, corresponding to the hypotheses

(4)
Ho: ud= ui
Ha: ud≠ ui

where ud is the mean number of pills used in the daily arm and ui is the mean number of pills used in the intermittent arm. The table gives the power for a range of differences and standard deviations, assuming the average number of pills used in the daily arm is 120 and a two sided test ($\alpha = 0.05$). The targeted sample size will provide adequate power to detect approximately 15-20% decrease in number of pills used. A much larger difference is expected so the trial is very well powered for this endpoint. In addition, we do not want to be powered to detect smaller differences in pill usage between the intermittent arm and the daily arm since small differences in pill-use do not represent a meaningful benefit of the intermittent arm.

Table 7.4 The power to detect the difference of average pill-use throughout study period between the daily arm and one intermittent arm, given a range of standard deviations and the differences, assuming the average number of pills used in the daily arm is 120, $\alpha = 0.05$ (two-tailed).

Difference between Daily arm and the intermittent arm	Standard Deviation (SD) of pills used in the study	The average number of pills used in the daily arm	Power
20	20	120	0.99
20	40	120	0.97
20	60	120	0.73
10	20	120	0.97
10	40	120	0.49
10	60	120	0.25

7.4 Random Assignment

Participants who meet the study eligibility criteria will be offered enrollment in the study, and those willing to take part will be assigned at random to one of three treatment arms. The randomization code will be developed and maintained by statisticians at the HPTN SDMC. Randomization will be stratified by site.

7.5 Data Analysis

7.5.1 Primary Analyses

Descriptive analyses will be carried out to determine if randomization has resulted in study arms that are similar with respect to key baseline measures.

The primary analyses will consist of a comparison of the proportion of sex acts covered by pill-use, percentage of pills taken among all pills that should be taken based on his/her assigned regimen and reported side effects/symptoms between the three randomization arms. All the analyses described here will be intent-to-treat. Analyses involving pill-use data will be carried out using the adjusted electronic and self-reported pill-use data. EDM pill-use data will be adjusted based on weekly interviews to take into account openings of the device not associated with pill consumption and pill consumption not associated with an opening (*i.e.* when more than one pill is dispensed at one opening, or pocket dosing). Information collected after HIV seroconversion, if any, will not be included in the analyses.

H_1: Study-drug coverage of risk events across the 24-week monitoring period will be statistically equivalent between the non-daily dosing arms and the daily dosing arm.
The sex and pill-use data collected weekly will be summarized for each participant as total number of sex acts and the total number of sex acts "covered'' by pill-use during the self-administer study period. Logistic regression will be used to compare the proportion of covered acts between randomized arms. The standard errors of parameter estimates will be scaled by the over dispersion parameter to account for extra binomial variability and robust standard errors will be used.

H_2: Non-daily arms will have fewer reported side-effects.
Symptom/Side-effects scores will be collected at regular intervals. They will be treated as ordinal repeated measures, or continuous measures depending on the type of tolerance score. For ordinal measures, a proportional odds model will be used for generalized estimating equation (GEE) analysis based on the cumulative logit function. For continuous scores, a linear model will be used for GEE analysis. In both cases, robust standard errors (GEE) will be used to correct for correlation between repeated measures on the same individual. Pre-randomization scores will be used as covariates in the analysis to adjust for heterogeneity between participants. Pairwise comparison will be conducted for three randomization arms. Nominal p-values will be provided and a permutation procedure will be used to provide comparisons between the arms that are corrected for multiple testing.

H_{3a}: Fewer total pills will be required for non-daily arms.
The minimum total number of pills needed to cover all sex acts during the self-administered period will be computed for each subject using the self-reported

sexual history data. The (mean of the) logarithm of the total numbers of pills will be compared between the three arms by ordinary linear regression and the log of the duration of follow-up will be included in the model as an offset term to account for (potentially) different follow-up periods for each participant

H_{3b}: Fewer total pills will be used for non-daily arms.
The total number of pills used during the self-administered period will be computed for each subject using the adjusted EDM data. The (mean of the) logarithm of the total numbers of pills will be compared between the three arms by ordinary linear regression and the log of the duration of follow-up will be included in the model as an offset term to account for (potentially) different follow-up periods for each participant.

7.5.2 Secondary analyses on coverage, pill-use and side effects/symptoms

Each of the analyses described above will be repeated for the WSM and MSM subgroups. Differences in effects between these subgroups will be tested although it is acknowledged that tests for effect modification usually have low power.

Another secondary analysis will consider 4 categories of coverage: not covered, pre-dose only taken, post-dose only taken, pre and post-dose taken (*i.e.*, covered). A 4 x 3 contingency table will be formed to describe the category of coverage by arm for each sex act and will use a randomization procedure (randomizing by participant) to test for differences between arms.

7.5.3 Secondary analyses on adherence, acceptability and sexual behavioral data

$H_{1:}$ Time- and event-driven arm participants will report greater preference for their assigned study arm at the Week 30 assessment than those in the daily arm.

The proportion of participants in each of study arms who accept the dosage recommendation at the Week 30 assessment will be computed and summarized. The rate of acceptability will be compared between arms using a chi-squared test.

$H_{2:}$ At Week 30 assessments, participants assigned to time- and event-driven arms will report higher levels of PrEP use related information, motivation, and behavioral skills, in comparison to those in the daily arm.

A score for PrEP use will be computed based on IMB (see Table 1, Section 5.10) for each participant and a Wilcoxan rank sum test will be used to compare the scores between treatment arms.

$H_{3:}$ Across all 24 weeks of on-drug monitoring, rates of adherence to one's assigned regimen will be higher in the time- and event-driven arms.

Self-reported adherence (SR adherence) will be calculated for each participant as the percentage of pills taken among all pills that should be taken based on his/her assigned regimen and (in the case of the intermittent arms) self reported sex events. Logistic regression will be used to compare the adherence rates between randomized arms. The standard errors of parameter estimates will be scaled by the overdispersion parameter to account for extra binomial variability and robust standard errors will be used. Analyses will be done with and without the unvalidated pill-use data, as described in Section 7.5.1.

We will also calculate adherence by pill count for each participant for each 4 week follow-up period. Adherence by pill count will be descriptively compared to SR adherence. A scatterplot of the two measures of adherence will be presented and the concordance correlation [69] will be computed for these two measures of adherence.

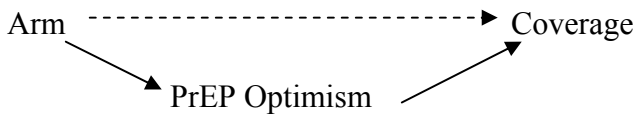
H_4: Across all 24 weeks of on-drug monitoring, proportion of participants requesting discontinuation of study drug will be lower in the time- and event-driven arms. The proportion of participants in each of study arms who discontinue study drug during follow-up will be computed. The rate of discontinuation will be compared between arms using a chi-squared test.

H_5: PrEP use will not uniquely contribute to increases in risk (non-condom use risk events) from baseline to final Week 30 assessment (null disinhibition hypothesis). The self-reported data on sex acts will be summarized for each subject to create the total number of sex acts and the number of sex acts with and without condom use. Rates of condom use relative to total sex acts, for those with at least one act reported throughout the 24 week monitoring, will be calculated based on data collected with CASI. Logistic regression will be used to assess whether the rate of condom use is different across arms. The standard errors of parameter estimates will be scaled by the estimated overdispersion parameter to account for extra binomial variability.

$H_{6\text{-}a}$: A relationship between intervention arm and coverage can be explained by PrEP optimism.

$H_{6\text{-}b}$ A demonstrated relation between PrEP optimism and coverage will be non-significant when controlling for the effects of general optimism in the model. The IMB model that has been proposed to describe PrEP prevention behavior (Figure 1-2) suggests a number of hypotheses to explain variations in PrEP related behavior (*e.g.* coverage and condom use) as a function of optimism about PrEP, general mood/optimism, behavioral skills, personal and social motivation and other factors. Here we illustrate just one set of analyses that we will do to explore these hypotheses and relationships. It is likely that additional analyses will be suggested by the results found in this and related analyses.

Suppose we find that coverage (for example) differs significantly by intervention arm. We may hypothesize that the observed effect of arm on coverage can be explained by changes in PrEP optimism between the intervention arms.

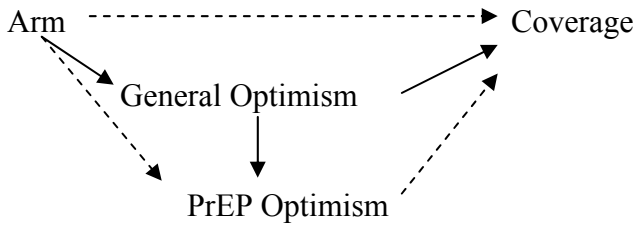


Where the solid arrows indicate the true causal pathway and the dashed arrow indicates a univariate (unadjusted) association that is not significant in the adjusted model. To investigate this we would run the following models (here, Y is the outcome, A is intervention arm, OP is optimism about PrEP):

$$Y \sim A$$
$$Y \sim A + OP$$
$$OP \sim A$$

If optimism about PrEP mediates the effect of arm on the outcome, then we would expect to see a strong relationship between the outcome and arm in the first model, a weak relationship between the outcome and arm after controlling for PrEP optimism in the second model, and a strong relationship between optimism about PrEP and arm in the third model.

We may further hypothesize that general optimism may explain the observed relationship between PrEP optimism and coverage:



The following series of analyses would allow us to discern the relative strengths of the relationships in this model

$$Y \sim A$$
$$Y \sim A + OP$$
$$Y \sim A + OP + GO$$
$$OP \sim A$$
$$OP \sim A + GO$$
$$GO \sim A$$

Analyses like these will be used to understand the behavioral factors underlying variations in coverage and condom use.

Additional hypotheses that will be investigated using these approaches include:

$H_{7\text{-}a}$: A demonstrated relation between PrEP optimism and total non-condom use risk events will be non-significant when controlling for the effects of general optimism in the model (null risk compensation hypothesis).

$H_{7\text{-}b}$: Risk behavior (non-condom use events) over the 24-week monitoring period will be a function of risk-related information, motivation, and behavioral skills, and positive PrEP beliefs will not significantly add to this explanatory model.

H_8: Planning for sexual events, prediction of risk events, and recognition of risk events will be superior at last on-drug assessment within time and event-driven arms compared to the daily PrEP arm.

7.5.4 Secondary analyses on safety outcomes

A listing of all AEs will be provided, including HIV infection, among the participants. For participants who become HIV-infected, this will describe any drug resistance and plasma HIV RNA levels. It is not anticipated that enough cases of HIV infection will be identified to make any comparative analyses possible.

7.5.5 Secondary analyses on drug concentration data

The initial 6-week lead in period including DOT will provide data for estimation of steady-state drug concentrations with the primary moiety of interest being TDF-DP. While drug concentration data collected during this period may allow estimation of PK parameters (clearance, volume of distribution, half-life), the sparse weekly sampling and fixed pre-dose schedule of blood collection will limit the precision of these estimates. The primary readout from this period is the pre-dose drug concentration at Weeks 4 and 5. These concentrations will be evaluated to test for steady-state and the "expected" pre-dose concentration for each individual. Week 4 and Week 5 data (Week 5 alone if steady-state has not been achieved) will provide a point estimate for the expected concentration at

steady-state and an estimate of intra-individual variability in this pre-dose concentration. Decay will be monitored from drug dose concentration data collected at Week 6.

All of the assays used will be validated and approved for use in NIH network studies by the Clinical Pharmacology Quality Assurance (CPQA) Program consistent with FDA standards for drug development. Currently, assays have been validated and CPQA approved for TFVs, TFV-DP, and FTCs. An assay for TFVh has been validated, but not yet approved by CPQA. None of these methods are published. All of these assays use LC/MS methods for analyte quantitation.

These data will be used to compute laboratory verified adherence (LV adherence) for participants in the unobserved dosing phase of the study. In contrast to self-report adjusted EDM-based adherence (defined in Section 7.5.3), LV adherence is computed as the ratio of observed and expected concentrations (where the expected concentration is based on the reported dosing) and can be greater than 1.0 due to random variability. Random error can be attributed to intra-individual variability and assay variability in the laboratory (<15% CV) with the validated assay used at the HPTN NL.

With scheduled dosing, the expectation of drug concentration can be estimated based on observed drug concentrations at the end of the DOT period by a simple simulation of drug concentration over time according to the prescribed regimen. The regimen itself is simply an invariant scalar that predicts the expected concentration. Event-driven dosing introduces an additional variability that decreases the precision of any LV adherence estimates. With sexual event dependent dosing, a similar simulation can be performed, using the time of sex and the PK parameters derived from the DOT period.

Based on available information, it is predicted that participants who take 4 or more pills in the previous 14 days will have detectable TDF-DP in their PBMCs, as measured at Weeks 10, 18 and 30. Undetectable drug levels in persons reporting using 4 or more pills is an indication of over-reporting. In a secondary, exploratory analysis, we will repeat the analyses of coverage (Section 7.5.1) and adherence (Section 7.5.3) and data from periods of over-reporting will be censored from the analysis. Persons reporting use of fewer than 4 pills in the last 2 weeks will be included in the analysis regardless of drug level. We will evaluate the amount of data censored by arm and we will compare the results obtained in this analysis to those obtained without censoring over-reporting periods.

7.5.6 Qualitative behavioral data analyses

Data collected via focus groups within each study arm at each site will be used in theory grounded and content analysis. Key informant interviews will be conducted with selected participants and clinic staff at each site. All material will be transcribed and results translated into English.

A representative portion of transcripts will be reviewed prior to coding to determine most appropriate unit to code (utterance, table turn, complete sentence, or some other integral). Once units are defined, transcripts will undergo two phases of qualitative analysis. The first phase utilizes grounded theory analysis.[70] [71] Grounded theory approaches use an iterative inductive process of reviewing content and identifying themes in the data that characterize, qualify, or define the phenomenon of interest.[72] The methodology recommended for grounded theory includes a phase of open-coding where transcripts are iteratively reviewed by individuals familiar with theories and formulations of the phenomenon (*e.g.*, pill-taking, PrEP) enough to provide an adequate level of theoretical sensitivity in the development of coding schemes. These reviews produce a set of general global categories which describe the concepts and properties of the phenomenon under study. Given the intended content of the focus group queries, it is anticipated that a priori phenomenon will include pill-taking, participating in a PrEP trial, risk reduction behavior (condom use), PrEP regimens, and social roles. However, additional phenomenon that emerge from focus group data will also be included. Open-coding can be further qualified by axial coding, defined as not only a comprehensive description of the phenomenon but also identification of the context in which it occurs (moderating content), intervening conditions for it to occur (mediating conditions), action strategies (activities done surrounding or in response to the phenomenon), and consequences (outcomes of activities). With adequate characterization of the data with open codes, consolidation of codes will lead to a final coding system that will be used to quantify the data. It is assumed that using this process, the focus groups will be characterized in terms of the main content describing discussions of critical aspects of pill-taking and PrEP participation defined both a priori and through the identification of emerging phenomenon that may not have been anticipated. Note that while constant comparison methods are used, we are also interested in applying principles of classic content analyses in that the relative frequencies of variable aspects of the axial codes are also of interest.[73] Because of this, we will evaluate agreement on a minimum of 10% of the coded units via double-coding.

Focus group data will also be used to inform the adapted IMB model employed in this research and to identify the relative type and frequency of theory-related barriers and facilitators via content (structural) analysis.[72] As opposed to grounded theory which uses the collected data to identify core constructs relevant to the phenomenon in question, content analyses is theory based in identifying content categories a priori and culling the data into units that reflect, or do not reflect, core content categories for summary (*e.g.*,

frequencies, relative proportions). It is anticipated that after completion of the grounded theory coding, coders will review content of the focus groups for references to barriers and facilitators of pill-taking and of prevention behaviors (*e.g.*, condom use). Each identified barrier and facilitator will be further coded for content that is informational, motivational or behavioral skills related. These non-orthoganol codes will characterize the kinds of barriers and facilitators reported in focus group discussions. Importantly, any barrier or facilitator not coded by IMB model determinants will be identified and further analyzed for emerging themes (content) that will be used in future applications of the model and to provide guidance for targets of pill-taking and condom use support strategies. Similar to the classical content analysis portion of the grounded theory approach, at least 10% of the units will be double coded to determine agreement. It is anticipated that data from focus groups will provide nuanced information about acceptability and feasibility of the various PrEP regimens and will characterize the factors that appear most influential to focus group participants in maintaining pill-use, as well as condom use in the context of PrEP.

Key informant interviews: Semi-structured interviews will be conducted after Week 34. The one-on-one interviews with selected participants and study staff will use an interview guide and responses will be recorded and transcribed. Responses will be reviewed by the team of interviewers and qualitative working group for the identification of units for coding (*e.g.* by specific interview item response, by distinct phrase or complete thought) and inductive generation of main content themes. Qualitative analytic strategies similar to those used in analyzing focus group data will be adopted for the key informant interview data as well.

Analysis for both qualitative components will be completed using CDC EZ Text or another similar qualitative software program.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent forms contained in Appendix III — and any subsequent modifications — will be reviewed and approved by the HPTN Scientific Review Committee (SRC) and DAIDS PSRC with respect to scientific content and compliance with applicable research and human subjects regulations.

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

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. IRBs and participants will also be informed of important new findings related to the effectiveness of PrEP. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office, via the HPTN CORE, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

8.2 Informed Consent

Written informed consent will be obtained from each study participant. Each study site is responsible for developing a study informed consent form for local use, based on the template in Appendix III that describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template form into local languages and verifying the accuracy of the translation.

Participants will document their provision of informed consent by signing their informed consent forms. Non-literate participants will not be eligible for the study. (Further details regarding DAIDS requirements for documenting the informed consent process are provided in the DAIDS standard operating procedure (SOP) for Source Documentation.)

Participants will be provided with a copy of their informed consent forms if they are willing to receive them.

8.3 Risks

Acute viral syndromes

The study is designed to defer enrollment of all participants who have signs or symptoms of acute viral syndromes, which may reflect acute HIV infection, or other acute viral infections such as H1N1 influenza. Persons with acute viral syndromes will not be enrolled. They can be enrolled after signs and symptoms resolve if they remain eligible in all other respects, including negative HIV antibody status. Persons suspected of acute HIV infection will be evaluated using HIV RNA testing.

Phlebotomy

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Confidentiality

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result.

Study Medications

TDF. The most common side effects associated with oral TDF in patients with HIV infection are nausea, headache, diarrhea, vomiting, asthenia, flatulence, abdominal distension/pain, and anorexia. Less common side effects of TDF include kidney toxicities and low blood phosphate. Other side effects reported in the post-marketing period include weakness, pancreatitis, dizziness, shortness of breath, and rash. In animal studies, TDF has been associated with decreased bone mineral density. These effects have not been seen in those taking TDF tablets for up to one year.

TDF is a pregnancy category B medication. A controlled human study of TDF among pregnant women has been conducted, but results are not currently available (HPTN 057: http://www.hptn.org/research_studies/hptn057.asp).

FTC. The following side effects have been associated with the use of FTC: headache, dizziness, tiredness, inability to sleep, unusual dreams, loose or watery stools, upset stomach (nausea) or vomiting, abdominal pain, rash, itching, skin darkening of the palms and/or soles, increased cough, runny nose, abnormal liver function tests, increases in pancreatic enzyme, increased triglycerides, and increased creatine phosphokinase.

In persons co-infected with HBV and HIV, liver function tests may increase, and symptoms associated with hepatitis may worsen if FTC is stopped.

FTC is a pregnancy category B medication. No controlled human studies of FTC among pregnant women have been conducted.

FTC/TDF combination tablet. No new or unexpected side effects are observed with the TDF 300 mg / FTC 200 mg combination tablet than those observed when each drug is given separately. For the daily arm, the FTC/TDF dosing regimens are consistent with package insert recommendations. Most participants in the time-driven and event-driven arms are anticipated to utilize FTC/TDF at a less frequent rate than package insert recommendations.

Nucleotide Analogues. Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may

result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness, and shortness of breath. These effects are not expected in this study involving a brief exposure to antiretroviral drug.

Antiretroviral drugs. Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in persons receiving antiretroviral drugs. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. These effects are not expected in this study involving a brief exposure to antiretroviral drug.

Drug Resistance. Drug resistance may occur during the study if a participant becomes HIV-infected. Multiple steps will be taken to minimize the risk of drug resistance. Rapid HIV testing will be performed at Screening and Enrollment, and then approximately every 4 weeks during the trial. Persons with acute viral syndromes that may reflect acute HIV infection will defer enrollment and be referred for evaluation of acute infection. If acute HIV infection is suspected after enrollment, the participant will undergo evaluation using rapid HIV antibody testing and GenAptima HIV RNA testing, as indicated. These steps should minimize the risk of drug resistance occurrence by identifying HIV infection in its early stages and stopping study drug. If any participant in HPTN 067 becomes HIV-infected during the study and develops TDF or FTC resistance, an alternative treatment regimen could be used that includes a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor, and an NRTI that is not affected by the M184V or K65R mutations.

8.4 Benefits

Several clinical trials evaluating the efficacy of FTC/TDF (administered daily) for PrEP are ongoing as described in Section 1.3. The earliest results from some of these studies are expected in the fall of 2010. These results will be shared with participants as they are made available.

Participants in this study will benefit from HIV education and prevention messages. They will receive free HIV and HBV serologic testing. Participants found to be susceptible to HBV will be offered standard HBV vaccinations. The services to be provided for HIV seroconverters include: laboratory testing for drug resistance, plasma HIV RNA level, and CD4 cell count. Participants who

acquire HIV infection during the study will be provided with referral for HIV services and evaluation of whether ART is needed and will continue to be followed in this study.

8.5 Incentives

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Incentives for responses to weekly phone contacts will be provided via payment at the next clinic visit. Site-specific reimbursement amounts will be specified in the study informed consent forms.

8.6 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions. During focus groups, participants will be encouraged to use a nickname or pseudonym to protect their identity. All focus groups and key informant interviews will be recorded and transcribed by qualified personnel. All participant identifiers will be removed from transcripts and the recordings, notes and transcripts will be destroyed according to DAIDS regulations. All local databases will be secured with password-protected access systems.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the U.S. CDC, NIAID and/or its contractors; Gilead Sciences, Inc. representatives of the HPTN CORE, SDMC, and/or NL, the U.S. FDA, other government and regulatory authorities, and/or site IRBs/ECs.

8.7 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.

8.8 Study Discontinuation

The study may be discontinued at any time by NIAID, the HPTN, the National Institutes of Mental Health (NIMH), Gilead Sciences, Inc., OHRP, the U.S. FDA, the US CDC, the Thailand Ministry of Public Health, the South African Medicines Control Council, and/or site IRBs/ECs.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the local laboratory (LL):

- Urine specimen for the following:
    - Pregnancy testing for women with reproductive capacity
    - Dipstick for protein and glucose
    - Storage
- Blood specimen for the following:
    - HIV rapid testing
    - HIV confirmatory testing with a Western blot or with the GenAptima HIV RNA test
    - Quantitative HIV RNA testing in any participant with confirmed HIV infection
    - CD4 cell count in any participant with confirmed HIV infection
    - HepBsAg
    - HepBCoreAb (if the test for HepBsAg is negative)
    - HepBsAb (if the test for HepBsAg is negative)
    - CBC
    - Serum creatinine
    - Serum phosphate
    - AST/ALT
    - Plasma for storage
    - Serum for storage
    - PBMCs for storage
    - DBS for storage
- Hair specimen for storage

Local laboratories will perform Chemistry, Hematology, and pregnancy tests as indicated in Appendix I. Laboratories performing these tests will be monitored by Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) and must demonstrate successful participation in the relevant External Quality Assurance (EQA) programs.

Local laboratories may also perform CD4 cell count testing and quantitative HIV RNA (viral load) testing as indicated in Appendix I. Laboratories performing these tests will be monitored by the Immunology Quality Assurance (IQA) and /or

Virology Quality Assurance (VQA) programs and must demonstrate successful participation in the relevant EQA programs.

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

All specimens will be shipped in accordance with International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the HPTN LDMS as described in the SSP Manual.

9.2 Network Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the HPTN NL:

Virology

The HPTN NL will perform testing to determine HIV infection status in selected cases (*e.g.*, indeterminate Western blot) and may also perform specialized assays to characterize HIV viruses and the immune response to HIV infection in participants who become HIV-infected during the study. This may include testing with assays used for analysis of HIV incidence. Additional assays may be performed at the HPTN NL or at an outside laboratory designated by the HPTN NL. This testing may include HIV genotyping, HIV phenotyping, HIV subtyping, minority variants assays, or other tests to characterize HIV viruses and/or the host response to HIV infection. Results from those tests will not be returned to study sites or study participants.

Pharmacology

Retrospective analysis of drug levels will provide an objective measure of adherence. Estimation of PK for each participant allows for drug concentrations to be used as objective measures of drug exposure and allows for an estimation of pill-use during the self-administered dosing phase of the study.

The level of TDF-DP in PBMCs will be monitored after directly observed doses during Weeks 4 and 5. Decay will be monitored at Week 6. Thereafter, levels of TDF-DP will be monitored in PBMCs at Weeks 10, 18, and 30. PBMC drug levels will be measured using assays that are validated and approved by the Clinical Pharmacology Quality Assurance Committee (CPQA). The PBMC assay measures intracellular TFV-DP; FTC-TP may also be measured. Aggregate results that do not identify individual study participants will be made available to study sites during the trial to provide information on adherence of participants to the study regimen. Data from individual study participants will not be returned to

study sites or study participants. Stored serum may be tested at the HPTN NL to measure extracellular drug levels of TFV and FTC, for comparison.

Hair will be collected and stored for possible measurement of drug levels at Weeks 4, 5, 6, 10, 18, and 30. Testing of hair for drug concentrations may be performed either at the HPTN NL or at an outside laboratory designated by the HPTN NL. If an outside laboratory is used, protocols for drug measurement must first be validated, after the laboratories are enrolled in the CPQA, and the assay must be approved by the CPQA before HPTN 067 specimens are tested.

Urine will be stored for possible future studies analyzing the relationship between TDF drug level and dose and the occurrence of renal proximal tubulopathy. Those laboratory studies would be funded separately if daily PrEP trials show that proximal tubulopathy occurs among HIV-uninfected persons at a higher rate after TDF exposure than among HIV-uninfected persons exposed to placebo. The testing would include fractional excretion of uric acid and phosphate (involving parallel testing of these analytes in serum and urine), urine protein, urine glucose, urine creatinine, and urine calcium.

Drug Resistance Testing Performed at a Commercial Laboratory

Samples from participants who become HIV-infected during the study will be shipped to the HPTN NL. A sample collected at the time of HIV diagnosis will be sent to a commercial laboratory (*e.g.*, Monogram Biosciences, South San Francisco, CA) for HIV resistance testing. Results from that testing will be made available to study sites at study closure. Results may be provided to study sites prior to study closure upon request, with approval of the HTPN NL and the Protocol Chair. Results from any other resistance testing (*e.g.*, minority variants analysis, if performed, see above) will not be returned to study sites.

9.3 Quality Control and Quality Assurance Procedures

The clinical sites will document that their clinical laboratories are certified under the Continuous Laboratory Improvement Act of 1988 (CLIA-certified) and/or participate in DAIDS sponsored EQA programs. NL staff will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control (QC) procedures, including proper maintenance of laboratory testing equipment and use of appropriate reagents. NL staff will follow up directly with site staff to resolve any QC or quality assurance (QA) problems identified through proficiency testing and/or on-site assessments. Throughout the course of the study, the HPTN NL will select a random sample of stored specimens to test for QA purposes. NL staff will follow-up directly with site staff to resolve any QA problems identified through this process.

All of the assays to be used in this study have been approved for use in HPTN studies by the cross-network CPQA program. The quality of the assays is also continuously evaluated by a twice yearly proficiency testing program administered by the CPQA. Satisfactory scores are required for the laboratory to be able to continue to use assays in support of HPTN studies. The Pharmacology Core Lab will adhere to Good Laboratory Practice (GLP) for processing all samples.

9.3.1 QC for HIV diagnostic testing

The HPTN NL will perform HIV diagnostic testing for QC.

Before performing HIV diagnostic testing, all sites must validate their testing algorithm, and the validation study must be approved by the HPTN NL. Local laboratories will perform testing for HIV diagnosis at Screening, Enrollment, and other scheduled visits. Algorithms for HIV diagnostic testing are provided in the SSP Manual.

Participants will be tested for HIV infection status using two HIV rapid tests, one of which must be FDA-cleared. Preference is given to FDA-cleared OraSure Oraquick HIV½, Clearview HIV½ Stat Pak, or Clearview Complete HIV½ in the U.S., and to the use of Abbott DETERMINE or Bioline and an FDA-cleared rapid test outside of the U.S. Participants with one or two reactive HIV rapid test results at Screening or Enrollment will not be eligible for enrollment, regardless of subsequent test results. In those cases, HIV infection status will be confirmed using local HIV testing guidelines. Participants who have one or two reactive HIV rapid test results at any other study visit will be further tested using an FDA-cleared Western blot or the GenAptima HIV RNA test. Further testing will be based on the results of the confirmatory testing, as described in the SSP Manual. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed using the GenAptima HIV RNA test. Regardless of whether HIV RNA testing is used for diagnostic testing, HIV infection must be confirmed in all cases using two independent samples.

9.3.2 QC for HIV RNA monitoring

Quantitative HIV RNA (viral load) testing will be performed at local laboratories to monitor HIV infection in any subject with confirmed HIV infection. Viral load testing will be performed in HIV-infected participants at the visit when HIV infection is confirmed, and at subsequent study visits. Note that this is distinct from use of qualitative HIV RNA testing that is performed to determine HIV infection status (see above). Local laboratories must participate in the DAIDS Virology QA (VQA) program, with EQA results that are deemed satisfactory by the HPTN NL.

9.3.3 QC for CD4 cell count determination

For participants who become HIV-infected during the study, CD4 cell count testing will be performed at the time when HIV infection is confirmed and at subsequent study visits. Non-U.S. laboratories performing CD4 cell count testing must be enrolled in the United Kingdom National External Quality Assessment Service (UK NEQAS) program through the DAIDS IQA program.

9.4 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 U.S. CDC. All infectious specimens will be transported in accordance with U.S. regulations [42 Code of Federal Regulations (CFR) 72].

9.5 Sample storage

Selected samples from HIV seroconverters and other participants will be shipped to the HPTN NL. At the discretion of the HPTN NL, samples may be transferred to a DAIDS-approved repository. Other specimens will be stored at study sites and shipped to the HPTN NL upon request.

Study site staff will store all PBMC, plasma, serum, urine, and hair samples collected in this study until all protocol-related testing has been completed, including QC testing and other testing performed at or coordinated by the HPTN NL. The study site will be informed by the SDMC when shipments to the NL are required, and will be instructed which samples to ship. In addition, study participants will be asked to provide written informed consent for their blood and urine specimens to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study.

10.0 ADMINISTRATIVE PROCEDURES

10.1 Study Activation

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

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

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

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

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

10.2 Study Coordination

DAIDS holds the Investigational New Drug (IND) application for this study (#71,859). Copies of all regulatory documents submitted to this IND by DAIDS will be forwarded to Gilead Sciences, Inc. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS and Gilead Sciences, Inc.

Study implementation will be directed by this protocol as well as the SSP Manual. The SSP Manual — which will contain reference copies of the DAIDS SOPs for Source Documentation and Essential Documents, as well as the DAIDS Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, dated January 2010 and the DAIDS Toxicity Tables — will outline procedures for conducting study visits, data and forms processing, AE assessment, management and reporting, dispensing study products and documenting product accountability, and other study operations.

Study case report forms and other study instruments (*e.g.*, CASI) will be developed by the study team and HPTN SDMC. Data will be transferred to the HPTN SDMC, processed, and cleaned. Quality Control reports and data queries will be generated on a routine basis and distributed to the study sites for verification and resolution.

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

10.3 Study Monitoring

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

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

Site investigators will allow study monitors to inspect study facilities and documentation (*e.g.*, informed consent forms, clinic and laboratory records, other source documents, and CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, NL, NIH, Gilead Sciences, Inc., and U.S. and in-country government and regulatory authorities including relevant IRBs/ECs. A site visit log will be maintained at the study site to document all visits.

10.4 Protocol Compliance

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

10.5 Investigator's Records

The IoR will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with Federal regulations, for each of the two investigational products tested, the IoR will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued.

Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

10.6 Use of Information and Publications

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

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APPENDICES

APPENDICES

Appendix I: Schedule of Study Visits and Procedures

Appendix IA. All study participants

	Screening (up to – Day 70)	Week 0 Enrollment	Weeks 1-5 DOT	Week 6 Randomization	Weeks 7-29 Self-admin dosing[1]	Week 30 End of drug dosing	Week 34 Post-Study Follow-up Visit
Administrative, Behavioral, and Regulatory Procedures							
Screening/Enrollment informed consent	X						
Locator information	X	X	X	X	X	X	X
Demographic information	X						
Social harms assessment			X	X	X	X	X
Randomization to a treatment arm				X			
Behavioral assessment (CASI)	X			X	X[2]	X	
Adherence/ behavioral monitoring (telephonic weekly)					X	X	
Focus groups and key informant interviews							X[3]
Clinical/Counseling Procedures							
Adherence and EDM orientation/ counseling and pill counts		X		X	X[4]	X[4]	
Complete medical history including medications	X						
Interim medical history including concomitant medications		X	X	X	X	X	
Adverse event (AE) assessment			X	X	X	X	X
Full physical exam		X					
Symptom-driven physical exam				X	X	X	
Once per week directly observed dosing		X	X[5]				
Study drug supply and associated counseling				X	X		
HIV pre-test, risk reduction, and post-test counseling	X	X	X[6]	X	X[7]	X	X
Laboratory Procedures *							
Sample testing:							
Urine for pregnancy[8]	X	X	X[6]	X	X	X	
Urine dipstick for protein and glucose	X			X	X[9]	X	X
Blood collection for:							
HIV rapid testing (with confirmation if indicated) [10]	X	X	X[6]	X	X[7]	X	X[12]
Complete blood count (CBC)	X				X[9]	X	
Serum creatinine	X		X[6]		X[9]	X	
Serum phosphate	X				X[9]	X	
AST/ALT	X		X[6]		X[9]	X	
Hepatitis B virus testing[13, 14]	X						
Sample storage: [15]							
Plasma for storage	X	X	X[11]	X	X	X	X[12]
DBS for storage			X[6]				
Serum for storage			X[11]	X	X[9]	X	
PBMC for storage			X[11]	X	X[9]	X	
Hair for storage			X[11]	X	X[9]	X	
Urine for storage			X[11]	X	X[9]	X	

* All rapid testing (for HIV infection, pregnancy, and urine protein) and all sample collection for testing and for storage should be completed prior to dosing study medication

Footnotes for Appendix IA

[1] Visits conducted at Weeks 10, 14, 18, 22 and 26.
[2] Week 18 only.
[3] Focus group discussions and key informant interviews may be done at any time within a three month window after Week 34 with selected study participants and site staff.
[4] Adherence orientation if necessary. Week 30 is the end of the self-administered dosing period and therefore will include pill counts only.
[5] Weeks 1-4.
[6] Week 4 only.
[7] HIV testing including pre-and post- test counseling will be performed at Weeks 10, 14, 18, 22 and 26.
[8] Biologic females who were not found to be pregnant at a previous study visit. Those with documented inability to become pregnant (tubal ligation, etc.) will not require testing.
[9] Weeks 10 and 18 only.
[10] HIV diagnostic testing must be performed at the indicated study visits according to the algorithms provided in the SSP Manual. The HPTN NL should be consulted in any case where HIV infection status is unclear, one or both HIV rapid tests is reactive, HIV seroconversion is documented, or acute HIV infection is suspected. CD4 cell count testing, viral load monitoring, and HIV drug resistance testing will be performed for participants with confirmed HIV infection only (see Appendix 1B). Participants that are confirmed to be HIV-infected according to the SSP Manual will have no further HIV diagnostic testing performed at subsequent study visits.
[11] Weeks 4 and 5 only.
[12] At Week 34, plasma should be stored if one or both of the HIV rapid tests is reactive.
[13] If the AST or ALT increases to a grade 3 or higher elevation after enrollment, the participant should be retested for HepBsAg.
[14] Evidence of immunity to HBV infection provided by any one or more of the following: detection of anti-HBsAb, documented history of two or more HBV vaccine doses and plans to complete the series in the following 5 months, or detection of anti-HBc and a negative test for HBsAg. Participants who are susceptible to HBV infection will be offered HBV vaccination. They may be retested for evidence of HBV immunity after the second dose of HBV vaccine. Participants should be retested for hepatitis at subsequent study visits if they express a concern about recent hepatitis acquisition, or have clinical signs/symptoms of hepatitis.
[15] Store samples on site until requested by the HPTN NL.

Appendix IB. Additional Procedures for Participants with Confirmed HIV Infection

	Time of diagnosis	Weeks 10, 18, and 30 (if after HIV diagnosis)	Weeks 14, 22 and 26 (if after HIV diagnosis)
CD4 cell count testing	X	X	
HIV viral load testing	X	X	
Shipment of samples to the HPTN NL[1]	X	X	
HIV genotyping[2]	X		
Other testing[3]	X	X	
Additional plasma storage	X	X	X
Cell pellet storage	X	X	X

[1] Stored samples from HIV seroconverters will be shipped to the HPTN NL; sites should store samples until they receive a request for shipping from the SDMC. At the discretion of the HPTN NL, samples may be transferred to a DAIDS-approved repository.

[2] The HPTN NL will coordinate HIV resistance testing using samples shipped to the HPTN NL. HIV genotyping results from this study visit (time of HIV diagnosis) will be provided to study sites at study closure. Results from this testing may be provided to study sites prior to study closure with approval of the HPTN NL and the Protocol Chair.

[3] Additional testing may be performed at the HPTN NL for research purposes; at the discretion of the HPTN NL, additional testing for research purposes may also be performed at another laboratory (*e.g.*, at one of the study sites, at the U.S. CDC, or at another laboratory with special expertise). Those results will not be returned to study sites or study participants. This testing may include additional HIV genotyping/sequencing assays, HIV phenotyping, HIV subtyping, minority variants assays, other assays to characterize HIV + viruses and/or the host response to HIV infection.

Note: Participants with confirmed HIV infection will continue in the study, off of study drug. Any enrolled participants who acquire HIV infection during the study will permanently discontinue study product and will be followed after Enrollment at regularly scheduled monthly visits and then every 12 weeks after Week 30 until the last HIV uninfected participant reaches Week 34.

Appendix II: Additional power calculation with a range of average coverage rates for two primary hypothesis tests.

Table 1 Non-inferiority region (δ) for hypothesis (1) assuming 60 participants or 120 participants depending on whether risk-group specific analyses or overall analyses is considered, 50 acts per participant, α =0.05 (one-tailed). Power is computed against the alternative that coverage is exactly equal in the two arms (*i.e.* δ = 0).

CV	Power	% ``uncovered'' sex in daily arm (1 – pd)	null δ	
			n=60	n=120
.4	.9	.2	0.053	0.037
.4	.95	.2	0.059	0.042
.6	.9	.2	0.071	0.050
.6	.95	.2	0.080	0.057
.8	.9	.2	0.091	0.064
.8	.95	.2	0.103	0.072
.4	.9	.05	0.020	0.014
.4	.95	.05	0.022	0.016
.6	.9	.05	0.023	0.016
.6	.95	.05	0.026	0.018
.8	.9	.05	0.027	0.019
.8	.95	.05	0.031	0.022

Table 2 Minimum detectable difference between the rate of covered sex acts in one intermittent treatment arm as compared to the other intermittent arm, assuming 60 participants or 120 participants depending on whether risk-group specific analyses or overall analyses is considered, 50 acts per participant, $\alpha = 0.05$ (two-tailed).

CV	Power	The rate of uncovered sex act in intermittent arm 1 ($1 - pi_1$)	Minimum detectable rate of uncovered sex in intermittent arm 2 ($1 - pi_2$)	
			n=60	n=120
.4	.8	.2	0.256	0.238
.4	.9	.2	0.267	0.245
.6	.8	.2	0.282	0.254
.6	.9	.2	0.299	0.264
.8	.8	.2	0.313	0.273
.8	.9	.2	0.338	0.287
.4	.8	.05	0.072	0.065
.4	.9	.05	0.076	0.067
.6	.8	.05	0.077	0.068
.6	.9	.05	0.082	0.071
.8	.8	.05	0.084	0.072
.8	.9	.05	0.091	0.076

Appendix III: SAMPLE INFORMED CONSENT FORMS

SAMPLE SCREENING AND ENROLLMENT INFORMED CONSENT FORM

The ADAPT study: A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP) (HPTN 067)

Final Version 1.0
September 20, 2010
DAIDS Document ID: 10852

Study Implementers: Thailand Ministry of Public Health - US Centers for Disease Control and Prevention Collaboration (TUC), Silom Community Clinic, Bangkok, Thailand; Emavundleni Desmond Tutu HIV Centre in Observatory, South Africa; Division of HIV/AIDS Prevention, US Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA; HIV Prevention Trials Network (HPTN), U.S. National Institutes of Health (NIH), Bethesda, MD, USA; US National Institutes of Mental Health (NIMH), Bethesda, MD, USA; Gladstone Institute, University of California at San Francisco, San Francisco, CA, USA.

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID), and U.S. National Institute of Mental Health (NIMH). Study drug is provided by Gilead Sciences, Inc.

PRINCIPAL INVESTIGATOR: [Insert Name]
PHONE: [Insert Number]

INTRODUCTION
You are being asked to take part in a research study. The goal of this study is to find out more about whether people can take a drug that may prevent HIV infection and what that experience is like for them. This drug is called Truvada®. Truvada® is commonly used to treat HIV infection. HIV is the virus that causes AIDS. This study is being done among [men who have sex with men/women who have sex with men] in your community. Whether you join the study or not is up to you. If you choose to join the study, you may stop taking part at any time.

There may be no direct benefits for you if you participate in this study. There also may be some risks with taking part in the study. Before you can make an informed decision about whether to take part in this study, you should understand the possible risks and potential benefits of being in this study. That process is called informed consent. This informed consent document will give you an idea of what will take place during the study and provides you with detailed information about this research study. This consent form might contain some words that are not familiar to you. Please ask us to explain anything that you do not understand before you sign this form. If

you state that you understand the study and have decided that you want to participate, you will be asked to read, sign, and date this form. You will also be offered a copy of this form to keep.

What happens if you do not want to take part?

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

- You do not have to be in this study if you do not want to and you can stop taking part in the study at any time without affecting the services you get at [insert clinic].
- If you decide to stop taking part in the study, you may still join another study if one is available and you qualify.
- Some people may not be able to join the research study because of information they provide during the screening process.
- During the study, you may be told of important new information about the study that may affect your safety. For example, if the study shows that you taking part in it may be bad for your health, we will tell you. It will be up to you to decide if you want to continue in the study. If you decide to stay in the study, we may ask you to sign an updated informed consent form. You will also be told when the results of the study may be available, and how to learn about them.
- If you have any major health problems during the study, the doctor may require that you stop taking study drug for your own safety.
- If you or your doctor decides that you should withdraw from the study we may ask you to come in for a final visit.
- If you are currently or have ever been part of another study to prevent HIV infection or HIV vaccine study, you may not be able to participate in this study. Please also tell us if you join another study after agreeing to take part in this one, as this may affect your health.

Why is this study being done?

Truvada® is a tablet that has two drugs in it. These drugs are called "emtricitabine" and "tenofovir". These drugs are commonly used to treat HIV infection. Truvada® is generally safe when used as treatment for HIV. Truvada® is not a cure for HIV or AIDS. When given together with other drugs, Truvada® may help to prevent or delay AIDS in people with HIV. The purpose of this study is to find out how different schedules of taking Truvada® affects how it works, whether these different schedules affects the safety of the drug and whether people like it.

About 360 people will take part in this study at two different study sites. In Thailand, we will enroll 180 men who have sex with men. In South Africa, we will enroll 180 women who have sex with men. People in the study will be asked to take part for a total of 34 weeks (approximately 8 months and 2 weeks). Everyone will take Truvada® for the first 30 of these 34 weeks (approximately 7 months and 2 weeks) based on their group.

In this study there are three groups based on how often they will take Truvada®

- Group 1 will be asked to take a pill once a day.
- Group 2 will be asked to take a pill twice per week (every three or four days) and another pill after sex.
- Group 3 will be asked to take a pill before and after sex.

Currently, several studies are going on to find out whether Truvada® may help to prevent HIV infection. We do not yet know the results of these studies. At this time we do not know whether Truvada® can prevent HIV infection. It is therefore important that if you decide to join this study, you continue to use condoms from start to finish every time you have sex.

What will happen during the study visits?

Screening visit: The first study visit is called the screening visit. The screening visit will take about 45 minutes. During this visit, we will ask you questions about your health, current medications and personal life to see if you are eligible to participate. Study staff will ask your name and contact information so that we can keep in touch with you during the study.

If you are eligible and willing to participate, you will be asked to complete an interview, using a computer, about your background and sexual practices. We will counsel you about HIV infection, risks you may be taking and how to avoid getting HIV. We will draw ~XX mL of blood (about X tablespoons). This blood will be tested for HIV, hepatitis B virus, and [insert other local testing as applicable]. We will also ask you for a urine sample. Your blood and urine will be tested to assess your overall health and whether your liver and kidneys are working normally. [Insert for women- If you are pregnant or breastfeeding, you cannot join this study. If you are a woman that is able to become pregnant, we will test your urine for pregnancy.] Study staff will inform you of the results of all tests which affect your health.

What if your blood shows that you have HIV?
We will give you the results of your HIV test during this visit. If the test shows you have an HIV infection, you cannot be in the study. If you have a test result at this or any study visit that indicates you may have been infected with HIV, we will arrange to confirm the test result. If the confirmatory tests show that you do have HIV infection, we will perform tests to see how well your body can fight off infections and measure the amount of virus in your blood. If we confirm that you are infected with HIV later in the study, you will have to stop taking Truvada®, but we will ask you to continue to come to the study clinic as scheduled. In this case, we will also test your blood to see if Truvada® can still be used to treat your HIV infection during these monthly visits. [Insert any additional local testing that may be performed]. [Insert any local reporting requirements.] We will also refer you for HIV treatment and care.

What if your blood shows that you have hepatitis?
To protect your health, everyone who takes part in the study must be immune to hepatitis B virus infection (either because you have already had the disease or because you have had the vaccine). This is because one of the drugs used in Truvada® can also be used to treat hepatitis B virus and taking Truvada® now might result in less effective treatments for hepatitis B virus if you were ever infected. If you are not immune, you will be offered a vaccine against the hepatitis B virus. **If you agree, we can give you the first vaccination immediately.** You will need to come back in two weeks to get the results of the testing for hepatitis B virus. The hepatitis B follow-up visit will take about 30 minutes. You will receive the second vaccination at the beginning of the enrollment visit and the third one after you have started the study. If you have a hepatitis B virus infection you cannot be in the study. If you later develop another form of hepatitis while in the study, you should stop taking the study drug.

Enrollment visit: If you are eligible and agree to participate, you will be asked to come back to the clinic to start the study. This will be your enrollment visit. The enrollment visit will take about an hour. During this visit, we will ask you questions about any changes in your health and medications and give you a full physical exam. Study staff will confirm your name and update your contact information. We will ask you about anything that has happened as a result of your study participation. We will again counsel you about HIV infection, risks you may be taking, and how to avoid getting HIV. We will draw ~XX mL of blood (about X tablespoons) and your blood will be tested for HIV. [Insert for women- If you are pregnant or breastfeeding, you cannot join this study. If you are a woman that is able to become pregnant, we will test your urine for pregnancy.] Study staff will inform you of the results of all tests which affect your health. We will give you an electronic pill box that sends an electronic message to our system when it is opened. We will explain to you how this pill box works and give you a supply of vitamins so that you can get used to using it.

Once we have completed all of these tests, we will give you your first dose of Truvada®. A nurse will observe you taking this dose and we will watch you to see how your body reacts to the study drug.

Weeks 1-5: For the first six weeks of the study after your enrollment visit, we will ask you to come to the clinic once a week and take Truvada®. A nurse will observe you doing this. You will not take a dose during week 5, but we will ask you to come to the clinic. At all of these visits, we will also take samples of your blood, urine and hair. We will draw ~XX mL of blood (about X tablespoons) and test it for HIV. You will be counseled about HIV and how to avoid it. This visit will last about an hour. If you miss any of these visits, we will remove you from the study.

Weeks 6-29, 30 and 34: At the beginning of Week 6, we will use a lottery-like system to determine which study group you will join. You will be given a 4-week supply of Truvada® and asked to take Truvada® according to the schedule in your group. Your Truvada® will come in a pill box just like the one provided to you at enrollment that sends an electronic message to our system when it is opened. This way we can monitor when you take Truvada®. A nurse will explain how this pill box works and we will ask you to use this box every time you take a pill. Study staff will also ask you to take notes in a journal about your sex life and pill-taking. This visit will last about two hours.

[For women] If you are a woman who is able to become pregnant, we will perform a pregnancy test at every study visit. If you become pregnant, you should stop taking Truvada®.

After six weeks, we will ask you to come to the clinic every four weeks for approximately seven visits. This visit will last about an hour. At every visit we will confirm your contact details and ask you about your health and any drugs you may be currently taking. We will ask you about any drug side effects you might be experiencing and discuss any health problems you might be having. At these visits, we will also take samples of your blood, urine and hair. We will draw ~XX mL of blood (about X tablespoons) and test it for HIV. You will be counseled about HIV and how to avoid it. We will ask you to bring the pill box with you to the visit as well as any remaining pills. A nurse will count your leftover pills. You will get a new supply of Truvada®. Every week until week 29, we will call you and ask you questions about the number of pills you have taken and when you had sex.

At some of these visits (weeks 6, 18, and 30) you will be asked to complete an interview (with a person or by using the computer) which will take about 30 minutes. During these interviews we will ask you questions about your sex life, pill-taking and whether you have side effects from taking Truvada®. At weeks 10 and 18, your blood will be tested to assess your overall health, whether your liver and kidneys are working normally and the amount of Truvada® in your blood. At week 30 you will stop taking Truvada®, but we will ask you to come in for one more visit at week 34 to have your blood tested for HIV. If you stop taking Truvada® before week 30, we will ask you to come for study visits at week 30 and 34 to complete the same procedures and we will also ask you why you chose to stop taking the study drug. We will ask you to return any unused study drug as soon as possible after you stop taking the drug.

Some people in the study may be asked to take part in a focus group or a one-on-one interview with site staff after they stop taking Truvada®. In these focus groups or interviews, people discuss their pill-taking and sexual behavior, HIV risk behavior, feelings about their group assignment, and whether they talked with anyone about pill-use or study participation. If you are asked to take part in a focus group we will explain more about this. In that case, you will also be asked to sign another informed consent form.

How Will Your Samples Be Used?

As part of the study we will collect samples of your blood, urine and hair. These samples will be used for a number of laboratory tests for your safety and measurements of study drug in your body. There may be some leftover samples of blood and urine samples after all of the study-related testing has been completed. We would like to use these samples for future research studies to develop new HIV tests, HIV vaccines and treatments. If you agree to this use of your samples, we will ask you to initial the end of this form. Samples of your blood, hair and urine will be sent to designated laboratories in the United States for further testing.

We may also want to examine the genes in your body, called DNA, since they might affect how your body responds to HIV. For instance, a person that is very tall probably has different genes than a person who is very short, or a person whose ancestors come from a certain place probably have different genes compared to the genes of a person from a far off land. No two persons in the world have exactly the same genes. That is what makes each of us different. We will also be looking at your genes to study your body's reaction to infections, including how genes turn on or off. Understanding these "genetic" differences may help us understand how the human body responds to HIV. These tests are being performed for research only and may be performed in a research laboratory that does not do clinical (patient care) testing. The type of DNA tests that would be performed are unlikely to have any direct impact on your health or future treatments. Some testing may be performed after the close of the study. For these reasons, the results of the DNA testing will not be reported back to the study investigators or to you. We will ask you at the end of this form if you agree to DNA testing. You do not need to agree to DNA testing in order to be in this study.

If you do not agree to have your left over samples stored you can still be in this study. If you agree to store your samples but change your mind later, you can contact study staff. We will then destroy your samples. If you agree, your left over samples will be stored indefinitely [insert local guidelines]. Any future use or the ability to store your samples longer needs to be reviewed and approved by the NIH and local authorities. If these studies involve other laboratories, we

will need approval from your local authorities to store or transfer them elsewhere. Your left over samples will not be sold or used for commercial reasons.

What Are the Possible Risks or Discomforts?

Study drug side effects

About 5 out of 100 people with HIV taking Truvada® tablets have these occasional side effects which usually go away after stopping the drug

- Upset stomach, vomiting, gas, loose or watery stools
- Dizziness or headache
- Abdominal pain
- Lack of energy/general body weakness
- Mild problems of kidney function that are only detected by laboratory tests
- Shortness of breath or cough
- Rash, including allergic reaction
- Anxiety
- Joint pain, muscle pain, or other pain syndrome
- Fever

Fewer than 5 out of 100 people with HIV taking Truvada® tablets have:

- Skin discoloration/darkening of the palms and/or soles of the feet

Potentially serious side effects are rare, but include:

- Liver function problems
- Serious kidney damage or failure
- *Low phosphate levels (a chemical in the blood)* or protein or sugar in the urine
- Inflammation or swelling and possible damage to the pancreas
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Allergic reaction
- Lactic acidosis (too much acid in the body tissues and blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications and death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, weakness, and shortness of breath.
- If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if emtricitabine or tenofovir is stopped.

Some people taking emtricitabine, one of the ingredients in Truvada®, experienced the following side effects:

- Inability to sleep, unusual dreams
- Runny nose
- Rash, itching, which sometimes can be a sign of an allergic reaction

- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides (fatty acid in the blood)
- Increased creatine phosphokinase (CPK; an enzyme found in tissues and cells of the body), which could mean muscle damage
- Skin darkening of the palms and/ or soles

Some people taking tenofovir, one of the ingredients in Truvada®, experienced the following side effects:

- Depression
- Inflammation or swelling and possible damage to the pancreas and liver
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue

The side effects listed above were reported in people with HIV infection. They used Truvada® for HIV treatment. We do not know the side effects of Truvada® when taken by healthy people who do not have HIV infection. A small number of people in this study may have these side effects or other side effects that we do not know about. However, we will screen your kidney function and overall health before you join the study. This will reduce the chances of having any side-effects.

Sensitive questions

The questions we will ask you about your sexual behavior or drug use may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time.

Blood and hair samples

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases, you may faint. There is also a slight chance of infection when blood is drawn. You may be nervous while you are waiting for your HIV test result. If the tests show that you have HIV, you may worry about your health and future. You will receive counseling before and after the test to help address your concerns. We will make every effort to protect your confidentiality during the study. However, it is possible that others may learn that you are part of this study and they may think that you are infected with HIV or are at high risk for infection with HIV. Because of this you could have trouble finding or keeping a job. You could also have problems with your family, friends and community.

Taking a sample of your hair may cause some discomfort. You may worry that this is painful or affects how you look. Approximately 100 strands of hair are needed for this procedure. This is about the number of hairs that a person loses from their body every day. The collection procedure involves cutting the shaft of the hairs near the scalp; the root of the hair will not be collected. Each hair will be cut carefully and will be sampled around your scalp, this way people will not be able to tell that your hair has been removed. We can also take a hair sample from another part of your body other than your scalp if you wish. If you do not wish to provide a hair sample, you can still participate in the study and it will not affect the care you would normally receive.

HIV resistance
If you become infected with HIV, you may not be able to take Truvada® to treat your HIV infection. In some people it may no longer work because it was taken when they became HIV infected. In this case the virus has become "resistant" to Truvada®. If you become infected with HIV during this study, we will test your blood to see if it is resistant to Truvada® and tell you if this is the case.

Other possible risks
We do not know of other risks if you are using any other drugs than Truvada®. These drugs may include herbal or diet pills or powders. Please tell study staff if you are using any of these.

[For Women] How will the study drug affect pregnancy or breastfeeding?
If you are pregnant or breastfeeding, you cannot join this study. If you become pregnant during the study, or within 28 days after completing the study, you should notify the study personnel right away for your safety. If you are still in the study, we would like you to continue to have study visits. If you become pregnant during the study, you will stop taking the pills right away. The study staff will refer you to available sources of medical care and other services for you or your baby. The study does not pay for this care.

Please tell your doctor during your pregnancy about your study participation. Your study doctor will ask that you, or your doctor, provide updates on the progress of your pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

We do not know if Truvada® tablets have any effect on babies whose mothers take it during pregnancy or when breastfeeding. Because of this, **women who are pregnant or breastfeeding cannot participate in this study**. Women who join the study must agree to use effective contraception and must have pregnancy tests at the Enrollment Visit, and at other visits while in the study (about every 4 weeks). Effective contraception includes barrier methods (including condoms), hormonal methods (such as the birth control pill or shot), intrauterine contraceptive device (IUD), and sterilization. Condoms are the only method which also protect you against HIV infection and should be used from start to finish every time you have sex even if you are using another contraceptive method.

What Are the Potential Benefits?
At screening and other study visits we will check to see if you have HIV infection. The counseling you get during this study may help you to avoid HIV and other sexually-transmitted infections. If you have or become infected with HIV, this counseling may help you to learn how to better care for yourself and avoid passing HIV to your sexual partners. If you become HIV infected, we will refer you for care and/or treatment. At the screening visit we will also check if you have hepatitis B infection. If needed, we will offer you a hepatitis B vaccination. During the study you will have tests to check on the health of your blood, liver, and kidneys. If any health problems are found, you will be referred for care. At every visit you will receive condoms and lubricant free of charge.

You may not receive any other direct benefit from being in this study however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

What are Some Reasons Why You May Be Withdrawn From the Study Without Your Consent?

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

- The research study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- The study investigators identify other reasons that they believe would prevent you from continuing in the study.
- You are unable to take the study drug doses here in the clinic during the first several weeks of study participation or you miss any of these visits.
- Finally, the study can be stopped by local authorities, such as the ethical review committee, or by other agencies, such as the study sponsor or other oversight agencies.

What are the alternatives to participating in this study?

[Sites to amend as applicable] There may be other studies going on at this study clinic or in the community for which you may be eligible. If you wish, we will tell you about other studies that we know about. There may also be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.

How will your privacy be protected?

All the information you give us as part of this study will be kept secret. All your laboratory test results will also be kept secret. You will get a unique study identification number that will be used instead of your name on your documents. However, at every study visit we will ask you to identify yourself. This is to make sure that it is you who provides samples and information to us. Also we want to make sure that no other person than you can get your confidential laboratory test results. Only the study staff will be able to see records that identify you by name. This information will not be shared with others. All records will be stored in locked files at the study clinic. Results of your laboratory tests will be made available only to you when you visit the clinic. Your name will never be used in any publication or presentation about the study.

The United States Food and Drug Administration (FDA) has been informed of this study and has allowed it to be done. Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH), US NIMH) and their representatives, ***[insert name of site]*** IRB/EC, study staff, study monitors and [insert applicable local regulatory authorities]..

What will be asked from you in this study?

In this study you will be asked to come to the study clinic at least 13 times; every week during the first six weeks, and then once a month for seven months (total 34 weeks). If you develop HIV during the course of the study, we will ask you to return to the clinic every 12 weeks after Week 30 until the study ends at this site. If we need to do additional tests for your health, we

may ask you to come for an additional visit. We will ask you to take Truvada® according to the schedule in your group. You will also be asked to remember every time you have sex and when you took Truvada®. You will be asked to complete a telephone interview every week (during Weeks 7-29) and a computer questionnaire at Screening, Weeks 6, 18 and 30. We will also take samples of your blood, urine and hair. If you are unable to come to the clinic for your study visits, or if you are unable or not willing to do any of these things, you should not take part in this study.

How will study staff keep in contact with you during the study?
You will be asked to provide your address and phone number(s). The staff will ask you for names of people who will always know how to find you and places where you can be found. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff have important information for you. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study.

What happens if you are injured by this research?
Taking part in this study may put you at risk for personal injury. You may develop side effects from the study drug. If such side effects happen, study staff will assist you in getting medical care. *[Sites to specify institutional policy:]* It is unlikely that you will be injured as a result of taking part in this study. If you are injured, the [*institution*] will give you the treatment needed for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

Who can you contact if you have any questions?
We are happy to answer any questions that you may have. It may be that you have questions about your rights as a study participant or that you think you have been injured because you were in this study. In this case you can contact [insert name of the investigator or other study staff] at [[insert telephone number and physical address].

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

What is the cost of study participation?
There is no cost to you for being in this study. You will receive [insert local amount] for your time, effort, and travel to and from the clinic for each study visit. In addition, you will receive [insert local amount] for each phone call with study staff to discuss your pill-taking and sexual behavior. If study staff has to call you to get this information, you will receive [insert local amount] for your time. You will be given condoms and lubricants, free of charge at each visit.

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US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)

Sponsor: NIAID, NIMH, NIH

SCREENING AND ENROLLMENT INFORMED CONSENT FORM

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

SIGNATURE PAGE

Samples Stored for Future Testing

Blood:

_____ My initials indicate that any left over blood samples may be stored for future testing after study-related testing has been completed.

_____ I do not agree to allow left over blood samples to be saved for long-term storage and future testing after study-related testing has been completed.

____ I agree to allow genetic (DNA) testing of my blood during the study and after the study-related testing has been completed.

____ I do not agree to allow genetic (DNA) testing of my blood.

Urine

____ My initials indicate that any left over urine samples may be stored for future testing after study-related testing has been completed.

____ I do not agree to allow left over urine samples to be saved for long term storage and future testing after study-related testing has been completed.

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

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

SAMPLE FOCUS GROUP INFORMED CONSENT

The ADAPT study: A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP)
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FOCUS GROUP INFORMED CONSENT FORM– STUDY PARTICIPANTS

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

Introduction

You have been invited to participate in a focus group with other participants from the Behavioral Aspects of PrEP Counseling for Intermittent Exposure (HPTN 067) study. A focus group is a discussion among a small group of people about a specific set of topics. Focus groups are led by a focus group leader. The comments made by focus group participants are studied by researchers to learn more about what participants believe concerning the topics that they discuss in the group. The goal of this study is to find out more about whether people can take a drug that may prevent HIV infection and what that experience is like for them. The purpose of this focus group is to help us learn more about:

- How you feel about taking Truvada® according to the schedule in your group.
- How taking part in this study made you feel about your risk for HIV.
- Whether you told your partners, friends and families about taking part in this study.
- How you feel about working with the staff at the study clinic.

Approximately 36 to 48 participants at [insert site] will take part in these focus groups. Approximately 6-8 participants at [insert site] in 6 focus groups (2 focus groups per arm). These focus groups will take place sometime after your Week 34 study visit. An equal number of people will take part in focus groups at [insert other site] for a total of 72 to 96 participants between (insert site) and (insert other site). The information from these focus groups will help us better understand what we learn from the rest of the study. We hope the information we learn will help us reduce the number of people who become infected with HIV in the future.

Procedures

The focus group will be led by a member of the study team. You will be asked to share your views about the use of certain drugs to prevent HIV infection and about how you make decisions about sex. You will also be asked why you think people in the community would or would not want to take part in a study like this one in the future.

In the focus group you will be asked to address each other by a made up name in order to ensure privacy and confidentiality. If any of the questions make you upset the focus group leader may ask you to leave the room, or may stop the focus group all together. You may also refuse to answer any questions during the discussion or leave the focus group at any time. You will also be provided with contact and referral information if any of the questions raise issues that you would like to talk about at a later time.

[To be modified to reflect site practices: The focus group will take place in a location that the study staff have determined will provide you with privacy and confidentiality such as a room at the clinic, or other appropriate places. The study team will talk with you about this so you know where to go for the focus group. ***]***

Each focus group should take about 2 hours. There will be no cost to you for participation. You will receive [insert local amount] for your time and effort.

To help assure that we get the best understanding possible from each focus group the participant answers **will be recorded**. After the focus group is finished, the recording will be typed (called a transcript) by qualified personnel. All identifying information will be removed from the transcript. Your name will **not** be included on the transcript. These recordings will be destroyed after all analysis is completed.

What Are the Potential Benefits?
You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

What Are the Possible Risks or Discomforts?
The questions we will ask you may make you feel uneasy. We hope that the focus group procedures described above will protect your confidentiality and minimize your discomfort when discussing sensitive topics. However, the greatest risk may involve your privacy and confidentiality. This is because confidentiality is limited in a focus group setting, since the other members of the focus groups are present during the discussion and we cannot guarantee that they will not discuss what you will say later. Additional steps that the study team has taken to protect your privacy are described below.

How Will Your Privacy Be Protected?
Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study. We encourage you to make up a name or use a nickname during this focus group.

The United States Food and Drug Administration (FDA) has been informed of this study and has allowed it to be done. Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH), US NIMH) and their representatives, ***[insert name of site]*** IRB/EC, study staff, study monitors and [insert applicable local regulatory authorities]..

Your participation in this focus group is voluntary. You are not required to participate in this focus group in order to remain in the rest of the study (HPTN 067). Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop your participation completely, at any time. If you choose not to participate in a focus group discussion or refuse to answer any of the questions, you will not lose any of the benefits of your regular medical care at [study clinic].

Persons to Contact for Problems or Questions
For questions about this study or a research-related injury, contact:

- **[site insert name of the investigator or other study staff]**
- **[site insert telephone number and physical address of above]**

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

- **[site insert name or title of person on the Institutional Review Board (IRB)/Ethics Committee (EC) or other organization appropriate for the site]**
- **[site insert telephone number and physical address of above]**

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US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)

Sponsor: NIAID, NIMH, NIH

FOCUS GROUP INFORMED CONSENT FORM – STUDY PARTICIPANTS

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

SIGNATURE PAGE

If you have either read or have heard the information in this consent form, if all of your questions have been answered and if you agree to take part in the focus group, please sign your name on the line below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

SAMPLE KEY INFORMANT INTERVIEW INFORMED CONSENT FOR SELECTED STUDY PARTICIPANTS

The ADAPT study: A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP)
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Sponsor: NIAID, NIMH, NIH

KEY INFORMANT INTERVIEW INFORMED CONSENT FORM FOR SELECTED STUDY PARTICIPANTS

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

Introduction

You have been invited to participate in an interview to discuss your study participation in the Behavioral Aspects of PrEP Counseling for Intermittent Exposure (HPTN 067) study. A Key Informant Interview is an individual discussion about a specific set of topics. The purpose of this interview is to help us learn more about:

- Perceived feasibility and acceptability of each of the regimens (pill-taking schedule)
- Facilitators and barriers to pill-taking overall and in relation to specific regimens
- Preferred regimen
- Best strategies to support pill-taking
- Continued condom use in the context of PrEP trials
- Best strategies to support staff and counselors working with PrEP users

Two persons per study arm at each of the two study centers will participate in key informant interviews after they have completed their Week 34 visit. This means a total of six participants at [insert site] and an additional six participants at [site 2]. The information from these interviews will help us better understand what we learn from the rest of the study. We hope the

information we learn will help us reduce the number of people who become infected with HIV in the future.
The information gathered from these interviews will be combined with the rest of the information that is collected during this research study.

Procedures
The interview will be led by a member of the research team. You will be asked to share your views about the use of certain drugs to prevent HIV infection and about how [insert local population] make decisions about sex. You will also be asked why you think people in the community would or would not want to take part in a study like this one in the future. You will be asked to share your views about the use of the study regimen you were assigned and the regimen demands.

If any of the questions make you upset either you or the interviewer may stop the interview at any time. You will also be provided with contact and referral information if any of the questions raise issues that you would like to talk about at a later time.

[To be modified to reflect site practices: The interview will take place in a location that the study staff have determined will provide you with privacy and confidentiality such as the clinic, or other appropriate places. The study team will talk with you about this so you know where to go for the interview.

Each interview should take about 2 hours. There will be no cost to you for participation. You will receive [insert local amount] for your time and effort.

What Are the Potential Benefits?
You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

What Are the Possible Risks or Discomforts?
To minimize any discomfort and to protect your privacy the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time. The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

How Will Your Privacy Be Protected?
Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study.

To help assure that we get the best understanding possible from the interview your answers **will be recorded**. After the interview is finished, the recording will be typed (called a transcript) by

qualified personnel. All identifying information will be removed from the transcript. Your name will **not** be included on the transcript. These recordings will be destroyed after all analysis is completed.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH), US NIMH) and their representatives, ***[insert name of site]*** IRB/EC, study staff, study monitors and [insert applicable local regulatory authorities]..

Your participation in this interview is voluntary. You are not required to participate in this interview in order to remain in the rest of the study (HPTN 067). Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop your participation completely, at any time and you will not lose any of the regular benefits of your regular medical care at [study clinic].

Persons to Contact for Problems or Questions
For questions about this study or a research-related injury, contact:

- **[site insert name of the investigator or other study staff]**
- **[site insert telephone number and physical address of above]**

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

- **[site insert name or title of person on the Institutional Review Board (IRB)/Ethics Committee (EC) or other organization appropriate for the site]**
- **[site insert telephone number and physical address of above]**

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US National Institutes of Health (NIH)

Sponsor: NIAID, NIMH, NIH

KEY INFORMANT INTERVIEW INFORMED CONSENT FORM FOR SELECTED STUDY PARTICIPANTS

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

SIGNATURE PAGE

If you have either read or have heard the information in this consent form, if all of your questions have been answered and if you agree to take part in the Key Informant Interview, please sign your name on the line below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

SAMPLE KEY INFORMANT INTERVIEW INFORMED CONSENT FOR CLINIC STAFF

The ADAPT study: A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP)
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KEY INFORMANT INTERVIEW INFORMED CONSENT FORM FOR SELECTED CLINIC STAFF

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

Introduction

You have been invited to participate in an interview to discuss your role as a provider to participants in their counseling or pill-taking in the Behavioral Aspects of PrEP Counseling for Intermittent Exposure (HPTN 067) study. A Key Informant Interview is an individual discussion about a specific set of topics. The purpose of this interview is to help us learn more about:

- Whether you think these regimens (pill-taking schedules) will work for and are accepted by participants
- What helps or prevents how well participants follow their regimens overall and in relation to specific regimens
- Preferred regimen
- Best strategies to support pill-taking
- Continued condom use in the context of PrEP trials
- Best strategies to support staff and counselors working with PrEP users

Approximately 3-4 clinic staff members directly involved in counseling or pill-taking during HPTN 067 at each of the two study centers will participate in key informant interviews after all participants have completed their Week 34 visit. This means a total of 6-8 participants from the

two study centers. The information from these interviews will help us better understand what we learn from the rest of the study. We hope the information we learn will help us reduce the number of people who become infected with HIV in the future.

Clinic Staff at [insert site] that provided care in the form of counseling or pill-taking in the Behavioral Aspects of PrEP Counseling for Intermittent Exposure (HPTN 067) will participate in these interviews after all participants have completed the Week 34 study visit. The information gathered from these interviews will be combined with the rest of the information that is collected during this research study.

Procedures

[Sites to adjust as needed] The interview will be led by an individual that is not directly a member of our research team here at [insert clinic], but is affiliated with our overall research organization. The individual will not be someone who has a supervisory role for your position. You will be asked to share your views about the use of certain drugs to prevent HIV infection and about how [insert local population] make decisions about sex. You will also be asked why you think people in the community would or would not want to take part in a study like this one in the future. You will be asked to share your views about the use of each of the regimens and how participants interacted with the study and the regimen demands.

If any of the questions make you upset either you or the interviewer may stop the interview at any time. You will also be provided with contact and referral information if any of the questions raise issues that you would like to talk about at a later time.

[To be modified to reflect site practices]: The interview will take place in a location that the study team have determined will provide you with privacy and confidentiality. The study team will talk with you about this so you know where to go for the interview.

Each interview should take about 2 hours. There will be no cost to you for participation. You will receive [insert local amount] for your time and effort.

What Are the Potential Benefits?

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

What Are the Possible Risks or Discomforts?

To minimize discomfort and to protect your privacy the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time. The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

How Will Your Privacy Be Protected?

Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the study team. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study. You will be identified by a code number known only to you and the study staff. This number – not your name – will mark all information about you. However, because there are only a few staff at your site working on this study, it is likely that researchers will know your identity and the information you share.

To help assure that we get the best understanding possible from the interview your answers **will be recorded**. After the interview is finished, the recording will be typed (called a transcript) by qualified personnel. All identifying information will be removed from the transcript. Your name will **not** be included on the transcript. The recording will be destroyed after all analysis is completed.

Your records may be reviewed by the US Food and Drug Administration (FDA), Gilead Sciences, Inc, the OHRP and the US Centers for Disease Control and Prevention (CDC) as well as the sponsor of the study (US National Institutes of Health (NIH), US NIMH) and their representatives, local regulatory authorities, ***[insert name of site]*** IRB/EC, study staff and study monitors.

Your participation in this interview is voluntary. You are not required to participate in this interview in order to remain employed at [insert site]. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop your participation completely, at any time.

Persons to Contact for Problems or Questions
For questions about this study or a research-related injury, contact:

- **[site insert name of the investigator or other study staff]**
- **[site insert telephone number and physical address of above]**

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

- **[site insert name or title of person on the Institutional Review Board (IRB)/Ethics Committee (EC) or other organization appropriate for the site]**
- **[site insert telephone number and physical address of above]**

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KEY INFORMANT INTERVIEW INFORMED CONSENT FORM FOR CLINIC STAFF WHO WERE DIRECTLY INVOLVED WITH PARTICIPANTS IN COUNSELING OR PILL-TAKING

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

SIGNATURE PAGE

If you have either read or have heard the information in this consent form, if all of your questions have been answered and if you agree to take part in the Key Informant Interview, please sign your name on the line below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date