PrEP Adherence Enhancement Guided by iTAB and Drug Levels for Women (AEGIS)

Version 1.4

A Pilot Demonstration Project to Operationalize
Pre-exposure Prophylaxis as part of Combination HIV Prevention
with Intensified Adherence Support Among Women in
Los Angeles and San Diego Counties

Sponsored by:

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3. GLOSSARY OF TERMS

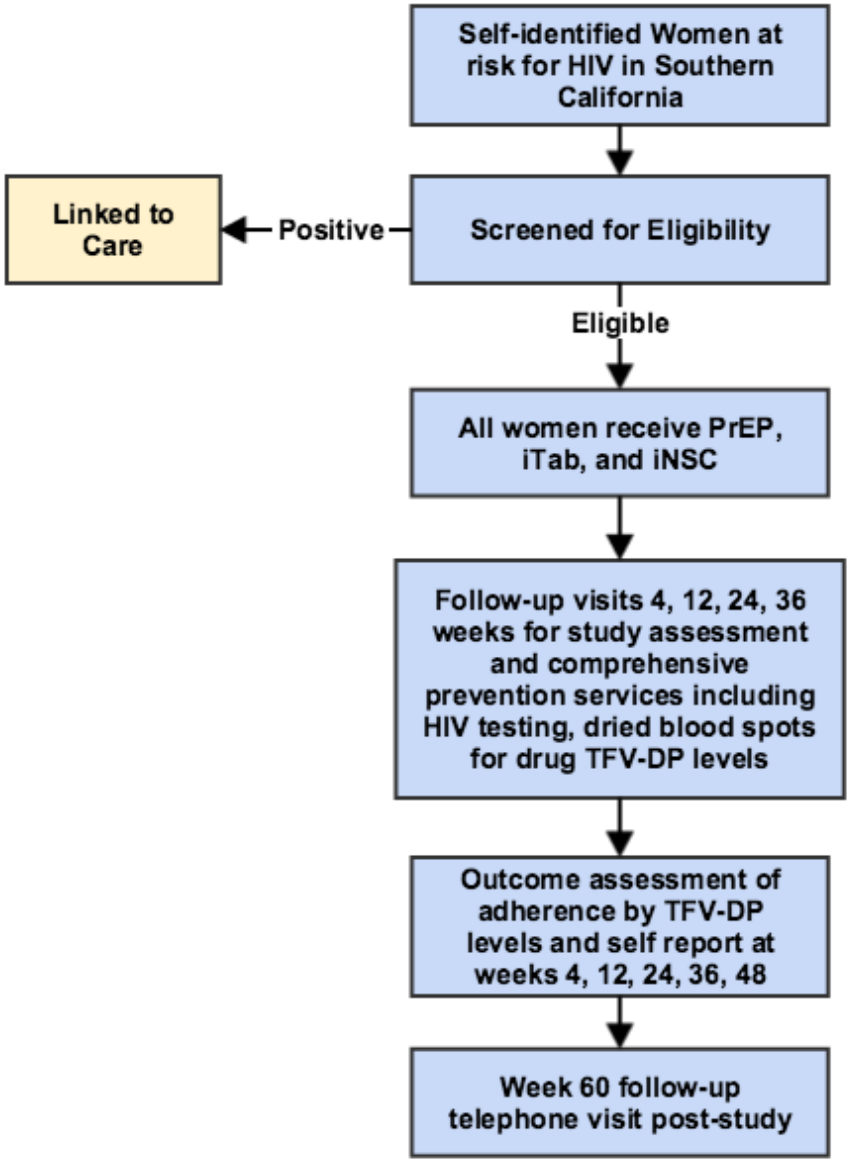
AE	Adverse Event
AEGIS	Adherence Enhancement Guided by iTAB and Drug Levels for Women
ALERT	Active Linkage, Engagement, and Retention to Treatment
ALT (SGPT)	Alanine Aminotransferase
ART	Antiretroviral Therapy
AST (SGOT)	Aspartate Aminotransferase
CASI	Computer Assisted Self-Interviewing
CBC	Complete Blood Count
CBT	Cognitive Behavioral Therapy
CCTG	California Collaborative Treatment Group
CD4	CD4 Lymphocytes
CDC	Centers for Disease Control and Prevention
CHRP	California HIV/AIDS Research Program
CRF	Case Report Form
CM	Contingency Management
CT	Chlamydia
D/C	Discontinue
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
DSMB	Data Safety and Monitoring Board
ELISA	Enzyme-linked Immunosorbent Assay
FDA	Food and Drug Administration
FTC	Emtricitabine
GC	Gonorrhea
HAART	Highly Active Antiretroviral Therapy
HBsAg/Ab	Hepatitis B surface Antigen/Antibody
HCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV-1	Human Immunodeficiency Virus – 1
IDU	Intravenous Drug Use
IRB	Institutional Review Board
iTAB	Individualized Texting for Adherence Building
LAC	Los Angeles County
LFT	Liver Function Test
MFM	Maternal Fetal Medicine
mITT	Modified Intention to Treat
MSM	Men who have Sex with Men
NAAT	Nucleic Acid Amplification Test
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
OB/GYN	Obstetrics and Gynecology
PBMC	Peripheral Blood Mononuclear Cells
PEP	Post-Exposure Prophylaxis
PI	Protease Inhibitor
PLWH	Persons Living With HIV/AIDS
PHI	Primary HIV Infection
PID	Patient Identification Number
PK-PD	Pharmacokinetic-Pharmacodynamic
PrEP	Pre-Exposure Prophylaxis

QA/QC	Quality Assurance/Quality Control
RNA	Ribonucleic Acid
RPR	Rapid Plasmin Reagin
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SoC	Standard of Care
SOE	Schedule of Events
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection
TBIL	Total Bilirubin
TDF	Tenofovir Disproxil Fumarate
TPB	Theory of Planned Behavior
TPPA	Treponema Pallidum Particle Agglutination Assay
VAS	Visual Analog Scale
VDRL	Venereal Disease Research Laboratory

4. STUDY SCHEMA

Design:	AEGIS is an open-label single-arm longitudinal clinical trial to estimate medication adherence and retention in a PrEP HIV prevention program that implements a combination intervention strategy that uses text-messages (iTAB) and a staged adherence counseling support strategy titrated from real-time drug levels in women at-risk for HIV acquisition.
Duration:	Each participant will be on PrEP with medication adherence support for 48 weeks after enrollment with a post study follow-up at 60 weeks. The primary endpoint will be measured at 48 weeks.
Sample Size:	A total of 135 participants will be enrolled (50 at CCTG sites and 85 at the LAC-PATH site).
Study Population:	Eligible participants will include HIV-uninfected cis-gender women at least 18 years of age and who are at risk for HIV acquisition.
Intervention:	All participants will be given PrEP with tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) fixed dose combination prescribed to be taken once daily. All participants will receive the combined intervention of iTAB text messaging adherence reminders and intensive Next Step Counseling (iNSC). The iTAB system consists of daily, personalized, automated 2-way text messages to maintain adherence and retention, and iNSC is a brief, strengths-based discussion initiated at each clinic visit, typically with delivery of negative HIV-test results, focused on promotion of sexual health protection through behavioral and biomedical (adherence) strategies. Participants that have a low intracellular tenofovir diphosphate (TFV-DP) concentration will receive escalated, targeted adherence support (see study schema). All participants will receive access to PrEP in accordance with standardized comprehensive methods of prescribing and clinical assessments that include safety monitoring as well as regular HIV and sexually transmitted infection (STI) screening.
Regimen:	TDF 300 mg + FTC 200 mg fixed dose combination will be given orally once daily starting at the baseline visit (month 0) and continued throughout the study.
Outcomes:	The primary outcome is adherence defined as the mean of quantitative intracellular TVF-DP in dried blood spots (DBS) at 4, 12, 24, 36 and 48 weeks on study. The proportion of women achieving TFV-DP concentrations > 1050 fmol/punch, thought to be reflective of protective levels of PrEP, will be characterized. Self-reported adherence as indicated by responses to the iTAB texting system will be compared to TFV-DP levels.

Figure 1: Study Participant Flow



5. STUDY OBJECTIVES AND HYPOTHESES

5.1. Study Primary Objective

To measure adherence to oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) at weeks 4, 12, 24, 36, and 48 using both biological (dried blood spots) and self reported measures through daily text messaging (iTAB).

5.1.1. Hypothesis I

Drug levels will be high among those who persist with PrEP over time, as measured by tenofovir-diphosphate (TFV-DP) levels > 1050 fmol/punch at weeks 4, 12, 24, 36 and 48.

5.1.2. Hypothesis II

Intracellular TFV-DP concentrations levels will correlate with self-reported adherence as measured by responses to daily iTAB text messages.

5.2. Study Secondary Objectives

5.2.1. To describe the characteristics including demographics, social characteristics, and risk behaviors of women seeking PrEP.

5.2.2. To describe PrEP awareness and acceptability prior to study enrollment among women.

5.2.3. To describe perceived barriers and facilitators to PrEP use among women.

5.2.4. To describe acceptability and feasibility of an HIV prevention program with a multimodal, intensive adherence package for PrEP delivery among women.

5.2.5. To describe retention among women in an HIV prevention program that includes PrEP.

5.2.6. To describe the safety and tolerability of daily TDF/FTC given for PrEP including discontinuation for any adverse event, serious adverse events and adverse events (grade 2 or higher).

5.2.7. To describe the factors associated with discontinuation of TDF/FTC at any time point including change in perceived and actual risk of HIV acquisition, fear of disclosure, demographics, socioeconomic status, social characteristics (e.g., medical mistrust, non-English language, cultural factors), co-occurring health problems or issues (e.g., untreated mental illness, ongoing substance use, violence, trauma), and low health/HIV and system literacy.

5.2.8. To estimate the HIV incidence in the observed cohort of female PrEP users.

5.2.9. To determine frequency of clinically significant resistance among seroconverters.

5.2.10. To estimate the baseline prevalence and incidence of non-HIV sexually transmitted infections (STIs) including chlamydia, gonorrhea, and syphilis.

5.2.11. To examine changes in sexual risk behavior over time in women.

5.2.12 To determine the ability to obtain and barriers to acquiring PrEP after discontinuation of study among women.

5.3. Exploratory Objectives

5.3.1. To explore patterns of adherence among women using iTAB responses as predictors of biologic outcomes.

5.3.2. To describe changes over time of self-reported adherence in real time by texting.

6. PROGRAM BACKGROUND AND RATIONALE

Women make up half of all persons living with HIV/AIDS (PLWHA) worldwide (1). In the United States, approximately 20% of the estimated 47,500 new infections in 2010 occurred in women according to the most recent CDC surveillance data (2). Two-thirds of the twenty-five percent of those infected through heterosexual contact were women. Racial and ethnic minorities are disproportionately represented amongst new HIV infections in US women. In spite of a declining trend, black women continue to be severely overrepresented with new infection rate 20 times that of white women and nearly 5 times that of Hispanic women (3). The HIV/AIDS epidemic among women in Southern California exemplifies this national trend in racial and ethnic disparities. Based on the California HIV/AIDS surveillance semi-annual report in June 2014, Los Angeles (LAC) and San Diego (SD) counties represent two of the top three counties in California with regards to number of reported HIV/AIDS cases, which in combination, total over half of the number of HIV cases in the state (4).

LAC alone is home to 5% of the total number of PLWHA in the US as of 2010. Approximately 10% of all HIV/AIDS cases in each of these counties occurred in women, of which heterosexual contact (69% SD and 70% LAC) is the primary mode of transmission (5, 6). By race/ethnicity, the highest proportion of prevalent HIV/AIDS cases in women in both counties was among Latinas. At the end of 2014, there were 1,332 women living with HIV/AIDS in SD County. Of the female HIV cases from 2007-2011 in SD, 38% were Hispanic and 35% White. Further, Black females make up 23% of all female HIV cases despite only being 5% of the county population (6). The AIDS rate in SD was almost 8 times higher among African American women and 2 times higher among Latina women as compared to White Women (6). Among female PLWHA in LAC, 45% were Hispanic, 35% Black, and 15% White as of December 2013; however, African-American women showed the highest rate of new HIV infection in 2012 (5). The known HIV-infected partners of female HIV patients may be intravenous drug users (IDU), men who have sex with men and women or have other risks and, importantly, may not disclose these risks to their female partners. The persistence of new cases supports the assertion that new prevention strategies are needed to inhibit ongoing spread of HIV infection.

Pre-Exposure Prophylaxis (PrEP) is the use of specific antiretroviral medications (ARV) in HIV-uninfected persons to augment protection against HIV acquisition in the event of

exposure to HIV infection. Presently, TDF/FTC is the only ARV approved for daily use indication for HIV prevention in the US. While no single prevention modality will realistically confer 100% protection against HIV infection, a combination of behavioral risk-reduction programming, social services, mental health and substance abuse referral services with novel biomedical technologies, such as PrEP, is an attractive multidisciplinary programmatic approach to HIV prevention.

In the iPrEx study (n=2499), an estimate of 42% [95% CI: 18-60%] protection against HIV infection was demonstrated in men who have sex with men (MSM) using orally administered TDF/FTC (7, 8). It is clear that adherence to daily PrEP was extremely challenging for many study participants, and that efficacy was strongly correlated with adherence to daily dosing. It is critical to note that in this study, efficacy was demonstrated in the context of monthly HIV testing, adherence counseling, sexual risk reduction counseling, condom provision, and regular sexually-transmitted disease (STD) testing and treatment. TDF/FTC for PrEP was generally well tolerated, with a statistically significant excess of nausea and weight loss in the treatment arm compared to placebo, which resolved by week 8 of the study. Other important safety issues were a non-statistically significant trend toward increased creatinine elevation (which resolved with medication discontinuation), and approximately 1% loss in bone mineral density over one year of treatment. M184V resistance was found among participants (n=2) who were in the “window period” of acute HIV seroconversion at study entry and who were treated with active TDF/FTC.

Data for the effectiveness of oral PrEP in clinical trials of heterosexual women has been conflicting. The Partners PrEP study and CDC’s TDF2 trial, found efficacy for oral TDF/FTC (63% [95% CI: 22-83%] and 75% [95% CI: 55-87%] efficacy) and Tenofovir (67% [95% CI: 44-81%] efficacy)-based PrEP in both men and women in heterosexual partnerships (9, 10). By contrast, two trials examining oral PrEP in African women alone-- Fem-PrEP and VOICE-- failed to confirm its efficacy. Both of these trials were stopped prematurely for statistical futility by their Data Safety Monitoring Board (DSMB), which found no benefit to oral PrEP compared to placebo. In Fem-PrEP, self-reported adherence to the TDF/FTC was 95% in both arms, but serum TFV levels suggested adherence rates between 15 and 38% (11). An excess of pregnancies was noted in the TDF/FTC arm, perhaps suggesting more general non-adherence in that arm, both to ART and to condom use. The VOICE [MTN-003] Trial demonstrated no efficacy of daily Tenofovir (alone), TDF/FTC, or a daily 1% Tenofovir vaginal gel in a population of heterosexual women in sub-Saharan Africa—likely due to extremely low rates of PrEP adherence as demonstrated on plasma drug level testing (12). Additionally, those at highest risk were less likely to use the study product than those actually at lower risk. Furthermore, recent data on tissue pharmacokinetics, as discussed further in the next section, suggest that women may require closer to perfect adherence to achieve higher levels of protection from HIV infection. Therefore, demonstrating maintenance of high PrEP adherence in women will be critical to both optimizing the protective efficacy of PrEP in women and informing implementation strategies for women (13, 14).

Notably, none of the published efficacy trials of PrEP to date have included US women, even though the FDA approved TDF/FTC for use in women at-risk for HIV acquisition. In the US, only data from focus groups have been published on PrEP for women (15, 16). A recent study further demonstrated existing interest by US women in potential PrEP use through qualitative analysis of data from focus groups in six US cities involving 144 at-risk women, of which 92%, were African-American and 10% Latino women. Less than 10% of the women had ever heard of PrEP prior to the study; however, upon being educated about PrEP as part of study conduct, participants recognized the importance of PrEP as an HIV prevention method and expressed willingness to try PrEP. When questioned regarding an acceptable

level of protection for use, women reported ideally desiring 99% efficacy but finding 50% sufficient and viewed PrEP as ancillary rather than a replacement for other prevention methods, such as condoms (17). Partial pharmacy-based prescription data compiled by Gilead (representing approximately 39% of retail pharmacies and <20% of Medicaid prescription) for individuals who started TDF/FTC for PrEP between January 2012 and March 2014 revealed that 42% of PrEP users were women. The overall proportion of female users decreased between 2012 and 2014, suggesting the need for more robust data and experience with US-based women in PrEP to support efforts to augment education and outreach efforts targeting at-risk US-based women (18). By exploring motivations for PrEP use and characterizing adherence patterns, behaviors, acceptability, safety and fertility goals in these women, we aim to expand the data set of oral PrEP in women to include US-based women and inform decisions and policy around further implementation and scale-up.

7. RATIONALE FOR TREATMENT REGIMENS

PrEP strategies that have been evaluated for efficacy have used the nucleos(t)ide reverse transcriptase inhibitor (NRTI) TDF alone or in combination with FTC, including a co-formulation of TDF/FTC in a once-daily pill (19). Agents active at the pre-integration stage of viral replication that may prevent the establishment of HIV-infected cells are thought to be more suitable than post-integration drugs like protease inhibitors (PI), although data to support this supposition are limited (20). In contrast to NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PIs generally achieve lower drug concentrations in the genital tracts of males and females as compared to blood plasma; a potential liability when attempting to reduce genital tissue susceptibility to infection (21). The availability of new drugs such as those that block viral DNA integration or entry through CCR5 are mechanistically attractive; however, comparative trials of different agents for PrEP have yet to be performed, and the optimal correlates of protection in all populations have yet to be defined (22). To date, only TDF/FTC with daily dosing has been FDA approved for HIV prevention among at-risk populations in the US.

A comprehensive understanding of the pharmacology of antiretroviral drugs in genital secretions and tissues is essential to define the most appropriate drug candidates and dosing strategies for PrEP. Correlating drug levels, drug dosing (including route and dose amount), and viral protection are critical parameters that are still being defined. Early findings from animal studies suggested that the high level of protection by pre-exposure dosing strategies may be related to the long persistence of TFV-DP and emtricitabine triphosphate (FTC-TP) in mononuclear cells. Rapid FTC distribution in tissues and long intracellular TFV persistence complement each other to maximize PrEP efficacy (23). The intracellular assay used in the iPrEx study was sensitive enough to detect drug for approximately 14 days after the last dose taken, based on TFV-DP half-life extrapolation, assuming the half-lives of 39 hours and 150 hours for FTC-TP and TFV-DP, respectively (24). Detectable (at the 10 ng/mL level) plasma concentrations of FTC and TFV, with half-lives of 10 to 14 hours, would be expected to last for approximately 2-3 days after dosing (25).

Estimates of TDF exposure from dried blood spots were further validated in the iPrEx open-label extension (26) and used in modeling studies to assess correlates of protection. Data from these modeling studies suggest that even imperfect daily adherence (as few as 4 doses per week) in MSM as assessed by dried blood spots can provide high-level protection against rectal exposures (26). Similar studies have not been performed in women, and given the two to three order-of-magnitude lower levels of TFV and TFV-DP that has been measured in cervicovaginal tissues compared to rectal tissues (27), this threshold may not translate over to women, and similar modeling has not been performed in women. Although

vaginal and cervical tissue concentrations of FTC have been shown to be 10- to 15-fold higher than in rectal tissue after single dose TDF/FTC, it is unclear if this is sufficient to compensate for reduced TFV to provide protection against vaginal exposures. Patterson et al. postulate that the active metabolite FTC-TP may have a shorter tissue half-life than TFV-DP, potentially attenuating the more robust concentration's effect on protection against vaginal exposures and making adherence a more critical component (27). Additionally, a recent Pharmacokinetic-Pharmacodynamic (PK-PD) modeling plus in vitro efficacy target study predicted that even with consistent daily TDF/FTC dosing, only 80% of women would reach protective target tissue levels of TDF (28). Data from this project may further inform field of PrEP pharmacokinetics in women.

A sample of whole blood will be stored (frozen at –70 C) for future pharamacogenomic analyses. Polymorphisms in genes responsible for drug metabolism have been demonstrated in HIV-infected patients to correlate with altered pharmacokinetics, AE profiles, and safety and efficacy outcomes (29). Participants who grant permission for storage of genetic material will have one tube of blood stored for future correlation of genetic haplotypes with toxicity and/or other medical outcomes in the study. Such analyses are planned to be combined with other CHRP-funded PrEP demonstration project datasets, but will utilize a distinct funding mechanism for assay and analysis.

8. RATIONALE FOR DOSING STRATEGY

This protocol will use a daily dosing of TDF/FTC. To date, only daily oral administration of TDF/FTC is FDA approved and CDC recommended in clinical practice for having prophylactic efficacy against HIV acquisition in at-risk populations. Although intermittent dosing is attractive, and the rationale is supported by the high FTC and TFV concentrations achieved in the male and female genital tract after oral administration (21), their long intracellular half-lives in humans (30), and the relatively small size of founder virus populations that initiate an HIV infection in the mucosa after sexual or trans-mucosal exposures(31) (although perhaps less so in MSM(32)), limited data exist to support the use of event-driven or intermittent PrEP (the non-daily dosing of ART as prevention in HIV sero-negative patients), and moreover, there is no clinical trial data in women to support this practice. Data from animal models support the efficacy of intermittent drug dosing with TDF or TDF/FTC where an extended window of protection was attributed to the long intracellular persistence of FTC-TP and TFV-DP in Peripheral Blood Mononuclear Cells (PBMCs). In human studies, it was additionally shown that some protection could be achieved with only pre- and post-coital dosing of a TFV 1% vaginal gel in women but this is not as good as oral daily dosing (33). Demonstrating oral daily dosing effectiveness is a priority for PrEP in women in the United States given the inconsistent data on women taking PrEP overall and almost no data among women taking PrEP in the US. In addition, daily dosing in women may be necessary to achieve protection in vaginal exposures comparable to that in rectal exposure at fewer doses based on PK-PD modeling (28).

9. RATIONALE FOR CONCOMITANT SERVICES

The psychology of risk-taking behavior is enormously complex, and such discussion is outside the purview of this protocol. However, it has been noted that risk-reduction behavioral programming and other behavioral interventions have had mixed results in accomplishing long-term benefit in terms of reduced HIV and STI acquisition (34). Recent studies have demonstrated incremental benefit of more intensive risk-reduction programming compared to standard counseling for highest-risk participants (35). It has been noted in mathematical models that if an intervention such as PrEP were to have the effect of

inducing even incremental increases in high-risk sexual activity, it may be sufficient to entirely abrogate any intrinsic protective efficacy afforded by the medical intervention (36). Although such so-called “risk compensation” has largely not been observed in biomedical prevention trials to date (8, 37-39) (circumcision trials being notably inconsistent in this regard (40)), it remains unclear what the effect on behavior will be when PrEP is implemented in a non-study setting, without placebo-controlled randomization, and with less assiduous follow-up.

The high rate of concomitant substance use associated with high-risk sexual behavior, makes facile referral to such services a logical partnership for appropriate participants (41). In addition, the need for mental health for a variety of mood and personality disorders and domestic/partner violence referral often parallels the need for substance abuse services, and referral to such services must be similarly seamless and part of any prevention package offered (42-44).

Participants may be particularly interested in PrEP for so-called “PrEP-ception” – conception in the setting of a serodiscordant partnership in which the female partner is HIV-uninfected and desires to accomplish conception through conventional intercourse under the “cover” of PrEP to prevent HIV acquisition despite the condomless intercourse required to achieve pregnancy. Referral to high-risk OB/GYN services (MFM, maternal-fetal medicine clinics) will be established and utilized to facilitate such referrals in cases of desired pregnancy.

As noted above, maximizing adherence is critical to intervention efficacy, and therefore HIV prevention success. In addition to multi-modal adherence support, intensive and proactive follow-up by study staff has been shown to be paramount in achieving participant follow-up and retention, including letters, telephone calls, and if applicable cell-phone text message and email reminders (38, 45-48).

10. RATIONALE FOR ADHERENCE MONITORING

Real-time dried blood spot intraerythrocytic TFV-DP drug level monitoring

In the iPrEx study, assessments of adherence both by self-report and sensitive drug level assays on blood plasma and PBMCs suggested a strong correlation between adherence to the daily intervention and efficacy (49, 50). The low overall level of adherence to daily pill-taking in the study was striking, with detectable drug found in 9% of seroconverters, and only 51% of non-seroconverters. The medication adherence data is in stark contrast to the overall study retention (86-88% at 48 weeks), and self-reports of medication adherence (95%). Analyses designed to adjust for adherence suggest that if TDF/FTC were taken with fidelity on a daily basis, there could be preventive efficacy of over 90% (8).

The STRAND study established plasma and PBMC steady-state tenofovir (TFV) drug levels achieved from directly observed dosing of TDF/FTC twice weekly, four-times weekly, and 7-times weekly. With twice-weekly dosing, mean PBMC levels were 11 fmol/mL, 4 days per week yielded 32 fmol/mL, and 7 days per week (daily) dosing yielded 42 fmol/mL. In iPrEx, seroconverters had PBMC drug levels on average of 11 fmol/mL, suggesting fewer than two doses per week on average. Non-seroconverters had mean PBMC levels of 16 fmol/mL. A model created from the iPrEx data calculating the protective efficacy which was likely at a given drug concentration in PBMCs demonstrated that the PBMC drug level at which 90% protection would be achieved was estimated to be 16 fmol/mL. Correlating the iPrEx model data with the STRAND data, two doses per week would be estimated to result in 76% (95% CI 56-96%) efficacy; four doses per week, 96% (95% CI, 90- >99%); seven doses per week (daily dosing), 99% (95% CI 96- >99%) (51).

The Partners-PrEP study (a population of heterosexual serodiscordant men and women in Kenya and Uganda) also found that drug levels strongly predicted TDF/FTC and TDF efficacy - detectable drug (using a more sensitive assay than the primary iPrEx data) predicted 86% efficacy for TDF alone, and 90% efficacy for TDF/FTC (contrast 67% and 75%, in the overall population, respectively). The Partners-PrEP study found three distinct patterns of adherence: 1. Seventy percent of participants had sustained TFV drug levels >40 ng/mL; 2. Ten percent of the population had levels that were detectable most of the time (10-40 ng/mL), but dipped occasionally to undetectable levels; and 3) Twenty percent of the population had persistently undetectable drug levels (52). It is probable that prospective, real-time identification of these non-adherent populations (although it remains unclear what percentage this would represent in iPrEx [the MSM population studied to date] – one would suspect the overwhelming majority) and applying intensive adherence interventions would be critical to the success of a PrEP effort.

In this study we will use intracellular TFV-DP from DBS as our primary outcome measure of adherence. Anderson and Castillo-Mancilla have developed technology using LC-MS/MS to measure intra-erythrocytic TFV-DP levels, which provide a measure of average tenofovir exposure (adherence) over the preceding 30-90 days, not unlike a Hemoglobin A1C measurement (53). Such measurements can be made from DBS samples, which are stable over time and easy to handle. The key characteristic that enables TFV-DP to be used as an adherence biomarker is the 17-day half-life of TFV-DP in red blood cells. A similar long-term objective measure of adherence, tightly correlated with virologic suppression has been validated using scalp hair samples (54). However, sampling of scalp hair has proven variably acceptable among diverse populations (unpublished data, ACTG A5257).

11. RATIONALE FOR DEMONSTRATION PROJECT

Daily oral PrEP with TDF/FTC as part of a combination prevention package has been shown to be effective for HIV prevention in randomized controlled trials of MSM and heterosexual men and women at risk of HIV infection (55-57). However, some studies in African women have shown lack of efficacy that is believed in large part due to inadequate PrEP adherence (11, 58). In addition, pharmacokinetic studies in women suggest that near-perfect adherence for TDF/FTC oral dosing may be more critical for protection against vaginal compared with rectal exposures. Taken together, these results imply that women may require substantially greater levels of adherence to oral TDF/FTC to effectively decrease HIV acquisition. Therefore, interventions to optimize adherence are particularly vital to maximizing the protective efficacy of PrEP for women. Although current FDA approval and CDC clinical guidelines for oral TDF/FTC as PrEP include at-risk women as candidates, limited clinical data exists on the use of PrEP in US women. Further research is needed to advance effective implementation, particularly taking into account the known challenges to achieving and maintaining high levels of adherence for women.

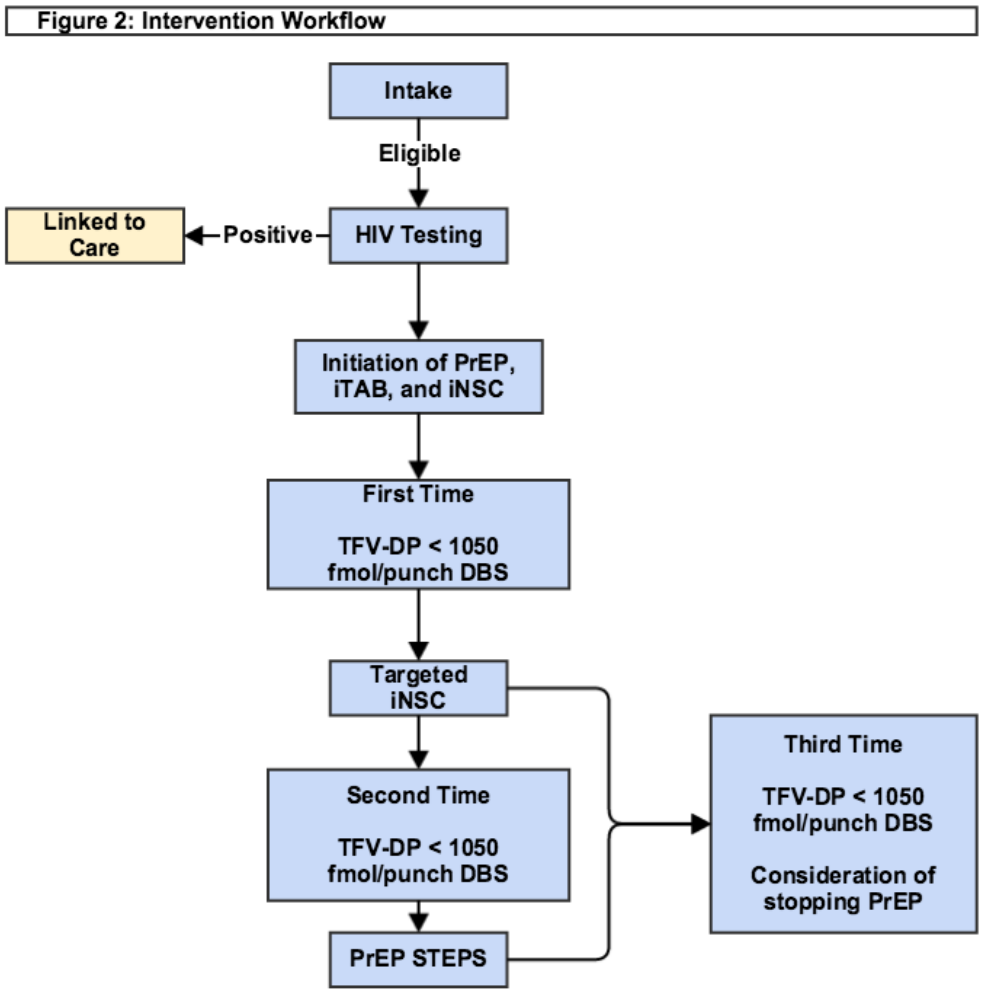
This pilot demonstration project is a single-arm, open-label, longitudinal study of oral TDF/FTC as part of a combined prevention package in heterosexual women age 18 years or older and are HIV-uninfected at project entry and at-risk of HIV acquisition. We will evaluate adherence to and acceptability of once-daily oral TDF/FTC as PrEP among HIV-uninfected women in Southern California who are at increased risk of HIV acquisition. Los Angeles and San Diego represent two of the top three counties in California of number of reported HIV/AIDS cases. In combination, they total half of the number of HIV vases in the state supporting the need for ongoing prevention efforts in all at-risk populations. Working in tandem, the LAC-PATH and CCTG partnership provides a unique opportunity to further collaborative research that has been fostered within the CHRP funding

structure, capitalizing on the strengths of existing individual projects in MSM and transgender women. The LAC-PATH group will enroll 85 women and the CCTG group will enroll 50 women for a total of 135 participants across five clinical sites in Los Angeles and San Diego counties. These clinical sites currently provide services to a racially and ethnically diverse population and will enable outreach to potential female participants disproportionately affected by the HIV/AIDS epidemic, with a focus on African-American and Latina women. Given the centrality of adherence to PrEP efficacy in women, this protocol sets forth a multi-modal, intensive strategy to support PrEP delivery that involves innovatively combining the use of technology, therapeutic drug monitoring and behavioral counseling.

Subsequent to the publication of the iPrEx results, the CDC issued clinical guidance for clinicians for the use of PrEP in MSM (59). These included practical guidelines for testing and follow-up, albeit in the absence of data for any other schedule for follow-up than the one used in the iPrEx study, which entailed monthly HIV-testing, laboratory monitoring, and adherence and risk-reduction counseling, and serve as the basis for screening and monitoring in this project.

Combination prevention services must be designed to be easily accessible, non-judgmental, community-based, culturally, ethnically, and linguistically appropriate to the relevant populations, and accessible regardless of ability to pay or insurance/documentation status. They will also provide vital linkages to ancillary support services, sexual risk reduction counseling, routine HIV testing, preconception planning and primary health care.

In its initial pilot project, five community-based sites will serve as facilities at which participants may present for screening for pre-exposure prophylaxis services, as well as sexually transmitted diseases. At the sites, eligibility criteria will be assessed, HIV, STD and laboratory testing will be performed, an initial 1-month supply of PrEP medication will be provided, and referrals will be initiated. All participants who are provided an initial 1-month supply will be required to return to the site for ongoing treatment, follow-up testing, adherence counseling, risk-reduction programming, and other appropriate referrals. Follow-up will be on a monthly basis for the first month, and then de-escalated to an every-3-month follow-up interval. Follow-up with participants by phone and email will be used as appropriate to maximize program retention.



12. ENROLLMENT OF PARTICIPANTS

Potential participants will be screened for a combination prevention intervention. After the participant reviews and signs the informed consent document, receives HIV testing (including 4th generation test or ELISA and nucleic acid amplification (NAAT) testing) to confirm HIV-uninfected status, and is evaluated using the inclusion and exclusion criteria, she will be considered enrolled in the protocol.

13. INCLUSION CRITERIA

(All must be satisfied)

Individuals who will be at most benefit from PrEP are individuals who are at recurrent and substantial risk for acquiring HIV infection.

<u>At-Risk Criteria (at least one):</u>

1) Condomless sex in the last 3 months with one or more male partners of unknown HIV status known to be at substantial risk of HIV infection (IDU, bisexual, sex for goods, recently incarcerated, from a country/ region with HIV prevalence >1%, interpersonal Partner Violence);

2) STI (rectal or vaginal gonorrhea or syphilis) diagnosis during the last 6 months.
3) Previous post-exposure prophylaxis (PEP) use during the last 12 months.
4) Has at least one HIV-infected sexual partner for ≥4 weeks.
5) Sex for exchange of money, goods or services

Other inclusion criteria:

Female at birth and identifies as female gender
Age 18 years or older
Able to understand and provide consent in English or Spanish
HIV negative by 4th generation test (Ag/Ab test) or combination of EIA and HIV RNA
Creatinine clearance ≥ 60 ml/min (via Cockcroft-Gault formula)

14. EXCLUSION CRITERIA

Pregnancy at enrollment.

Any condition, which in the opinion of the provider, will seriously compromise the participant's ability to comply with the protocol, including adherence to PrEP medication dosing, such as active, untreated or unstable major mental illness (i.e. untreated psychotic disorder).

Use of prohibited medications, in particular, agents known to be nephrotoxic or drugs slow in renal excretion (as detailed in the MOPS)

Previous participation in an HIV vaccine trial. Participants that were documented to have received only placebo are not excluded.

Signs or symptoms suspicious for Primary HIV Infection (PHI). If the participant presents with symptoms consistent with PHI, such participants should be referred to expert HIV clinical care immediately for further evaluation and treatment. For management of suspected PHI, see Section 26.3.

15. STUDY ENROLLMENT PROCEDURES

Enrollment may only be initiated in person. To enroll, a participant must present to one of the clinical site facilities.

15.1. Screening

At a screening visit, Informed Consent will be reviewed. An intake of inclusion and exclusion criteria will be performed by program personnel. HIV-testing (4th generation test, or EIA and HIV RNA) and screening laboratories as noted in the Schedule of Evaluations (SOE) will be performed. If all inclusion and no exclusion criteria are met, a baseline visit will be scheduled within 28 days. A detailed locator form will be completed including primary contact telephone, paper-mail, email, social-network, and emergency contact information. This information will be verified at each subsequent visit for changes and/or updates. At screening, individuals will also be asked to complete a brief computer assisted self-interview (CASI)-based assessment evaluating HIV risk; PrEP awareness, barriers and facilitators; and willingness to take PrEP.

15.2. Baseline Visit

At the baseline visit, a needs assessment, including a CASI-based sexual risk assessment will be conducted. Although the intent is that the CASI is entirely self-administered, research staff will be available to assist participants who have questions about

operation of the CASI instrument or content. Initial STI testing and coordination of necessary referral services will be performed. Fertility intentions also will be assessed. All women who meet criteria for use will be offered daily oral TDF/FTC as part of a combination prevention package. A patient identification number (PID) will be assigned to each patient screened for the study. PIDs will include site code and be formatted to be compatible with the YoungLabs data core. PIDs will not be reassigned even if the participant fails to enter the study. The PID must be included on every CRF and participant specimen during the study. Each site must maintain a master list of PIDs in a central location. The patient registration and inclusion/exclusion CRF must be completed on the online system. Procedures in the study visits are shown in the schedule of evaluations (Section 18).

16. REGIMENS, ADMINISTRATION, AND DOSING

The PrEP regimen to be used will be TDF/FTC, provided as a fixed-dose combination tablet as Truvada®. Dosing of TDF/FTC is one tablet by mouth once daily. For participants with creatinine clearance <60 mL/min or on hemodialysis, TDF/FTC should not be used. No other regimen is available or recommended in the event of intolerance or adverse events attributable to TDF/FTC.

In the event of toxicity, intolerance, or allergy, see Toxicity Management, below.

16.1. High Risk Exposures While on PrEP

In the event of a clinical indication for 3-drug PEP participants will be referred to locally available PEP services and may resume protocol participation upon completion of the PEP medications course with documentation of HIV-uninfected status at or after 4 weeks of PEP provision.

16.2. Missed Dose Instructions

A missed dose should be taken when remembered on a given calendar day. Instructions to participants will be not to take more than one tablet daily regardless of missed doses.

16.3. Duration of Therapy

TDF/FTC should be taken daily for 48 weeks (336 days). Participants may receive study treatment until their last study visit. Further plans for continued availability of TDF/FTC for PrEP after the first 48 weeks will be determined based on the results of the current pilot demonstration study.

16.4. Drug Supply, Distribution, and Accountability

TDF/FTC (emtricitabine 200mg/tenofovir 300mg) will be available in bottles of 30 tablets to be taken as one tablet by mouth daily. Site pharmacies will be responsible for dispensing a 4-week supply of TDF/FTC at the baseline visit, an 8-week supply of TDF/FTC at the 4-week follow-up visit, and a 12-week supply of TDF/FTC at the 12-week, 24-week, and 36-week follow-up visits, in appropriate packaging based on manufacturer's instructions (USP equivalent tight containers). Pharmacies at sites will be responsible for documentation of all medication dispensation, and tracking of all program-related medications.

Participants *must* follow-up at the site of enrollment to receive the remaining treatment course and associated testing and services. Further supplies will *not be re-dispensed* in the event that medication is lost.

16.5. Adherence Assessment and Intervention

At each study visit, adherence will be assessed by self-report metrics via CASI. DBS specimens will be performed for real-time intraerythrocytic TFV-DP drug level assays.

16.5.1. **Real-time intraerythrocytic drug levels**

Blood will be collected for intraerythrocytic TFV-DP drug level assays at each follow-up visit. Prior pharmacokinetic/pharmacodynamics studies have established levels for categorization of dosing for interpretation of DBS levels. Given the high adherence requirement for women to achieve protective levels, a threshold of 1050 fmol/punch corresponding to 6 or more doses per week will be used as the threshold for optimal adherence (28, 60). Levels below this threshold will be considered to represent suboptimal adherence and will trigger intensification of adherence support as outlined below.

16.5.2. **iTAB System**

iTAB is a personalized, two-way, text-messaging intervention developed to improve medication adherence in diverse difficult-to-treat cohorts such as HIV-infected with comorbid psychiatric (i.e. bipolar disorder) and substance use disorders (i.e. methamphetamine dependence) and more recently for PrEP adherence (61-63).The system has several components identified in the broader literature as integral to long-term engagement and effectiveness of text messaging interventions in supporting medication adherence, including: 1) interactive, two-way, communication; 2) individually tailored message content; and 3) delivery of messages to match dosage timing (64, 65). To personalize our text-messaging interactions, we will use a combination of focus-group derived content in certain thematic areas (61), as well as allow participants to create their own messages. Patients develop brief statements called “implementation intentions” integrated into text messages, which ensures personalization capitalizing on the persuasiveness of their own language and phrasing, “When I brush my teeth, I will take my PrEP.”

The iTAB system builds from a variety of behavioral theories used in HIV prevention studies, including the Health Belief Model, Social Cognitive Theory, and the Theory of Planned Behavior (TPB) (66, 67). While these theories differ in some aspects, they also contain a number of shared underlying constructs (68). For example, interventions that focus on the intention to change risk behaviors via changes in self-efficacy and perceived behavioral control (aspects of TPB) are associated with greater condom use (69, 70). Our iTAB intervention primarily targets individual or intra-personal aspects of behavior and is directed primarily by the TPB, which suggests that behavior is driven by: i) attitudes toward the proposed behavior, ii) social norms/perceptions of others, and iii) beliefs that they can control the behavior, which feed into behavioral / implementation intentions (e.g., “I plan to take my PrEP).

iTAB has found to be associated with high adherence and valid as a measure of self-reported adherence in CCTG 595, an open-label, two-arm, controlled, randomized 1:1 clinical trial of iTAB versus standard of care (no iTAB) as a demonstration project evaluating retention and adherence to PrEP in 400 MSM and transgender women over 48 weeks. In a preliminary analysis of intracellular TFV-DP levels in Week 12 DBS among the first 152 participants in the iTAB arm (71), we found that adherence in the iTAB arm was high with a

mean TFV-DP of 1352 fmol/punch, which equates to taking 6 of 7 doses of PrEP a week. Since CCTG 595 is an ongoing study, the comparison of iTAB to a control arm that did not receive iTAB text has not been performed yet. The preliminary data also show a significant correlation between TFV-DP concentrations and proportion of positive ("Yes, I took my meds.") iTab responses (r=0.26, p=0.01) supporting iTAB as a valid measure of adherence. These findings support the use of iTAB as a valid self-reported measure for adherence that can discriminate between adequate and inadequate PrEP adherence.

In this study, all participants will receive text messaging through the iTAB system. At the baseline visit, the study coordinator will introduce the participant to the iTAB texting system and provide training on iTAB framework for texting supportive reminder messages and tracking adherence. If a participant does not have unlimited text messaging, the study will provide participant reimbursement to pay for unlimited text messages. In cases where a participant does not have a phone, an appropriate cell phone with an unlimited texting plan will be provided.

Daily dosing reminders will be sent for the duration of the study. Both reminder timing and message content can be individualized and will be arranged at the baseline visit. The study coordinator will work with the participant to select and refine 10 personal reminders from a list of pre-determined reminders that cover various themes shown to be effective in improving adherence (i.e., social support, loss frame, health gain) as well as 5 categories of factoids (i.e., food, history, science). Participants will receive 2 personal reminders and 5 factoids each week for the duration of the study. These themes will be developed through focus groups and targeted group feedback. Participants can choose to create their own reminders if they prefer, and messages can be modified throughout the course of the study. The coordinator will work with each participant individually to ensure that adherence reminders are programmed to be sent at times consistent with when the patient typically takes her medication. Reminder times can vary for different days of the week to accommodate for changes in schedule (e.g., 8 M-F, and 10 AM on Sat/Sun). Once the preferred dosing time is identified, the text reminder system is automated. Patients will confirm medication taking via text responses to the personalized reminders. If a participant does not respond on three consecutive occasions, a high alert message (chosen by the participant) will be sent. If the participant does not respond to this message, the study coordinator will initiate phone calls to contact the participant to determine reason for no-reply. At any point, if a participant initiates a text that is not one of the expected responses, the study team will review that text and contact the subject if there is a concern. Participants will be informed not to use texting for emergencies. The content/reasons for iTAB requests for assistance will be documented and summarized post study,

16.5.3. Integrated Next Step Counseling, Targeted Integrated Next Step Counseling and PrEP-STEPS

iNSC has two yoked components- a focused discussion of all things the person is doing or thinking of doing to protect their sexual health besides PrEP which then turns to discussing continued desire for PrEP as part of one's protection plan, and, if so, current approaches to ensuring dosing in the present context/demands of participant's life. Thus, regardless of whether or not the participant is receiving PrEP at any clinical visit, one (just the non-PrEP portion) or both parts of iNSC are implemented. During the first PrEP dispensation visit, the focus of the discussion is on preparing participants for adherence through enhancing literacy around PrEP and adherence, formulating a concrete plan for daily dosing and brainstorming potential barriers and discussing what to do if side-effects are experienced. The groundwork for discussing sexual health protection and approach that the study will adopt with an invitation for participants to fully engage in discussions and

openly share PrEP experiences and desires. Subsequent visits follow basic process where experiences are discussed, participants are asked about their sense of what, if anything, would make sexual health protection (non-PrEP strategies) easier or more manageable, ways to meet those needs explored, strategies discussed and a plan identified by the participant, which then transition to checking in with whether or not PrEP is still something they want as part of their plan (or if they want to add it if eligible and not on PrEP), and if so, PrEP dosing experiences are explored, needs identified, strategies discussed and a plan developed. Discourse is documented and will be summarized at the end of the study,

The main difference between iNSC and targeted iNSC focused on exploring whether or not PrEP is something the participant wants to continue with (given low drug level and relatedly low afforded PrEP benefit), and if so a strengths-based exploration (when dosing did occur, what facilitated it) precedes exploration of specific barriers to dosing (what specifically prevented consistent dosing), needs are identified, strategies discussed and an adherence plan created. Because participants all engage in iTAB, plans will also emphasize use of iTAB to ask for help. Participants no longer interested in PrEP will be engaged in discussion around that decision and their plan for how to stay HIV negative using other strategies discussed.

PrEP-STEPS is a four-session weekly intervention with two subsequent monthly booster sessions modeled after an evidence-based ART adherence intervention (LifeSteps) which is a Cognitive Behavioral Therapy (CBT)-based counseling approach to facilitate PrEP adherence. This program will be deployed at in-person sessions and is the highest intensity level intervention.

The 3 interventions will be used as three “stages” or levels of intensity of adherence support. One intervention is deployed for a given participant, titrated based on the history and chronology of real-time measured DBS TFV-DP levels.

All participants will receive iNSC at the baseline/entry visit and at all subsequent visits [see the MOPS for structure of the standard iNSC intervention]). Suboptimal adherence (TFV-DP levels of <1050 fmol/punch (representing fewer than mean 6-7 daily doses per week)) will trigger “targeted iNSC” which will be implemented when drug levels are obtained by the site- typically about 10 days after the clinic visit (72). Participants in this sub-optimal range are contact by the counselor, informed of their results and asked to come in for a specific conversation (targeted iNSC). This first level of more intensive support may be deployed by telephone or in person. There will not be additional compensation for participating in these sessions. Details of the targeted iNSC intervention are provided in the MOPS. If this is a repeat sub-optimal level the counselor schedules the participant for the first of 4 (+2 booster) PrEP-Steps sessions.

Details of the PrEP-STEPS Program with Content Optimized for Women program are provided in the MOPS.

All sites will be trained in the standard iNSC, targeted iNSC, and PrEP-STEPS interventions prior to initiation of participant enrollment. A booster-training will be scheduled once sites are operational. Regular conference calls will be arranged between the protocol adherence teams and site staff, and the protocol adherence consultant will be available for questions and/or troubleshooting as needed during study conduct. Participants will be asked for additional consent to have their adherence support sessions audio-recorded, and a subset of these audio recordings will be reviewed by the adherence consulting team for fidelity to the intervention; such audio recordings will be destroyed after review.

Refusal to participate in adherence interventions may be sufficient reason for participant to be considered for PrEP medication discontinuation, at the discretion of the Protocol Chairs.

17. FERTILITY INTENTIONS ASSESSMENT

CDC/DHHS guidelines on use of PrEP in women include guidance on counseling serodiscordant couples who want to conceive a child (73, 74). Periconception use, or "PrEPception" (75), is a potential area in which PrEP may be beneficial in reducing risk of HIV acquisition. As a result, women will not be excluded based on fertility intentions. Fertility intentions will be assessed as part of the initial intake at baseline, and pregnancy testing will be performed at follow-up visits for monitoring as outline in the schedule of events. As detailed in the MOPS, the study will use a designated Informed Consent for women who become pregnant on-protocol, and a separate complementary schedule of follow-up for pregnant women, who will be followed in clinical collaboration with high-risk obstetric (Maternal Fetal Medicine Service) providers.

18. STUDY ASSESSMENTS

The 10 domains to be covered include:

a. Adherence
b. Substance Use
c. Sexual Behavior/Risk
d. Psychosocial Constructs
e. PrEP Efficacy
f. Willingness to Take PrEP
g. Violence and Trauma
h. Healthcare and Referrals
i. HIV Knowledge and Perception
j. Family Planning

At the screening visit, CASI-based assessments will be administered which will include the domains of Sexual Behavior/Risk, PrEP efficacy, Willingness to take PrEP, Violence and Trauma and HIV knowledge and Perception and Family Planning.

At the baseline visit, additional CASI-based assessments will be administered which include Adherence, Substance Use, Psychosocial Constructs, Violence and Trauma and Healthcare and Referrals.

During follow-up visits (4, 12, 24, and 36 weeks) CASI-based assessments will continue which will include Adherence, Substance Use, Sexual Behavior/Risk, Psychosocial Constructs, Violence and Trauma and Healthcare and Referrals, and Family Planning.

At the End of Study (week 48) visit, CASI-based assessments will include, in addition to above, PrEP efficacy and HIV knowledge and Perception.

Study visits will also include discussions with study staff about substance use, depression and domestic violence. Concern about substance abuse will trigger referral for substance abuse counseling. A screen for depression and/or psychological distress or any request for mental health services will trigger referral for appropriate mental health services. Any report or suspicion of domestic/partner violence will trigger referral for appropriate partner services.

In terms of risk reduction counseling, all participants will be provided a sexual health counseling session at every study visit starting at baseline (see below). All participants will be counseled that condoms should be used for all forms of penetrative non-oral sexual contact.

Full contents of the CASI and assessments will be specified in MOPS.

19. RISK REDUCTION COUNSELING INTERVENTION

As noted above, the iNSC addresses both behavioral and biomedical strategies to promote protection of sexual health. iNSC will be provided at each study, preferably early in the study visit and in conjunction with delivery of an HIV-uninfected rapid test result. The structure of the intervention is provided above in section 16.5.3 and detailed in the MOPS.

20. SCHEDULE OF CLINICAL AND LABORATORY EVALUATIONS

Table 1. Schedule of Evaluations

	Screen	Study Weeks of Follow-up				Interim	
	Within 28 days	Baseline	Wk 4	Week 12 and every 12 weeks	End of Study or premature D/C	Suspected HIV or STI infection	Interim for Missed Visit
Visit Window		± 14 days					
Informed Consent	X						
Demographics	X						
Locator Form	X						
Medical/Medication History	X						
Concomitant medications	X	X	X	X	X	X	X
Limited physical exam	X	X	X	X	X	X	X
Clinical assessment	X	X	X	X	X	X	X
Fertility intent assessment	X	X	X	X	X	X	X
Contraceptive counseling	X	X	X	X	X	X	X
Domestic/partner violence assessment	X	X	X	X	X	X	X
Systems review and iTAB setup		X					
PrEP dispensation		X	X	X			
Adherence/ risk reduction/ Sexual health counseling		X	X	X	X	X	X
Self-reported tablet assessments[1]	X	X	X	X	X	X	X
PrEP adherence assessment			X	X	X	X	X
Laboratory							
HIV EIA/VL or Ag/Ab[2]	X						
Rapid HIV Test		X	X	X	X	X	X
HBsAg and HBsAb	X						
Urine beta HCG	X	X	X	X	X	X	X
Cr and GFR	X		X	X	X	X	X
LFT and CBC		X					
Serum RPR		X		[X]	[X]	X	[X]
3-site STI Screening		X		[X]	[X]	X	[X]
HSV-2 Screening		X			X[5]		
DBS for RBC TFV-DP			X	X	X	X	X
Banked plasma specimen[3]			X	X	X	X	X
HIV RNA, CD4, genotype						X	
Whole blood						X	

Table 1. Schedule of Evaluations

	Screen	Study Weeks of Follow-up				Interim	
	Within 28 days	Baseline	Wk 4	Week 12 and every 12 weeks	End of Study or premature D/C	Suspected HIV or STI infection	Interim for Missed Visit

[1] Domains include: Adherence, Substance Use, Sexual Behavior/Risk, Psychosocial Constructs, PrEP Efficacy, Willingness to Take PrEP, Violence and Trauma, Healthcare and Referrals, HIV Knowledge and Perception, and other instruments.
[2] Positive or indeterminate rapid HIV ELISA testing will be confirmed with a viral load. If baseline occurs > 28 days after screening, HIV EIA/VL must be repeated.
[3] Plasma will be drawn and stored at indicated time points. If seroconversion to HIV occurs, these samples will be run fl or HIV-1 RNA (viral load) and genotyping.
[4] In case of seroconversion, sample to be shipped to UCSF and used for determining viral reservoir during hyperacute HIV infection.
[5] Repeat HSV-2 screening at Week 48 or End of Study only if negative at Baseline.
[X] Weeks 24 and 48 months only

21. CLINICAL ASSESSMENTS

21.1. Complete Physical Exam

A complete physical exam will be done at baseline and documented in the source documents only. A complete physical examination is to include an examination of the skin, head (including eyes and nose), mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam, genital exam (as needed), skin exam, examination of the lower extremities for edema, and a brief neurological assessment. The complete physical exam will also include signs and symptoms, height in centimeters/inches, weight in kilograms/pounds, diagnoses, and vital signs (temperature (°C), pulse, respiration rate, and blood pressure).

21.2. Targeted Physical Exam

Targeted physical exam will be done at all visits subsequent to the baseline visit and documented in the source documents only. A targeted physical examination is to include height in centimeters, vital signs (temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit. Staff should inquire about symptoms, as indicated.

21.3. Review of Systems

A complete review of systems will be done at baseline and reviewed at all subsequent visits. This should be documented in the source documents only. Review of systems is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit.

21.4. Concomitant Medications

Concomitant medications will be assessed at initial intake, reviewed at every study visit, and recorded on the appropriate CRF. Include actual or estimated start and stop dates. All concomitant medications (prescription and non-prescription) including alternative/complementary medications (e.g., herbs, vitamins, etc.) taken within 30 days prior to enrollment and anytime thereafter during study participation will be collected in the study participant's chart and recorded on the appropriate CRF. Concomitant medication lists will be reviewed by program pharmacy staff for potential drug interactions as appropriate.

22. HIV LABORATORY TESTING

Rapid or conventional ELISA testing will be used. All positive rapid EIA results will be confirmed with both a conventional blood EIA test and a viral load (negative rapid tests are not further confirmed, except as per individual study site policy, and positive conventional blood EIA tests are only confirmed by viral load testing). As indicated in the protocol, 4th generation test (Ag/Ab), or NAAT testing in addition to EIA, will be used at screening and entry to exclude occult primary/acute HIV infection.

23. ADDITIONAL LABORATORY TESTING

23.1. STI Screening

All participants will be screened at baseline for rectal (rectal swab), cervical (self-collected vaginal or urine) or pharyngeal (throat swab) gonorrhea and chlamydia using a verified NAAT test and for T. pallidum (syphilis) by serum treponemal/RPR testing. Asymptomatic STI screening will be conducted at 6-month intervals while on-study. Serologic testing for HSV-2 will be completed at Baseline, and again at Week 48 or End of Study if previously negative at Baseline. Positive results will trigger referral to appropriate private or SD/LA County STD program sites for treatment. Intervening signs or symptoms consistent with STIs should trigger referral to appropriate private or SD/LA county STD program services.

23.2. Hepatitis Testing

Treatment with TDF/FTC or its components or congeners in participants with chronic active hepatitis B (Hepatitis B surface antigen (HBsAg) positive) has been associated with flares of hepatitis upon discontinuation of treatment. Such participants will be referred to appropriate medical care for monthly liver function testing subsequent to treatment completion and/or consideration of ongoing Hepatitis B treatment. HBsAg negative participants will be referred for appropriate vaccination.

23.3. Serum Creatinine

Serum creatinine will be checked at screening to determine appropriate TDF/FTC dosing, and then again at Weeks 4, 12, 24, 36 and 48.

23.4. Liver Function Tests

AST (SGOT), ALT (SGPT), Total Bilirubin (TBIL), and alkaline phosphatase will be checked at baseline for all participants, and in a symptom-directed fashion as needed.

23.5. Complete Blood Count

Hemoglobin, hematocrit, white blood cell count and platelet count will be checked at baseline for all participants, and in a symptom-directed fashion as needed.

23.6. Pregnancy testing

Urine beta HCG will be performed to assess for pregnancy at screening, baseline, weeks 4, 12, 24, 36, and 48, and in a symptom-directed fashion.

24. PLASMA COLLECTION

Plasma will be collected and stored at Weeks 4,12, 24, 36 and 48. If seroconversion to HIV occurs, plasma samples will be run for HIV-1 RNA (viral load) and genotyping. These specimens may also be used for safety labs, or for tests whose needs become apparent during the course of this study. Additional whole blood will be collected at the visit seroconversion was detect and 24 weeks post seroconversion to determine viral reservoir size and immune responses.

25. DRIED BLOOD SPOT COLLECTION

Blood will be collected for and spotted onto Whitman Protein Saver Card for DBS analyses. All specimens will be stored at -80C. DBS samples available from weeks 4, 12, 24 and 36 will be sent to the University of Colorado lab once weekly for real-time analysis.

26. POST-TRIAL ACCESS TO PREP

During study conduct, the team will initiate discussions about continuation mechanisms at either the 24- or 36-week visit to prepare for the 48-week transition off study, allowing ample time for discussion of intentions to continue PrEP post-study, assessment of insurance status, choice of healthcare location and provider, and prescription benefits optimization.

The team will conduct a phone call follow-up of all participants 3 months post-study completion to determine post-trial access to and use of PrEP. Survey content will be based on an instrument developed by the PrEP Demo Project based in San Francisco (77). Information will be collected including current medical access and care, HIV testing, interest in remaining on PrEP, access to and use of PrEP, gaps in PrEP coverage, monthly cost, barriers to getting PrEP, and changes in HIV prevention strategies. Surveys may be conducted in person, via internet, or over the phone.

27. CLINICAL MANAGEMENT ISSUES

27.1. Toxicity Management

27.1.1. General

In the event of intolerance, including but not limited to rash, nausea, vomiting, clinical jaundice, or abdominal pain, an “unscheduled visit” should be made in which a directed clinical assessment and laboratory evaluations including creatinine, liver function tests, and complete blood count are performed. Alternative regimens may not be substituted.

Only toxicities related to study medication provided through this study (TDF/FTC) will be considered in the toxicity management section. The grading system is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, available at the DAIDS RCC Web Site: http://rsc.tech-res.com. Grade 1 creatinine elevations will have an expanded definition: In addition to those defined as having Grade 1 creatinine elevations by DAIDS AE Table, the Grade 1 definition will include A) those whose creatinine increased to 1.5x the baseline value (baseline value will be defined as the average of screening and enrollment for the participant) and B) estimated creatinine clearance of <50 ml/min (calculated using Cockcroft- Gault).

Adverse events will be reported for Grade 2 and above clinical and laboratory abnormalities. In addition, all bone fractures and all creatinine elevations will be reported. Serious adverse events (SAEs) will be defined in accordance with the ICH, as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

All Grade 1 or 2 adverse events may be managed according to the discretion of the provider, except as noted below.

Grade 3 adverse events, if asymptomatic and not thought to be attributable to study medication, may be managed conservatively with continuation of TDF/FTC treatment.

All Grade 3 symptomatic and all Grade 4 (regardless of symptomatology) events should prompt cessation of TDF/FTC therapy, with weekly monitoring until resolution to ≤ Grade 2. If a clear alternative explanation for the Grade 4 adverse event exists, TDF/FTC may only be continued with the approval of the Protocol PI. Once the AE has regressed to ≤ Grade 2, the participant may be rechallenged with TDF/FTC at the discretion of the provider. Any recurrence of the AE should prompt permanent medication discontinuation.

27.1.2. **Impaired Creatinine Clearance**

Any participant with a calculated creatinine clearance (CrCl) <60 mL/min should have the value confirmed within 14 days. For those participants with a confirmed (i.e. two consecutive) reduction in CrCl to <60 mL/min, TDF/FTC should be discontinued. If the site investigator determines that another condition caused the decrease in CrCl, then TDF/FTC may be restarted if approved by the protocol PI. Participants should be followed as medically indicated (at least weekly) until the serum creatinine returns to Grade ≤ 2 or baseline.

27.1.3. **Nausea (with or without vomiting) and/or Diarrhea**

Although common, nausea following initiation of therapy with study medications usually subsides or resolves during the first few weeks of treatment.

With the onset of Grade ≥1 nausea, advise participants to take study medications with food. Participants may also be treated as needed with anti-emetics given orally or by suppository.

In participants with persistent nausea, consideration should be given for evaluation of pancreatitis, hepatitis, hyperlactatemia/lactic acidosis, or hypercalcemia with evaluation for each if clinically indicated.

For Grade 1 or 2 diarrhea, therapy should be continued with symptomatic treatment with antimotility agents. If Grade ≥3 diarrhea occurs and is unresponsive to antimotility agents, and an alternative etiology (e.g., infectious diarrhea) is not established, all study medications should be interrupted until resolution of diarrhea to Grade ≤2 or return to baseline. If Grade ≥3 diarrhea recurs upon the resumption of the study medications, all study medications should be discontinued permanently.

27.1.4. **Pregnancy**

Any woman who should become pregnant while on study will have the option of remaining on TDF/FTC and follow a separate complementary schedule of follow-up in clinical collaboration with high-risk obstetric (MFM) providers and. Details of this follow-up can be found in the MOPS. All such individuals will be reported to Gilead per FDA-mandated post-marketing requirements and registered by Gilead in the antiretroviral pregnancy registry to be followed until pregnancy outcome can be determined.

27.2. Social Harms

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 core investigators to be serious or unexpected will be reported to the IRB(s) 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.

27.3. Management of Suspected Acute Seroconversion (Primary HIV Infection - PHI)

Should an enrolled participant present with signs and symptoms consistent with PHI, this should trigger immediate HIV EIA and Viral Load (VL) or NAT testing; any positive result should prompt immediate resistance testing and referral to HIV specialty care. Participants who seroconvert within the protocol will undergo evaluation as in the schedule of events (see Section 19) and be provided assistance as needed to establish care. If the subject is currently taking TDF/FTC a third antiretroviral would be recommended as soon as possible. If there is a delay in obtaining care then TDF/FTC should be discontinued until an adequate antiretroviral regimen can be started. If the seroconverting individual is not taking TDF/FTC they will be advised not to take TDF/FTC until a complete regimen can be acquired.

27.4. Seroconversion Schedule of Events

Table 2: Schedule of events for seroconversion	Detection of Seroconversion	4-week visit[1]
Visit Windows	**±7 days**	**±7 days**
CD4 panel	**X**	**X**
Viral load	**X[2]**	**X**
Stored Plasma	**X[3]**	**X[3]**
Whole Blood	**X**	
Linkage Services Provision/Assessment	**X**	**X**
Behavioral Risk and Drug and Alcohol Assessments[4]	**X**	**X**

[1]If visit unobtainable, then phone call will be made to participant for follow-up on linkage to care.
[2]Viral load will be run on blood plasma stored from seroconversion visit and all prior study visits, done sequentially from date of seroconversion visit until undetectable viral load in blood plasma.
[3]If not already being done as part SOE assessments.
[4]Assessments will be based on those in the main SOE, and details can be found in the MOPS.

28. CRITERIA FOR DISCONTINUATION

28.1. Temporary Medication Interruption

Attempts should be made to avoid temporary interruption.

Symptoms should be managed aggressively and proactively in an attempt to avoid discontinuation, provided there is no laboratory evidence of toxicity and any symptoms are Grade 1 or 2. In the event of symptomatic Grade 3 or any Grade 4 toxicity, TDF/FTC should be discontinued immediately, the only exception being a toxicity indisputably not attributable to TDF/FTC administration, with the permission of the protocol PI.

In the event of inadvertent discontinuation due to missed appointments, loss of medication, or other unforeseen circumstances, treatment should be resumed as rapidly as possible. Treatment should ONLY be reinstituted in the absence of signs/symptoms of PHI (Table 1 above).

If the amount of time since last dosing of TDF/FTC exceeds 14 days when the participant wishes to reinitiate PrEP, a negative rapid HIV EIA and HIV VL should be documented PRIOR to PrEP reinitiation. If a serum creatinine has not been performed for study purposes within the past 30 days, serum creatinine too should be repeated (and Creatinine Clearance calculated and documented) prior to medication re-initiation.

28.2. Permanent Medication Discontinuation

Permanent medication discontinuation prior to 48 weeks of treatment should be limited to participants who withdraw consent, have laboratory evidence of acute or chronic HIV infection, are so advised by HIV-treatment experts, or have severe toxicity as noted above.

Such participants should continue to be followed per the protocol SOE (Cohort or seroconversion, as appropriate), even though they are no longer taking study medication.

Additionally, participants who have persistently low TFV-DP levels (<1050 fmol/punch), are referred for targeted iNSC (first instance) and PrEP-STEPS (if followed by a suboptimal (<1050 fmol/punch) TFV-DP level at subsequent visit(s)). Refusal/failure to participate in PrEP-STEP programming by attending ≥1 visit within 30 days of request by study staff may be considered for medication discontinuation in discussion with the Protocol Chairs.

28.3. Program Discontinuation

Participants should be discontinued from the program under the following circumstances:

Request by the participant to withdraw from the program
Participant, in the judgment of program physicians, is unable to comply with provisions of the protocol in such a way as to be more likely to result in harm to the participant

*Discontinued participants should return any unused study medication to the site for destruction, per program SOPs.

29. DATA COLLECTION, STORAGE, AND MONITORING

29.1. Protocol

This protocol will be available in hardcopy and PDF formats with the current version and date.

29.2. Secure Database

The study will utilize existing CCTG informatics infrastructure provided by the UCSD Center for AIDS Research Bioinformatics and Information Technologies (BIT) Core. The BIT Core will provide study staff at CCTG and LAC-PATH sites access to OCCAMS, open source biomedical research data platform, to manage overall study flow, including the collection of data between and during participant visits including self-assessment questionnaires, iTAB text messages, specimen, laboratories, STI results, medication use, reported side effects, etc. All data will be stored in the secure and redundant BIT Core informatics infrastructure that uses a robust security modeling consisting of a multi-level hardware/software firewalled network, secure hardware and software encryption, data auditing and access tracking procedures and completely redundant services hosted from two physically separated server facilities. This infrastructure will also provide regulated access and reporting of study data to the biostatistics research team and relevant providers on a need-to-know basis. It is the responsibility of the CCTG Data Unit to assure the quality of computerized data for this study.

Case report forms (CRFs) will be provided for each participant. Instructions concerning the recording of study data on CRFs will be provided by the CCTG Data Unit. Participants must not be identified by name on any CRFs. Participants will be identified by the PID provided by the CCTG Data Unit upon registration and the linkage to the PID will be kept in paper copy only in a locked cabinet in a secure office at the study sites available only to the site investigators. Participant self-reported surveys that are performed electronically will be automatically stored in the electronic database secured by the CFAR BIT group for the CCTG.

29.3. Participant Confidentiality

In an effort to maintain confidentiality but allow tracking of public health resources, all program entrants will have a unique patient identifier code based on their study site. A date of birth will be requested from participants to allow two methods of identification required for study sample identification. All obligatory laboratory specimens, evaluation forms, and other records will be identified by coded PID and participant date of birth (DOB). All records will be kept in a locked cabinet**.** All computer entry and networking programs will be performed with only PIDs. Clinical information will not be released without written permission from the participant, except as necessary for monitoring by protocol QA/QC, IRB, sponsor(s) or FDA. All participants will sign and receive a copy of HIPAA regulations prior to study commencement. The original will be placed in the study chart, and a copy will be given to the participant.

29.4. Data Collection and Monitoring

Close cooperation between the Protocol Chairs, study site Investigator(s), 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.

During the course of the study, enrollment rates, with a racial/ethnic breakdown, will be provided to California HIV Research Program (CHRP) on a monthly basis. Study conduct (in terms of assessment completion, successful sample collection, and data completeness) will be reviewed on a quarterly basis by the protocol team. Follow-up rates for each visit as well as the number of screened participants versus the number of participants enrolled, including a tabular list of reasons for screen-failure, will be reviewed on a monthly basis by the Protocol Chairs.

The study site Investigators are responsible for continuous close monitoring of all AEs that occur among study participants after informed consent is signed. Accrual and summary of all Grade ≥2 signs and symptoms and all Grade ≥3 laboratory abnormalities will be prepared by the study team and reviewed by the Protocol Chairs monthly. The study team will also prepare a quarterly report of all AEs (regardless of grade), including the number and percentage of adverse events, to be reviewed by the Protocol Chairs. Serious adverse events, Grades 3 and 4 will be tabulated separately and reviewed by the Protocol Chairs.

29.5. Clinical Site Monitoring and Record Availability

A clinical study monitor will perform an on-site review of individual participant records, including: consent forms, CRFs, and laboratory specimen records. Monitoring will ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitor will also inspect regulatory files to ensure requirements are being met. Pharmacy drug storage and dispensing records will be reviewed to ensure appropriate pharmaceutical product storage and management.

Monitoring visits will occur when 10 participants are enrolled at each site, and then at 3-6 month intervals during the remainder of study conduct.

30. STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will be drafted and finalized prior to database lock. The SAP will contain a more detailed and/or comprehensive presentation of statistical methods and is the final authority for all statistical analyses. The following section briefly describes the planned statistical analyses. In case the language in this section differs from the language in the SAP, the SAP takes precedence.

30.1. Sample Size Rationale

The LAC-PATH group will enroll 85 women and the CCTG group will enroll 50 women for a total of 135 women who will start PrEP. The target goal of the multimodal triaged adherence intervention for women will be to achieve 90% of women with a DBS level > 1050 fmol/punch at any given time. The proportion and 95% confidence interval will be calculated. If we assume 90% of women with a DBS level > 1050 fmol/punch at any given time and 100 women enrolled in the study, then the 95% binomial distribution confidence interval around the estimate will be 6% (i.e., 90% ± 6%).

30.2. Statistical Analysis Plan

The overarching goal of this proposal is to study the implementation of PrEP combined with comprehensive HIV prevention services for women living in Southern California. The research aims are to: i) measure PrEP adherence by intracellular TFV-DP and FTC-TP, self-report via text messages and CASI-based adherence assessments; ii) explore the characteristics of women seeking PrEP and assess PrEP awareness and knowledge including barriers and facilitators to PrEP; and iii) determine acceptability and feasibility of a multi-modal adherence-based HIV-prevention program.

Primary Objective: To measure adherence to oral TDF/FTC at weeks 4, 12, 24, 36, and 48 using both biological (dried blood spots) and self-reported measures through daily text messaging (iTAB).

Hypothesis I
Drug levels will be high among those who persist with PrEP over time, as measured by tenofovir-diphosphate (TFV-DP) level > 1050 fmol/punch at weeks 4, 12, 24, 36 and 48.

Hypothesis II
Intracellular TFV-DP concentrations levels will correlate with self-reported adherence by daily texting through iTAB,

For the primary analysis, we will measure adherence using a drug level cutoff consistent with 6 or more doses per week, as measured by TFV-DP level > 1050 fmol/punch at weeks 4, 12, 24, 36 and 48. This will be in the as-treated group who are on-PrEP (censoring those on permanent or temporary discontinuation). A descriptive analysis of the proportion of women achieving adequate adherence by week of study will be conducted. Baseline versus 48 weeks proportion of adherence will be compared via Fisher's exact test.

In order to examine drug adherence surrounding the implementation of intensified interventions specific to women receiving targeted iNSC and those receiving PrEP-STEPS we will compare the change in levels pre- and post-intervention.

Additional sensitivity analyses will be performed using alternative cutoffs of adherence. Intracellular FTC-TP levels will be compared to TFV-DP for discrepancy of recent dosing that would be reflective of the short half-life of FTC (past day) versus the past week of dosing that is informed by the long half-life of TDF.

Subgroup analysis will compare adherence and other outcomes between risk categories of women (e.g. serodiscordant partnerships with and without conception intentions, partner of elevated HIV risk, sex worker, recent STI, injection drug use, PEP users).

Adherence will be measured by self-report using daily text messaging through iTAB. We will validate iTAB reported adherence in women using the TFV-DP levels for correlation with the proportion of positive responses in the 34 days prior to the drug level (i.e. two half lives of TDF) in week 12, 24, 36 or 48 using the Spearman correlation coefficient.

The average days of adherence per week during this time will be calculated as number of days reporting doses taken in past 35 days divided by 35 multiplied by 7 and rounded to the nearest whole number. For each number of days per week of adherence (i.e. 0, 1, 2,3, 4,

5,6 and 7) the TFV-DP will be reported from mean (95% confidence interval) and median (IQR).

Secondary Objectives:
To describe the characteristics of women seeking PrEP, a descriptive analysis will be performed for the following secondary endpoints:

- PrEP awareness and acceptability prior to study enrollment
- Perceived barriers and facilitators to PrEP use
- HIV knowledge pre- and post-study

Implementation secondary outcomes will include:

- Acceptability and feasibility of an HIV prevention program with a multimodal, intensive adherence package for PrEP delivery defined on a Likert scale
- Retention in an HIV prevention program that includes PrEP defined by making study visit
- Safety and tolerability of daily TDF/FTC given for PrEP including discontinuation for any adverse event, serious adverse events and adverse events (grade 2 or higher)
- HIV incidence in the observed cohort of PrEP users
- Frequency of clinically significant resistance among seroconverters

Additional sensitivity regression modeling will be performed for the factors associated with loss to follow up and discontinuation of TDF/FTC. Factors will included change in perceived and actual risk of HIV acquisition, fear of disclosure, demographics, socioeconomic status, social characteristics (e.g., medical mistrust, non-English language, cultural factors), co-occurring health problems or issues (e.g., untreated mental illness, ongoing substance use, violence, trauma), and low health/HIV and system literacy.

Risk compensation during study will be assessed by changes in the incidence of STIs (chlamydia, gonorrhea, HSV-2 and syphilis) during study and self reported sexual risk behavior over time by number of sexual partners (by HIV status) and number condomless sex acts.

All descriptive results will be reported as point estimates (mean or odds ratios as appropriate) and interval estimates (95% confidence intervals, interquartile ranges). All tests of significance for the secondary outcomes will be 2-sided and no adjustments will be made for multiple comparisons. A p-value of 0.05 will be considered statistically significant. Statistical analysis will be conducted using the statistical software R 3.1.1 (www.r-project.org).

31. INFORMED CONSENT

The study will be overseen by the Institutional Review Boards of UCLA, UCSD, and participating clinical sites, and the study and all related study documents will be approved by all IRBs.

Although PrEP is recommended by the CDC and TDF/FTC has received FDA approval for a preventive/prophylactic indication, it is important that participants accessing resources understand the limitations of knowledge regarding PrEP, including effectiveness estimates, with precise efficacy dependent on, and likely proportional to daily adherence rates.

All participants will be required to sign a one-time consent for documenting understanding of study procedures, risks to self and intimate contacts, course of treatment including a behavioral risk-reduction component and adherence counseling activities, all as described in the informed consent and protocol.

32. EXPERTS IN HIV CLINICAL CARE

Numerous references are made to conditions for invoking opinion or consultation with experts in HIV clinical care, including:

- Incidental finding of HIV-positivity on rapid screening on initial intake
- Signs or symptoms consistent with PHI (Section 22.3, Table 1)
- Toxicity or intolerance to TDF/FTC requiring discontinuation
- Unclear attribution of toxicity to TDF/FTC and/or appropriate work-up

The HIV Clinical Care Expert will be considered the site PI, or if unavailable the protocol chair or his designee.

33. HUMAN PARTICIPANTS

33.1. Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for the oversight of the study. A signed consent form will be obtained from the participant. The consent form will describe the purpose of the study, the procedures to be followed and the risks and benefits of participation. A copy of the consent form will be given to the participant.

33.2. Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be stripped of any patient identifiers (name, birthdate, medical record number) and only identified by the coded PID in order to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only and analyzed centrally without any possibility of linking participant identity with participant data. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by IRB and governmental agencies.

34. PUBLICATIONS AND FINDINGS

Publication of the results of this trial will be governed by LAC-PATH/CCTG policies. Any presentation, abstract or manuscript will be made available for review by pharmaceutical supporters prior to submission.

35. 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 Centers for Disease Control and Prevention and the National Institutes of Health.

All infectious specimens will be transported using packaging mandated in the Federal Code of Regulations, CDC 42 CFR Part 72. Please also refer to individual carrier guidelines, e.g., FedEx, Airborne, for specific instructions.

36. FUNDING

California HIV Research Program
Drug Supply from:
Gilead Sciences
Foster City, California

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