UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

1. PROJECT TITLE

CCTG 603: Randomized Controlled Trial of iTAB plus Motivational Interviewing for PrEP Adherence in Transgender Individuals (The iM-PrEPT Study)

CCTG 603 Sub-study I: Pharmacology of PrEP in Transgender Persons

CCTG 603 Sub-study II: Diversity and Prevalence of *Neisseria gonorrhoeae*-reduced Antimicrobial Susceptibility

CCTG 603 Sub-study IV: Impact of Biologic Factors on Cervicovaginal Fluid Tenofovir Levels Sub-study

2. PRINCIPAL INVESTIGATOR

Sheldon Morris, M.D., M.P.H

3. FACILITIES

University of California, San Diego (UCSD)
Antiviral Research Center (AVRC) & HIV Neurobehavioral Research Programs (HNRP)
220 Dickinson Street
San Diego, CA 92103

Family Health Centers of San Diego (FHCSD) The Night Clinic (TNC)
4094 4th Avenue
San Diego, CA 92102

Los Angeles Lesbian, Gay, Bisexual, and Transgender (LALGBT) Center
1625 N. Schrader Blvd
Los Angeles, CA 90028

4. ESTIMATED DURATION OF THE STUDY

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. This will be a 4-year study.

Participants taking part in the extension will continue to receive PrEP at Week 48 and every 12 weeks thereafter up to 24 weeks until approval of CCTG 605 (HRPP# 191001) or FDA approval of emtricitabine/tenofovir alafenamide (F/TAF) for use as PrEP.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The purpose of this study is to evaluate and compare adherence to Pre-Exposure Prophylaxis (PrEP) in transgender-identifying or gender non-conforming individuals who receive daily, text message-based medication adherence reminders (iTAB) with vs. without brief Motivational Interviewing. This study will enroll 300 individuals (up to 100 at UCSD) to take PrEP for 48 weeks.

6. SPECIFIC AIMS

Study Primary Objective: To compare adherence to fixed dose TDF/FTC, as measured by intracellular levels of TFV-DP $\geq$ 1246 fmol/punch, between subjects randomized to receive iTAB with versus without brief Motivational Interviewing, when used for adherence support to pre-exposure prophylaxis among transgender / gender non-conforming (TG / GNC) individuals at elevated risk for HIV acquisition.

Hypothesis*: Subjects randomized to the iTAB intervention plus MI-b will have higher adherence, as measured by intracellular levels of TFV-DP $\geq$ 1246 fmol/punch, at both week 12 and their last visit after week 12 up until 48 weeks (eg week 24, 36 or 48), compared to those with iTAB alone in those that complete those visits and have a measureable level. To be considered adherent they must have attended the week 12 visit; if week 12 was attended but was the last visit, then only the week 12 visit will be required for the endpoint.*

Study Secondary Objectives

1. To compare adherence to fixed dose TDF/FTC, as measured by intracellular levels of TFV-DP $\geq$ 719 fmol/punch, between subjects randomized to receive iTAB with versus without brief Motivational Interviewing, when used for adherence support to pre-exposure prophylaxis among transgender / gender non-conforming individuals at elevated risk for HIV acquisition.

Hypothesis: *Subjects randomized to the iTAB intervention plus MI-b will have higher adherence as measured by intracellular levels of TFV-DP ≥ 719 fmol/punch, at both week 12 and their last visit after week 12 up until 48 weeks (eg week 24, 36 or 48), compared to those with iTAB alone in those that complete those visits and have a measureable level. To be considered adherent they must have attended week 12 visit; if week 12 was attended but was the last visit then only the week 12 visit will be required for the endpoint.*

2. To compare adherence to TDF/FTC in the iTAB+MI-b versus iTAB alone arms using
   a) a continuous outcome of DBS TFV-DP drug levels at weeks 12 and 48 in participants who attended both visits
   b) TFV-DP intracellular levels of ≥ 1246 fmol/punch and ≥ 719 fmol/punch at both week 12 and week 48
   c) a stratified analysis of drug level outcomes within male-assigned at birth and female-assigned at birth groups
   d) a composite endpoint with the outcome defined as "all attended visits (regardless if they missed week 12)" with levels of ≥ 1246 fmol/punch and ≥ 719 fmol/punch.
3. To compare self-reported adherence to TDF/FTC in the iTAB+MI-B versus iTAB arms over 48 weeks using
   a) adherence defined as "the proportion of text-reported doses over all possible doses over 48 weeks"; missing text messages or early discontinuation of the study will be considered as no doses taken
   b) a continuous measure of the percentage of days adherent by self reported measures (iTAB, cumulative 3 day recall, and the visual analog scale) in an "as treated" analysis for those that are retained on study
   c) stratified analysis of 3a and 3b outcomes within male-assigned at birth and female-assigned at birth groups
4. To compare study retention between arms, defined as the proportion of participants that complete all study visits regardless of whether they were on drug or not
5. To determine factors associated with poor adherence (< 719 fmol/punch over 48 weeks) and discontinuation of TDF/FTC

   Factors considered to be associated with poor adherence to TDF/FTC will include demographics, socioeconomic status, perception of HIV risk, ongoing substance use, intimate partner violence, low health/HIV and health systems literacy, and stigma
6. To determine the rate of linkage and continuation of TDF/FTC at 12 weeks after study completion between arms
7. To determine the rate of HIV seroconversion in TDF/FTC-using transgender / gender non-confirming individuals and compare the proportion of seroconversions over 48 weeks between arms
8. To measure the acquisition of other sexually transmitted infections (STIs) and compare rates of acquisition of new STIs at any site between arms
9. To evaluate changes in risk behavior after PrEP initiation (risk compensation) by comparing the numbers of HIV positive partners, partners of unknown HIV status, unprotected insertive and receptive anal or vaginal acts between Baseline and subsequent visits
10. To evaluate the safety and tolerability of daily TDF/FTC as PrEP as measured by discontinuations due to
    a) any adverse events
    b) serious adverse events and
    c) grade 2 or higher adverse events

Sub-study I Primary Objective: To determine whether csHT interacts with PrEP in male-assigned at birth (MAAB) persons that would affect efficacy of PrEP, measured by intracellular TDF concentrations in DBS.

Hypothesis: *Among transgender MAAB persons on csHT who report perfect adherence by iTAB in the past 34 days (ie, two intracellular half-lives) the mean intracellular tenofovir-diphosphate (TFV-DP) concentrations, as measured in DBS, will be equivalent to the levels of perfect adherence previously defined in MSM.*

Sub-study I Secondary Objectives

1. To determine whether csHT interacts with PrEP in MAAB persons that would affect hormone effectiveness, measured by estrogen concentrations assessed at Weeks 0 and 12 of study follow-up.

   Hypothesis*: Among transgender MAAB persons on csHT, estrogen concentrations will not change significantly between baseline (Week 0) and Week 12 in individuals taking PrEP and receiving stable estrogen therapy (controlling for route and formulation).*

2. To determine TFV-DP in MAAB of all adherence levels compared to not taking csHT, adjusting for confounding factors.
3. To determine TFV-DP in MAAB taking versus not taking antiandrogen medications (i.e., spironolactone, finasteride)
4. To measure the change in testosterone concentrations between baseline and Week 12 in female-assigned at birth (FAAB) taking PrEP and receiving stable testosterone therapy.
5. To determine emtricitabine-triphosphate (FTC-TP) concentrations (a measure of recent adherence) in TG / GNC persons of all adherence levels taking versus not taking hormones.
6. To determine changes in desired effects of csHT in TG / GNC persons taking PrEP as measured by the Body Image Scale (BIS).

Sub-study IV Objectives:

1. To determine the impact of genital STIs on CVF TFV levels.
2. To determine the impact of cytokine mediators of CV inflammation on CVF TFV levels.
3. To determine the impact of CV microbiome on CVF TFV levels.

7. BACKGROUND AND SIGNIFICANCE

Study Background

PrEP studies in subpopulations of persons at risk for HIV are needed as is evident from the variable efficacy found in studies of PrEP by gender (35-37). Adherence may especially differ among transgender persons due to: i) individual psycho-social factors (e.g., sense of stigma, finances); ii) beliefs about medication (e.g., real or perceived side effects, concerns about PrEP interactions with hormones and uncertain efficacy of PrEP); iii) barriers to adherence (e.g., irregular routines, life crises, drug and alcohol use, mental illness); and iv) informational deficits (e.g., lack of competent medical providers, mistrust of the medical system, negative feedback from social networks) (38).

Pharmacokinetic studies have demonstrated that an intracellular TFV-DP level of 719 fmol/punch is the lower end of the inter-quartile range for healthy participants taking four doses of tenofovir a week (39). This level or greater was associated with a 90% reduction in HIV acquisition in MSM when applied to iPrEx data (40). Perfect adherence (7/7 dose a week is associated with a lower quartile value of 1246 fmol/punch and is associated with a 99% reduction in HIV incidence. IN CCTG 595 we studied the efficacy of daily text messaging to improve adherence in PrEP in MSM and transgender women. Our results suggested that daily text messages sustained perfect adherence better than standard of care over 48 weeks. There was a 13.5% improvement in adherence at week 48 with daily text messages. Still only 50% of participants achieved perfect adherence at week 48 who were on PrEP and when considering if they maintained perfect adherence at week 12 and their last visit this was only 33.5%. Therefore, there is room for improvement in maintaining perfect adherence with text messaging.

Successful adherence interventions leverage information technology and patient-specific factors. This includes

understanding the patient's unique attributes, and tailoring adherence interventions to match them (41). Given the diversity of issues that characterize PrEP for the transgender community, person-based tailoring will be critical for a successful adherence intervention. Prior work has shown that poorly adherent HIV-infected individuals increase adherence from 42% to over 70% when receiving texting reminders (42). In this proposal, our iTAB system will be adapted to deliver adherence-promoting text messages tailored to the diverse transgender community, capitalizing on mobile technology already incorporated into people's lives (43). Our iTAB data from studies of ART and PrEP adherence support the benefits of text messaging for adherence improvement (Section V D3). No studies, however, have assessed gains in adherence from further real-time counseling for self-reported non-adherence reported by daily texting.

Motivational Interviewing (MI)

MI is a widely accepted and used technique for promoting behavioral change such as medication adherence in HIV-infected individuals and persons at-risk for HIV (44-46). MI consists of one or more counseling sessions that promote goal-oriented behavior change by soliciting and strengthening a person's own motivation and rationale for altering their actions (47). The process includes providing feedback and reflections on current behavior, expressing empathy and support for an individual's self-efficacy to modify their actions, and eliciting strategies for addressing problem behaviors (48). In combination with other approaches such as the Theory of Planned Behavior (TPB), MI has been used to improve HIV testing rates and HIV medication adherence (49-52). Although MI can include multiple sessions, pilot studies have reported successful behavioral change with only one MI interview (53, 54). Recent studies have used MI sessions delivered over the phone to improve medication adherence and reduce substance use (55-60). Phone MI has also been demonstrated to successfully reduce alcohol-related risk behaviors and decrease high-risk sexual behavior (55, 59, 61, 62). Our objective in the current application is to improve and maximize PrEP adherence by using an innovative approach that combines a transgender-focused iTAB with brief MI (MI-B) administered as an effective rapid response tool for episodes of suboptimal adherence.

Sub-study on Interaction of Hormones and TDF/FTC

Ace measured by TFV-DP predicts efficacy in MSM, but similar studies have not yet validated these cut-off points among transgender persons. It is possible that even higher levels of adherence may be needed for other populations. Such studies are necessary because in iPrEx Ole, transgender subjects had 30% lower levels of TFV-DP for reasons that were not determined but could be from poorer adherence, different pharmacokinetics or both (20). Therefore, a cut off for TFV-DP drug levels alone may not accurately address the question of PrEP adherence in the transgender population until similar dose-related TFV-DP levels are confirmed. Additional data is needed on use of hormones by transgender and the levels of TFV-DP and FTC.

Study Rationale

TDF/FTC has been approved by the FDA as an agent for PrEP. As noted previously, little research assesses the uptake and adherence of PrEP in transgender persons. CCTG 603, will implement PrEP at five sites in Southern California (UCSD, Harbor-UCLA, USC, LALGBT and FHCSD) to explore the PrEP use in transgender persons and methods to maintain adherence to drug. CCTG 603 will perform a randomized study of the iTAB+MI-B versus iTAB alone for TDF/FTC adherence for PrEP. This study will test if adherence can be enhanced (and by what degree) over and above personalized daily text reminders by real-time motivational interviewing techniques provided by telephone.

Sub-study II Background

One of the challenges to the use of PrEP in transgender individuals is the concern over the potential interaction of hormone therapy (exogenous estrogen and antiandrogens) with TDF/FTC and subsequent hormone and drug levels. Currently no evidence or clinical studies examine whether drug interactions occur between TDF/FTC and cross-sex hormone therapy (csHT) for gender transition. Concerns about these drug interactions could operate in a bi-directional manner and in our focus group and community consultations there was a particular concern among transgender women taking feminizing hormones. Recent studies examining willingness to take PrEP in transgender women suggest that decreased efficacy of hormone therapy may be a major barrier (90, 91). In the iPrEx open-label extension study, PrEP concentrations in DBS were lower among transgender women with an

adjusted OR of 0.72 (CI 0.55-0.94) (20). While this finding may be accounted for by lower adherence, there are some theoretical reasons for hormones to interact with PrEP.

The majority of studies examining the effect of estrogen and ARV concentrations have been conducted in HIV-infected women on ART and hormonal contraception for birth control. Overall, detailed pharmacokinetic (PK) studies support that ARVs can alter systemic concentrations of hormonal contraception and vice versa (92). The only published drug-drug interaction study of TDF and combined oral contraceptive pills was done with 20 women using ethinyl estradiol and triphasic norgestimate which was lower but this was not statistically significant (93). In the Partners PrEP study of PrEP efficacy in HIV-serodiscordant couples, PrEP had no adverse impact on contraceptive effectiveness for pregnancy prevention in those taking contraceptive pills, injectable DMPA and hormonal implants (94). However, potential interactions between the high doses of estrogen used in csHT and ARVs have never been studied.

Evidence from iPrEx indicate that for MSM with TFV-DP intracellular concentrations commensurate with 4 or more doses a week is 96% protective against HIV infection (>719 fmol/punch or the lower quartile value for the range of DBS concentrations in the PK studies. To validate these protective concentrations in transgender women, TFV-DP concentrations should approximate the same concentrations as seen in a MSM cohort. PK modeling of HIV-uninfected adults has shown that perfect adherers (i.e. daily dosing for 7 days) have TFV-DP concentrations of 1560 (IQR 1246-2029) fmol/punch (39). Therefore, if transgender women with perfect adherence have DBS concentrations that are not inferior to this level the efficacy estimates that were described in the iPrEx should hold true for transgender women who are sufficiently adherent.

Preliminary Data

The CCTG has experience in measuring PrEP adherence through self-report and intracellular TFV-DP in DBS and found that iTAB text message reporting was validated by the measured TFV-DP levels. Overall, almost three-quarters of subjects had high adherence with TFV-DP levels commensurate with 6-7 doses per week. Only 11 subjects had levels consistent with taking 3 doses or less per week.

Using 152 MSM iTAB subjects categorized into perfect (37), high (n=85) and moderate (n=40). Those found 37 (24%) reporting perfect adherence in the past 34 days (representing two TFV-DP half lives) with mean TFV-DP concentrations of 1457 fmol/punch +/-694 fmol/punch. This corresponds almost exactly with predicted DBS concentrations for drug exposure of 7 doses per week in controlled pharmacokinetic studies where perfect adherence was associated with a level of 1460 fmol/punch (39). These data can therefore be used as the comparison to data derived in transgender women on csHT with perfect adherence by iTAB.

Sub-study IV Background and Significance

Daily oral pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) has been shown to be safe and effective to reduce risk of HIV infection in clinical trials of heterosexual men and men who have sex with men (MSM).(1-3) In contrast, clinical trials using oral PrEP with cisgender women have had mixed results with some studies demonstrating efficacy (2, 3) and others finding no efficacy.(4, 5) Further, there have been no PrEP clinical trials that have included transgender men who have sex with men. While low PrEP efficacy has been associated with poor PrEP adherence, there is a scientific and clinical knowledge gap as to whether daily oral PrEP is a viable HIV prevention tool for cisgender women and transgender men. Results from these clinical trials(4, 5) and pharmacokinetic studies(6, 7) suggest that individuals who have vaginal sex may require nearly perfect adherence of oral PrEP to be protective against HIV acquisition. These divergent results may suggest that factors beyond adherence are responsible for the gender differences in the effectiveness of PrEP.(8) While strides are being made in our understanding of the pharmacokinetics (PK) of PrEP in individuals who engage in vaginal sex, the impact of biologic factors (e.g., inflammation from sexually transmitted infections (STIs), alterations in the vaginal microbiome) still remain poorly described. Inflammation may impact intracellular TFV levels and has been proposed as a risk factor for HIV acquisition(9). As part of this study, we will leverage our open label PrEP in transgender individuals study to describe the impact of STIs, inflammation and the vaginal microbiome on genital tenofovir (TFV) levels. TFV levels in cervicovaginal fluid (CVF) were shown in a large microbicide trial to correlate with protection against HIV infection(10) and thus provide a surrogate for local drug efficacy.(11) Our overarching goal is to provide a better understanding of the biological factors that modulate drug

levels in genital secretions within two testable aims and one exploratory aim.

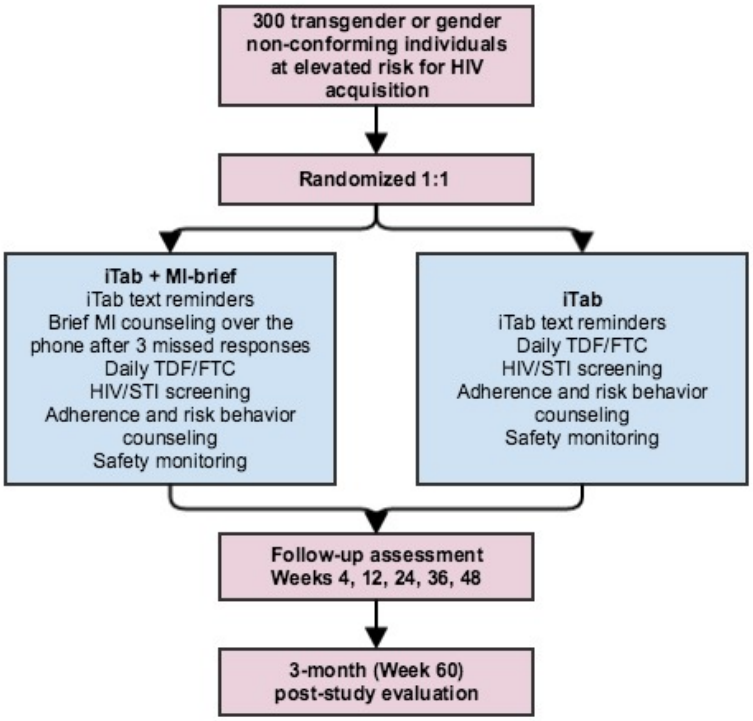
8. PROGRESS REPORT

Not Applicable.

9. RESEARCH DESIGN AND METHODS

STUDY DESIGN

CCTG 603 is an open-label, two-arm, randomized (1:1) clinical demonstration project to determine if brief Motivational Interviewing (MI-b) added to a text message-based adherence intervention (iTAB) improves adherence to PrEP among transgender / gender non-conforming persons.



Site Initiation

Before implementing this protocol, sites must be registered with and approved by the CCTG Core to initiate, and must have the protocol and informed consent form approved by the local institutional review board (IRB).

Screening Visit (approximately 1-2 hours)

Screening occurs prior to the participant completing any assessment or taking any study medications, treatments, or interventions. The Screening Visit and study enrollment may only be initiated in-person; to enroll, a participant must present to one of the clinical site facilities.

Registration Prior to the Screening Visit

Each participant will be assigned a patient identification number (PID) and a study identification number (SID). Both PIDs and SIDs must be included on every source document and laboratory sample for that participant. Each site is responsible for maintaining a master list of PIDs and SIDs in a central location.

- PIDs will be generated automatically by the study's Electronic Data Capture (EDC) system upon participant registration. Each unique person will be assigned only one PID that will be used across all studies; if a person has been assigned a PID from a previous study, a new PID will not be generated.
- SIDs will be assigned using the site's SID Assignment List and will be used for that study only. SIDs will not be reassigned should a participant screen fail, withdraws from the study, or ultimately does not provide written consent.

During the Screening Visit

All participants interested in screening for CCTG 603 will sign an Informed Consent Form (ICF) that had been approved by a site's local IRB.

Screening procedures will include:

- Assessment of inclusion and exclusion criteria
  - Confirmation of HIV status and screening for acute HIV symptoms using NAT or equivalent test (antigen/antibody).
- Laboratory evaluations
  - HBsAg
  - Calculated creatinine clearance (Cockcroft-Gault)
  - Urinalysis
  - Urine for β-HCG performed for participants capable of becoming pregnant.
    - Laboratories obtained as part of regular clinical care may be used to satisfy screening evaluations. Results must be less than 30 days old by the time of Baseline and must be filed as a source document in the participant's chart.
- Assessment of HIV acquisition risk
- Detailed medical history including medical insurance status, and current medical and psychiatric conditions.
- Detailed medication history including cross-sex hormone therapy (csHT), if applicable, and other concomitant medications.
- Collection of height and weight
- Computer-assisted self-interview (CASI) assessments

If a subject qualifies and signs consent the window to complete the baseline assessment and start PrEP will be 30 days.

Baseline Visit (Week 0; approximately 2 hours)

Baseline may occur as soon as all eligibility criteria are confirmed. Baseline procedures include:

- Randomization, stratified by site, sex assigned at birth, and prior history of PrEP use, to either the iTAB + MI-b intervention or iTAB alone arm.
  - Study coordinators will configure a participant's iTAB account based on each individual's preferences.
- A targeted physical examination, including weight
- Laboratory evaluations
  - Rapid HIV screening (required; cannot be substituted by an earlier rapid test)
  - 3-site (throat, rectal, urine) STI NAT screening for gonorrhea and chlamydia
  - Syphilis RPR
  - Plasma hormone levels (sub-study only)
  - CBC and liver enzymes
  - Urine β-HCG will for participants capable of being pregnant
- Sample collection for banking
  - Dried blood spot (DBS) for intracellular drug levels will be collected for participants already on PrEP at the

time of Baseline

- Whole blood, plasma, and serum
- Urine
- Rectal swabs

- CASI assessments
- Introduction to motivational interviewing for participants randomized into the iTAB + MI-b arm.
- Medication dispensation. Participants will be provided enough medication to last until the next scheduled visit through the investigational pharmacy.
- Risk reduction and medication adherence counseling. Health educators will provide HIV transmission risk reduction counseling and detailed information about the use of PrEP, including the risks, potential adverse events and the critical importance of drug adherence.
  - Standard of care HIV risk education counseling will be provided to all participants consistent with routine practice.
  - An informational pamphlet on TDF/FTC will be provided that will summarize the label package insert information for patients (in English or Spanish) with changes made to tailor the information for someone that is not HIV infected.
  - Participants will receive episodic adherence counseling within the confines of routine clinic visit.
- Participants will be directed to take one pill once a day routinely at a convenient time.
  - If there are missed doses, participants will be told to take the dose if on the same calendar day or, if the missed dose was at night, participants will be told to take the dose if still within 12 hours the following morning. Participants will be warned not to take any additional pills to catch up.
  - Bottles with any remaining tablets will be returned to the pharmacy at the time of medication renewal and the number of untaken doses will be recorded.

Same Day PrEP Visit (Combined Screening and Baseline; approximately 3 hours)
Participants may elect to combine their Screening and Baseline visits for same day PrEP initiation. Participants will be provided a temporary partial waiver of inclusion/exclusion criteria and will be dispensed study medication following completion of the visit. Continuation will be dependent on meeting all inclusion/exclusion criteria upon receipt of safety laboratory results.

Same day PrEP initiation procedures are as follows:

Registration Prior to the Same Day PrEP Visit
Each participant will be assigned a patient identification number (PID) and a study identification number (SID). Both PIDs and SIDs must be included on every source document and laboratory sample for that participant. Each site is responsible for maintaining a master list of PIDs and SIDs in a central location.

- PIDs will be generated automatically by the study's Electronic Data Capture (EDC) system upon participant registration. Each unique person will be assigned only one PID that will be used across all studies; if a person has been assigned a PID from a previous study, a new PID will not be generated.
- SIDs will be assigned using the site's SID Assignment List and will be used for that study only. SIDs will not be reassigned should a participant screen fail, withdraws from the study, or ultimately does not provide written consent.

During the Same Day PrEP Visit
All participants interested in screening for CCTG 603 will sign an Informed Consent Form (ICF) that had been approved by a site's local IRB. Visit procedures include:

- Assessment of inclusion and exclusion criteria
  - Inclusion Criteria 4.1.4 and 4.1.5 may be temporarily waived pending laboratory results
  - Exclusion Criteria 4.2.2 and 4.2.6 may be temporarily waived pending laboratory results
  - Rapid HIV screening (required; cannot be substituted by an earlier rapid test). A negative rapid result will be sufficient for same day PrEP initiation
- Laboratory evaluations
  - Confirmation of HIV status and screening for acute HIV symptoms using NAT or equivalent test (antigen/antibody).
  - HBsAg
  - Calculated creatinine clearance (Cockcroft-Gault)
  - Urinalysis
  - Urine for β-HCG performed for participants capable of becoming pregnant.
  - 3-site (throat, rectal, urine) STI NAT screening for gonorrhea and chlamydia
  - Syphilis RPR
  - Plasma hormone levels (sub-study only)
  - CBC and liver enzymes
  - Laboratories obtained as part of regular clinical care may be used to satisfy screening evaluations. Results must be less than 30 days old by the time of Baseline and must be filed as a source document in the participant's chart.
- Sample collection for banking
  - Dried blood spot (DBS) for intracellular drug levels will be collected for participants already on PrEP at the time of visit
  - Whole blood, plasma, and serum
  - Urine
  - Rectal swabs
- A targeted physical examination, including weight and height
- Assessment of HIV acquisition risk
- Detailed medical history including medical insurance status, and current medical and psychiatric conditions.
- Detailed medication history including cross-sex hormone therapy (csHT), if applicable, and other concomitant medications.
- CASI assessments. Participants may complete both sets of CASIs in-clinic or complete the Screening set in-clinic and the Baseline set at home.
- Randomization, stratified by site, sex at birth, and history of PrEP, to either the iTAB + MI-b intervention or iTAB alone arm.
  - Study coordinators will configure a participant's iTAB account based on each individual's preferences.
- Introduction to motivational interviewing for participants randomized into the iTAB + MI-b arm.
- Medication dispensation. Participants will be provided enough medication to last until the next scheduled visit through the investigational pharmacy.

- Risk reduction and medication adherence counseling. Health educators will provide HIV transmission risk reduction counseling and detailed information about the use of PrEP, including the risks, potential adverse events and the critical importance of drug adherence.
    - Standard of care HIV risk education counseling will be provided to all participants consistent with routine practice.
    - An informational pamphlet on TDF/FTC will be provided that will summarize the label package insert information for patients (in English or Spanish) with changes made to tailor the information for someone that is not HIV infected.
    - Participants will receive episodic adherence counseling within the confines of routine clinic visit.
- Participants will be directed to take one pill once a day routinely at a convenient time.
    - If there are missed doses, participants will be told to take the dose if on the same calendar day or, if the missed dose was at night, participants will be told to take the dose if still within 12 hours the following morning. Participants will be warned not to take any additional pills to catch up.
    - Bottles with any remaining tablets will be returned to the pharmacy at the time of medication renewal and the number of untaken doses will be recorded.

Phone Call Follow-up Assessment (Week 2; approximately 10 minutes)
A phone call follow-up will be scheduled for Week 2 after Baseline. During the follow-up, study coordinators will assess the participant's tolerability of the study medication, document any reported adverse event, and troubleshoot iTAB technical issues, if any.

For participants electing same day PrEP initiation, the Week 2 visit may be conducted as soon as all pending safety laboratory results have been received. Study coordinators will inform participants that they either may continue or must discontinue the study medication.

PrEP Continuation
For participants that completely meet inclusion/exclusion criteria, the following additional procedures will be conducted:

- Randomization, stratified by site, sex at birth, and history of PrEP, to either the iTAB + MI-b intervention or iTAB alone arm.
    - Study coordinators will configure a participant's iTAB account based on each individual's preferences.
- Introduction to motivational interviewing for participants randomized into the iTAB + MI-b arm.

PrEP Cessation
For participants with disqualifying safety laboratory results, the study coordinator will instruct the participant to immediately cease study medication and an interim screen failure visit will be scheduled at the clinic. The following procedures will be conducted at the screen failure visit:

- Participant will return any remaining study medications.
- Participants with disqualifying creatinine or creatinine clearance values may request to re-screen into the study but may not repeat a same-day PrEP initiation visit.
- If HBsAg positive, the participant will be referred to care.
- If HIV positive, study coordinators will follow the procedures outlined in 6.11.4 and 6.11.5 in the Protocol.
- Participant will be terminated from the study as a Screen Failure.

In-Clinic Study Visits (Weeks 12, 24, 36, and 48; approximately 1 hour)
Participants will be asked to return to the clinic at week 12 and every 12 weeks up to week 48. Study visit procedures include:

- Assessment of adverse events since last contact
- Targeted medical history and physical examination, including collecting weight
- Review of concomitant medications, including detailed csHT use
- Laboratory evaluations
  - Rapid HIV screening
  - 3-site (throat, rectal, urine) STI NAAT screening for gonorrhea and chlamydia (weeks 24 and 48 only)
  - Syphilis RPR (weeks 24 and 48 only)
  - Calculated creatinine clearance (Cockcroft-Gault)
  - Plasma hormone levels for participants on csHT (week 12 only, sub-study only)
  - Urine β-HCG for participants capable of being pregnant.
- Sample collection for banking
  - Dried blood spot (DBS) for participants on PrEP
  - Whole blood, plasma, and serum
  - Urine
  - Rectal swabs (week 48 only)
- CASI assessments
- Medication dispensation. Participants will be provided enough medication to last until the next scheduled visit through the investigational pharmacy. Participants will not be provided PrEP at week 48.
- Risk reduction and medication adherence counseling. Counseling will not be performed at week 48.
- End of Study assessment (week 48 only). This survey will assess participant's experiences over the course of the study, including changes in their medical insurance status, access to other healthcare services, changes in perceptions of PrEP and of their own health, and their opinions about the intervention.
  - Participants that express the desire to continue PrEP after completing the study will be provided information regarding access and payment strategies. Considerations for transitioning should begin at week 36.

Post-Week 48 Extension (approximately 1 hour)

Participants at UCSD who reach Week 48 (+4 week window) still on PrEP and who intend to enroll in CCTG 605 (HRPP# 191001) may choose to participate in the post-Week 48 Extension. The purpose of the extension is to provide participants with the opportunity to avoid gaps in PrEP coverage while awaiting FDA approval of emtricitabine/tenofovir alafenamide (F/TAF) for PrEP indication.

Participants taking part in the extension will continue to receive F/TDF for PrEP with medication adherence support at Week 48 and every 12 weeks thereafter up to 24 weeks. The study extension, along with any associated F/TDF dispensation, will continue until F/TAF has been approved for PrEP indication and CCTG 605 (191001) has been approved by the UCSD IRB.

Study visit procedures include:

- Assessment of adverse events since last contact
- Targeted medical history and physical examination, including collecting weight
- Review of concomitant medications, including detailed HRT use

- Laboratory evaluations
  - Rapid HIV screening. If the participant has stopped PrEP for more than 14 days or has had a high-risk event, HIV Ag/Ab will be collected at this visit
  - Calculated creatinine clearance (Cockcroft-Gault)
  - Other labs, as clinically indicated or at the discretion of the study investigator.
- Medication dispensation and continuation of iTAB adherence support. Participants will be provided TDF/FTC at 12-week intervals through the investigational pharmacy.
- Risk reduction and medication adherence counseling
- If HIV positive, study coordinators will follow the procedures outlined in 6.10.4 and 6.10.5 below.

Post-study Phone Call Follow-up (Weeks 60; approximately 30 minutes)

Study coordinators will contact participants at week 60 for a phone call follow-up evaluation. The purpose of this follow-up is to examine HIV risk behavior, current HIV and STI status, PrEP uptake and adherence, and the impact of transition after cessation of study-provided PrEP.

The week 60 visit should be performed for all participants, even if the participant withdraws from the study unless the participant expressly requested not to be contacted.

Follow-up procedures will assess a participant's:

- HIV and STI status since EOS
- Ability to access and maintain their PrEP regimen since EOS
- Ability to access health insurance coverage since EOS
- If participant has not accessed PrEP and/or does not have health insurance, the participant will be asked for their reasons and possible barriers to uptake
- Adherence (if on PrEP)
- HIV risk behavior
- Perceptions of PrEP efficacy

Schedule of Evaluations for Subjects On-study, Off-medications

At any point of the study, participants may elect to stop study medication but remain on study. Participants not on study medication will follow the same schedule as defined in the schedule of evaluations until the end of study, with the following exceptions:

- Medication will not be dispensed
- Adherence counseling and monitoring of medications will not be performed
- DBS will not be collected
- iTAB account for participant will be switched to "inactive"

Schedule of Evaluations		Study Weeks of Follow-up							Interim[7]	
	Screen	Wk 0	Same-day PrEP	2	12, 24, 36	48 / EOS	48 EXT ◊	60	Visit	Phone
Window		30 days		+/- 1 week	+/- 4 weeks				+/- 4 weeks	
Informed Consent	X		X							
Inclusion / Exclusion	X		X							
Randomization		X	X							
iTAB setup		X	X							

Medical/medication history and targeted physical exam	X	X	X		X	X	X		X	
HIV risk reduction counseling		X	X		X		X			
Adherence counseling[1]		X	X		X		X			
TFV/FTC dispensed[1]		X	X		X		X		(X)	
Telephone follow-up				X				X		X
Adverse events assessment[1]				X	X	X			(X)	(X)
Computer assisted self-interview (CASI) surveys	X	X	X		X	X				
End of Study survey						X				
Post-study survey								X		
Laboratory										
HIV EIA / NAT or Ag/Ab test	X		X		(X)[2]		(X)[2]		(X)[2]	
HBsAg	X		X							
Creatinine and GFR (calculated CrCl)[1]	X		X		X	X	X			
Urinalysis	X		X							
Urine β-HCG[3]	X	X	X		X	X			(X)	
CBC, liver enzymes		X	X							
Rapid HIV		X	X		X	X	X		(X)	
STI screen†: GC, CT, syphilis		X	X		X[5]	X			(X)	
GC Treatment†									(X)	
Plasma hormone levels[4]		X	X		(X)					
Dried Blood Spot (DBS)[1]		(X)[6]	(X)[6]		X	X			(X)	
Banked whole blood, serum, plasma		X	X		X	X				
Banked urine		X	X		X	X				
Banked rectal swabs (x2)		X	X			X				
HIV confirmatory test if HIV+	(X)		X		(X)	(X)	(X)	(X)	(X)	
CD4, HIV RNA, and HIV genotype if HIV+ after baseline			X		(X)	(X)	(X)	(X)	(X)	

[1]Only for participants currently taking PrEP. Participants requiring PrEP dispensation during an Interim visit will receive enough PrEP to last until the next regular study visit.
[2] Participants with medication interruption greater than 14 days will require confirmation of HIV seronegative status prior to re-initiation of PrEP. Re-initiation must be achieved prior to the end of the week 36 visit.
[3] Only for participants capable of becoming pregnant
[4] Only for participants currently taking csHT. Baseline and Week 12 only.
[5] STI screen only at week 24
[6] Week 0 DBS collected only if participant is already taking PrEP at Baseline
[7] Interim visit for: HIV testing if off PrEP for over 1 week and had high risk event, consider NAT or Ab/Ag; STI testing only if has symptoms (urethral discharge, genital sore); if seroconverted outside study: adverse event assessment
† UCSD-only sub-study evaluation. Additional specimens will be collected from anatomic site of positive GC at time of treatment.
◊ UCSD-only study extension

Adherence and Behavioral Assessments

We will measure adherence using the self-report daily text messages. These texts will include a personalized lead-in reminder message (e.g., ”Those who are closest to you care about your health”) and participants will be asked “Did you take your dose today? Reply: Y) Yes N) No P) Postpone”. If ‘Postpone’ is selected, participants will receive a follow-up message 1 hour later asking them if they took their medication (Yes or No). Participants will also have the option of determining the word used to describe the study drug (e.g., ‘med’, ‘dose’, or other personal choice). Nonresponse or a ‘No’ response will be counted as not taking their dose. At each follow-up

visit, the ACTG four-day questionnaire will be administered using the web-based data capture system. The instrument tracks the number of doses skipped over the past four days and reasons why medications may have been skipped. In addition, we will ask their ability to adhere by Likert scale and use the Visual Analog Scale (VAS), which appears as an ordinal scale representing the percent of medication taken relative to that which has been prescribed over the past 4 weeks. Subjects are presented with a line anchored at 0% and 100% and are asked to mark a line on the scale indicating their own PrEP adherence [26]. Finally, we will administer other self-report questions that have been shown to get people off of the ceiling as it relates to self-reported adherence.

In the standard study visit, the coordinator will perform HIV testing and blood work, review test results, provide TDF/FTC prescriptions, discuss medication use, adherence, risk reduction and troubleshoot any barriers. The standard behavioral survey will include assessment of TDF/FTC adherence, HIV transmission risk behaviors, substance use, depression scores and other risk behavior details (e.g., sexual partnerships, sexual acts, condom use).

Regimens, Administration, and Dosing

Emtricitabine/tenofovir disoproxil fumarate fixed-dose combination containing 200 mg of emtricitabine and 300 mg tenofovir disoproxil fumarate will be administered orally as one tablet once daily with or without food.

Enough study product should be dispensed to last until the subject's next in-person scheduled visit.

Subjects will be randomized 1:1 to one of the two treatment arms:

ARM A: FTC/TDF 200/300 mg once daily + iTAB

ARM B: FTC/TDF 200/300 mg once daily + iTAB + MI-B

Participants will participate in this study until 48 weeks. Subjects will receive study treatment for the duration of the study unless they meet criteria for discontinuation.

Personal Health Information Data Collection

As part of this study, we will also collect, via the Case Report Forms (CRFs), the subjects' demographics (e.g., age, gender, race) and personal health information which includes health information in their medical records and information that can identify them. Because this information may be useful with the design of future studies and also allows us to contact subjects for future studies, we would like to take this information and put it into the CCTG 603 database. Subjects will have the option of allowing us to add this information to the database or not. If they opt out and do not want us to store this information in the CCTG 603 database they can still participate in the study without any jeopardy to their medical care or study participation. The demographics and personal health information may include their name, address, phone number or medical record number. Medical history and laboratory results (e.g., CD4+ cell count, viral load, HIV resistance genotype test result should they seroconvert) may also be included.

For security measures, the database is password protected, fully encrypted and only accessible by the Data Manager. Data management for this study will be provided through the Open Source Clinical Content Management System (OCCAMS) developed by the CCTG Data Core. OCCAMS provides integrated, flexible, and secure tools for complex clinical study data management using only a web browser. The Data Core ensures data security though a robust security model 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. Therefore the input and extraction of this data is only done by personnel with appropriate access to the system. Study personnel will use OCCAMS from a web browser to manage all data storage, quality control, and retrieval. Each staff member will be provided a login and password and will be assigned to the appropriate role-based groups using the UCSD campus active directory. Membership in these role-based groups will provide users with the necessary web views to complete their assigned tasks on a need to know basis. Information from the database will only be shared with the research team. The research team includes the researchers and people hired by the University or an outside company who contracts with the University to sponsor the research activities being done at the AVRC.

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; attention to any changes of substance to planned analysis procedures relative to those indicated in the protocol will be submitted as an amendment. The SAP 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.

Primary Endpoints

The primary endpoint will be a composite adherence outcome determined by dried blood spot intracellular tenofovir diphosphate (TFV-DP) levels. A subject will be considered adherent if the TFV-DP levels are above 1246 fmol/punch (consistent with 7 doses in past week) at both week 12 and the last study visit over the 48 weeks. All randomized subjects that were dispensed PrEP at baseline will be included in the modified intent-to-treat analysis. Participants not achieving week 12 will be considered non-adherent.

Secondary Adherence Endpoints

- A key secondary endpoint will be a composite outcome determined by TFV-DP levels at both week 12 and the last study visit associated with adequate adherence (>719 fmol/punch).

Self-reported adherence to PrEP through 48 weeks is defined as the proportion of text-reported doses over all possible doses in 48 weeks. Missing responses due to either missed text messages or early discontinuation of the study will be considered as no doses taken. Sensitivity analysis will also be done on the 'as-treated' population (i.e. treat missing as missing).

Additional self-reported adherence measure will be >90% adherence (i.e. on the ACTG 4-day recall at weeks 12, 24, 36, and 48); >90% dosing by VAS at each study visit.

- Poor adherence is defined as < 4 doses a week or discontinuation of study drugs. Subgroup analysis will explore the endpoint for discontinuation for reasons other than lack of risk or confirmed adverse event.
- Safety and tolerability outcomes are defined as incidence rates of: i) discontinuation of TDF/ FTC for any toxicity; ii) grade 2 or higher adverse event (symptoms or laboratory toxicity); iii) serious adverse events; iv) death

Randomization and Stratification

Subjects will be randomized (1:1) to one of two arms: the **iTAB** or the **iTAB+MI-B** enhanced adherence arm. Randomization will be stratified by clinic site, sex assigned at birth (male vs female), and prior history of PrEP use. Participants assigned "intersex" at birth will be included in the female group. A total of 300 subjects (150 per arm) will be randomized and followed in the study for 48 weeks after enrollment of the last subject.

Once eligibility and consent are confirmed, randomization will occur using the web-based CCTG data management system.

Study Power and Sample Size Justification

The study is powered to compare the primary adherence rate between the two study arms using a two-sample, two-sided proportion test. Expected drug-level adherence based on a previous study of MSM using iTAB for PrEP for this composite endpoint (>=1246) was 33%. Assuming the adherence rate of the transgender iTAB alone group will be the same the study has 77% power to detect a difference of 16% between the iTAB+MI group and the iTAB alone group, with 150 subjects per group.

Monitoring

The study team will review all adverse events during PrEP therapy as cumulative reports in both arms combined, on monthly team calls. Adverse events will be graded using the ACTG toxicity grading scale and recorded using standard CCTG AE electronic data capture. An independent Data Safety and Monitoring Board (DSMB) will not be used for this study because the drugs are licensed for this indication and relatively non-toxic.

Statistical Analysis Plan
In general, analyses of efficacy will incorporate the modified intent-to-treat (mITT) principle, namely, all randomized participants dispensed study medication will be included in the analysis. For all secondary analyses of efficacy, no adjustments for multiple comparisons will be made and a p-value of 0.05 will be considered statistically significant. Analyses of safety will be focused on "as treated" populations.

Demographic and baseline measurement variables will be summarized via standard descriptive statistics. There will be no interim analyses for futility or efficacy conducted.

Analysis of Primary Outcome
Descriptive analysis will be performed on the primary adherence outcome via a frequency table and Fisher's exact test. Logistic regression modeling will be conducted to assess the group differences while adjusting for potential covariates.

Analysis of additional Secondary outcomes
Descriptive analysis will be performed for all the secondary outcomes. For comparisons between the two study arms, Fisher's exact test will be used for categorical outcomes; t-test or Wilcoxon rank sum test will be used for continuous outcomes. Multivariable logistic regression model will be used to study factors associated with poor adherence. Factors will include demographics, substance use, untreated mental illness, socieconomic status, low health/HIV and system literacy, fear of disclosure and non-English language. To evaluate changes in risk behavior after initiation of PrEP, descriptive summary will be provided for the number of HIV positive/unknown status partners and any unprotected anal intercourse with an HIV positive/unknown status partner by visit (at w12, 24, 36 and 48). Wilcoxon signed rank test will be used for comparison at each follow-up visit to the baseline visit. GEE model will be used to assess the change in risk behavior over time.

Safety analysis
Safety data will be reported for all the randomized subjects while they were taking or immediately (30 days) after taking study drug (as treated analysis). Tables will summarize the number of serious adverse events, adverse events (grade 2 or higher), PrEP discontinuation due to adverse events, by study arms and overall. Fisher's exact test will be used to compare the rates between the two groups. The time to TDF/FTC discontinuation due to adverse events will be compared between groups using the log-rank test and plotted using Kaplan-Meier curves.

SUB-STUDY I DESIGN
This pharmacologic sub-study will use the main study cohort to determine the interaction of cross-sex hormone therapy (csHT) on PrEP efficacy as measured by TFV-DP and FTC-TP DBS intracellular levels, and of PrEP on csHT effectiveness as measured by quantitative hormone levels in plasma.

SUB-STUDY I PROCEDURES
Subjects will be consented for participation in the sub-study at the main study's Screening Visit.

As part of the main study, plasma and DBS samples will be collected at Baseline and every 12 weeks. A Baseline DBS sample will be collected only if the subject is already on PrEP at the time of Baseline. Detailed concomitant hormone use, including route and frequency, will be collected at every clinic visit. Daily iTab responses will be used as a self-reported adherence measure.

At Weeks 0, 12, and 48, applicable subjects will complete the Body Image Scale (mBIS) questionnaire, and answer questions about general hormone therapy satisfaction.

SUB-STUDY STATISTICAL CONSIDERATIONS
Sample Size and Power
The primary aim of this analysis is to determine if PrEP interacts with hormone therapy in either direction that would impact either i) efficacy of PrEP to reduce HIV acquisition or ii) hormones to achieve desirable gender traits. Of our 300 person cohort, we estimate that 280 individuals will be MAAB Of those 280 MAAB, we predict that 70% will be taking feminizing hormones (n=196) and 30% will be on no hormonal therapy (n=84), based on previous population estimates (97). Based on adherence results in individuals randomized to iTAB (98), we estimate that 25% of participants will have perfect adherence to PrEP.

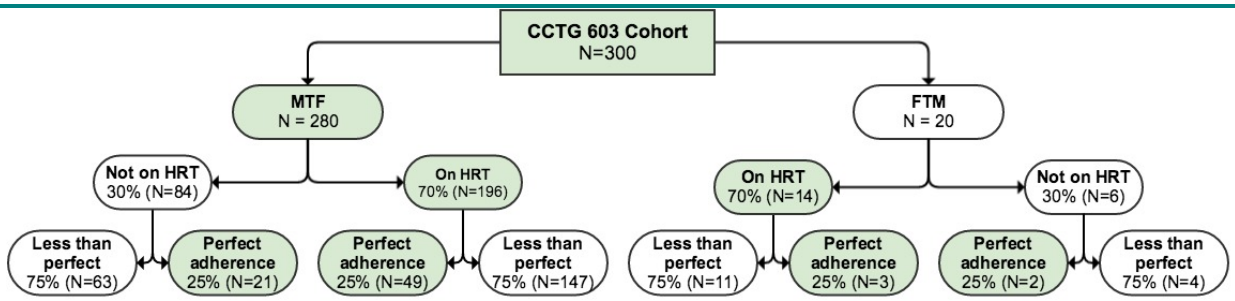


Figure 2: Predicted Numbers of Individuals on HRT and PrEP

Statistical power is based on a one-sample non-inferiority test to see if the TFV-DP concentration of perfectly adhered MAAB persons is equivalent to MSMs on average under an acceptable margin. The following assumptions are made: i) Using PK modeling of HIV-uninfected men and women, it has been shown that perfect adherers (i.e. daily dosing for 7 days) have TFV-DP concentrations of 1560 (IQR 1246-2029) fmol/punch as determined in MSM; ii) Since this is a non-inferiority study, we will assume the expected sample mean for MAAB is around 1560 fmol/punch, or slightly lower. In other words, we will assume the mean difference in TFV-DP concentrations between MAAB and MSMs is approximately 0 (ranges from -180 to 50); and iii) We believe that a difference of less than 230 fmol/punch (equivalent to 1 tablet per week dosing) in the TFV-DP concentration can be considered non-inferiority which will be the lower limit of acceptable variation. Thus, we will set the non-inferiority margin to be 230.

Assuming the standard deviation is 350, if the true mean TFV-DP concentration for MAAB is 1360 fmol/punch (ie, 100 fmol/punch lower than MSMs), then 45 subjects are required to be 80% confident that the lower limit of a one-sided 95% confidence interval of the mean difference between MAAB and MSMs will be above the non-inferiority limit of -230.

Analysis Plan

The primary outcome is the intracellular TFV-DP levels, as measured in DBS, which is a continuous variable. Comparison between the MAAB and the existing MSM data that will be compared using a two-sample t-test. Differences in the means between the two groups, along with the standard deviations (SD) and their 95% confidence intervals will be reported. As a secondary/sensitivity analysis, multiple regression analysis will be performed to study the association between clinical and demographic factors (age, race, ethnicity, education, socioeconomic status, sexual risk behaviors, substance use, depression, concomitant medications) and group, adjusting for baseline demographic, stratification variables, and clinical characteristics. Variables significantly associated with both group and outcome ($p<0.10$) will be included in a multiple regression model as covariates.

For the main secondary hypothesis, in MAAB on csHT, to determine the change between baseline and week 12 estradiol levels in individuals taking PrEP and receiving stable estrogen replacement (controlling for route, dose and formulation), we will use a paired t-test. As estradiol concentrations can be unpredictable, we will measure estradiol concentrations in individuals choosing not to initiate PrEP at the same time points. Similar to 3A, multiple regression models will be developed if there are factors that require adjustment in this model.

Other secondary analyses will explore further interactions between PrEP and csHT in MAAB we will perform analyses of the following potential interactions: a) TFV-DP in transgender persons (MAAB and FAAB) of all adherence levels compared to not taking csHT, b) TFV-DP in MAAB taking versus not taking antiandrogen medications (i.e. spironolactone and finasteride) and c) emtricitabine-triphosphate (FTC-TP) concentrations (recent adherence measure) in transgender persons of all adherence levels taking versus not taking hormones. These analyses will be analogous to the descriptive analyses in the primary outcomes. For FAAB transgender individuals, to determine the change between baseline and week 12 testosterone levels in individuals taking PrEP and receiving stable testosterone replacement (controlling for route, dose and formulation), we will use a paired t-test. For hormone therapy satisfaction, the main outcome of interest to these individuals is maintaining the physically desirable characteristics that the csHT provide. Thus, it is not the hormone levels that are as important

as the satisfaction with these traits. For the entire cohort of MAAB who are on stable csHT dosing (as defined as no change from baseline to week 12) from baseline to week 12 and from baseline to week 48 we will compare the hormone satisfaction with physical traits ranked for satisfaction using the BIS and summed for overall satisfaction score to compare between weeks 0, 12 and 48. Similarly, we will use the BIS for FAAB on stable csHT assessing physical traits compared at weeks 0, 12 and 48.

SUB-STUDY IV PROCEDURES

At Baseline, eligible participants will consent for additional sub-study sample collection on the main study informed consent form. Genital collection for *Neisseria gonorrhoeae* and *C. trachomatis* will be done at Baseline and Week 24 as part of the main study STI screening procedures.

For the sub-study, two genital swabs for microbiome and cytokine testing will be collected at Baseline and Week 24. Additional genital swabs for a vaginitis multiplex assay, herpesvirus and HPV testing as well as CVF collection via aspirator for TFV levels will be collected at Week 24.

Sub-study IV Schedule of Evaluations	Study Weeks of Follow-up		
	Screen	Wk 0	Wk 24
Window	14 days	30 days	+/- 4 weeks
Informed Consent	X		
CV swab for cytokine testing		X	X
CV Swab for microbiome		X	X
CVF collection for drug concentration TFV			X
Vaginal swab for herpesvirus and HPV			X
Vaginal swab for vaginitis multicomplex			X

Sub-study IV Statistical Considerations

Aim 1: To determine the impact of pro-inflammatory STIs on CVF TFV levels.

We will quantify CVF TFV levels of participants at week 24 and compare levels in those with and without the presence of active vaginal infections using methods for continuous measures (i.e., the Student t test or Wilcoxon test depending on distributions). The primary analysis will compare those with any infection to those with no detected infection. We will examine individual organisms in subanalysis. We will also compare the proportion of participants with TFV levels in steady state (≥50 ng/mL) to those with levels that are not (<50 ng/mL) at week 24 for vaginal infections using Fisher's exact test. The threshold of ≥50 ng/mL was selected based on previously reported CVF steady state trough concentrations at 24 hours achieved by oral dosing (31).

Sample Size: Based on an estimated mean concentration of 119 ng/mL and a standard deviation of 58 ng/mL in CVF TFV in a steady state PK study(32), we have 80% power with a one-sided lower bound alpha of 0.05 to detect a difference in individuals with STIs versus those without STIs of 33 ng/mL or 28% reduction in CVF TFV levels in a sample of n=40.

Aim 2: To determine the impact of CV inflammation on CVF TFV levels.

We will compare TFV levels as a continuous measure with $\log_{10}$-transformed cytokine levels at week 24 using the Pearson correlation test or Spearman correlation test if they are not normally distributed. For assessment of chronic inflammation and TFV levels, we will compare those with and without elevated cytokine levels of at least one cytokine (MIP-1α and β, IP-10, IL-6 and IL-8) that remains higher at both baseline and week 24 using Student t-test or Wilcoxon depending on distributions. If cytokine levels are below the level of detection in ≥40% of samples, these will be converted to categorical variables (detectable versus undetectable).

Exploratory Aim: To assess the impact of the CV microbiome on CVF TFV levels.

Sequence Analysis: We will use Quantitative Insights into Microbial Ecology (QIIME) to perform taxonomic dependent and independent classification.(33) While with taxonomic dependent classification we can investigate the dynamics of specific group of bacteria (i.e. *Lactobacillales*) in relation to clinical and immunological variables, taxonomic independent classification will provide measures of total microbial community composition. We will classify bacteria at the order level and we will use the alpha diversity as measurement of diversity. We will characterize (cross-sectionally) the composition of the CV microbiome in our study groups and determine any associations with TFV levels. We will describe species diversity in participants with TFV levels ≥50 ng/mL and

levels <50 ng/mL at week 24. Associations between cytokine concentrations and STIs with the presence or absence of vaginal microbiota species will be assessed using Student t-tests.

10. HUMAN SUBJECTS

The study will enroll about 300 self-identified transgender or gender-nonconforming individuals ages 18 and older at all participating sites. UCSD and FHCSD plans to enroll up to 100 subjects.

Main Study Inclusion Criteria

1. Transgender identity, defined as identifying differently from sex assigned at birth.
2. Age 18 years or older.
3. Risk of acquisition of HIV as evident by one or more of the following:
   I. Has at least one HIV infected sexual partner for ≥4 weeks.

OR

   II. Anticipated or concern of unprotected anal or vagina sex with a partner in the next 3 months

OR

   III. Any partner in the past 12 months AND at least one of the following:
      a. any condomless anal or vaginal sex in the past 12 months;
      b. any STI diagnosed or reported in the past 12 months;
      c. exchange of money, gifts, shelter, or drugs for sex;

OR

   IV. Post Exposure Prophylaxis (PEP) use in the past 12 months.

4. Negative for HIV infection by nucleic acid test (NAT) or other sensitive method such as 4th generation antibody- antigen test.
5. Acceptable renal function as measured by calculated creatinine clearance of at least 60 mL/min by the Cockcroft-Gault formula (eCcr (male) in mL/min = [(140 – age in years) x (lean body weight in kg)] / (72 x serum creatinine in mg/dL) in the past 30 days.

Main Study Exclusion Criteria

1. Unable to give informed consent.
2. Active hepatitis B defined by a positive hepatitis B surface antigen (HBSAg)
3. Substantial medical condition, that in the opinion of the investigator would preclude participation, as defined by
   - gastrointestinal condition that would impair absorption of study drugs.
   - Known condition of reduce bone density (e.g. osteoporosis or osteogenesis imperfect) that significantly elevate the risk of bone fracture
   - Neurological or severe psychiatric condition that would significantly impair the ability to adhere to PrEP.
   - Tubular or glomerular kidney disease that could be exacerbated by tenofovir
   - Other medical condition that would unacceptably increase the risk of harm from study drug or significantly impair the ability to adhere to PrEP.
4. Suspected sensitivity or allergy to the study drug or any of its components.
5. Currently using an essential product or medication that interacts with the study drug such as the following:
   - Other antiretroviral agent (including nucleoside analogs, non-nucleoside reverse transcriptase inhibitors,

integrase inhibitors, protease inhibitors or investigational antiretroviral agents) – if currently on TDF/FTC for PEP or PrEP they can switch to study provided drug but can not continue any other antiretroviral agent.

- Agents with known nephrotoxic potential:
  - aminoglycoside antibiotics (including gentamicin)
  - IV amphotericin B
  - cidofovir
  - cisplatin
  - foscarnet
  - IV pentamidine
  - IV vancomycin
  - oral or IV gancyclovir
  - other agents with significant nephrotoxic potential
- Drugs that slow renal excretion
  - Probenecid
- Immune system modulators
  - Systemic chemotherapeutic agents (i.e. cancer treatment medications)
  - Ongoing systemic corticosteroids (with the exception of short courses of tapering steroid doses for asthma or other self- limited condition).
  - Interleukin-2 (IL-2)
  - Interferon (alpha, beta, or gamma)
- Other agent known to have a significant interaction with TDF or FTC

6. Proteinuria 2+ or greater by urine dipstick
7. Pregnancy (if individual has a uterus)
8. Other condition that in the opinion of the investigator would put the participant at risk or interfere with participation, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

Participation into Sub-study IV will be only be offered to a subset of 20 transgender men/gender non-conforming individuals with vaginas enrolled at the UCSD AVRC. Transgender women enrolled at the UCSD AVRC who have undergone gender reassignment surgery with neovaginas will also be offered participation, although we expect this number to be quite low.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Adaptive recruitment strategies will be employed as necessary. Our sites provide significant HIV testing for transgender individuals and the number of testers is enough to supply enrollment to this project. We will also use specific targeted recruitment and outreach to supplement the enrollment directly coming from the testing programs. Any recruitment materials will be submitted to the IRB for approval prior to use. One lesson learned from a previous PrEP study was that social network referral was a significant driver of enrollment. In our formative work through consultation with community advisory boards (CABs) and focus groups with members of the transgender community, it was evident that individuals within the transgender spectrum represent diverse and unique populations that are typically highly connected through interpersonal social networks. We will focus outreach efforts on social media sites, publications, and advocacy groups that specifically serve the transgender

community.

Additionally, UCSD and FHCSD are affiliated with numerous healthcare organizations throughout San Diego County that we will target for enrollment outreach, including the San Diego County Health and Human Services Agency (SDHHSA) and San Ysidro Health Center. The UCSD Early Test Program provides screening for acute HIV infection and reaches many at-risk individuals in San Diego (1-2% of tested are transgender) and can be used to access high-risk individuals. FHCSD is a community-based health organization that is the largest provider of services for minority, uninsured, indigent, and transgender populations in San Diego. FHCSD provides dedicated healthcare services to trans individuals, including PrEP, at their North Park "The Night Clinics" (TNC).

Recruitment materials/avenues will be developed by the AVRC Outreach Department, including sign-up sheets for participants to volunteer contact information at outreach events, recruitment business cards with study coordinator contact information, and classifieds advertising on websites and print media (e.g. newspapers, magazines). Any other recruitment materials e.g., flyers/posters, online recruitment materials, and e-mails to community doctors will be submitted to the IRB for review and approval prior to posting.

This study will utilize several social networking services to increase outreach and recruitment efforts, including *Grindr* and *Studykik* (www.studykik.com). The study will be promoted in *Grindr* in-app prompts and banners displaying IRB-approved language. All prompts and banners will link to a study-specific website that includes contact information for interested participants.

Studykik is a clinical research recruitment service connecting interested individuals to studies via social media communities. Studykik manages studies' social media presence on networking services including Instagram, Snapchat, Facebook, Twitter, Pinterest, and Google and other search engines. Our study will provide Studykik with basic inclusion/exclusion criteria, study site location, and IRB-approved recruitment language. Studykik will filter their database based on proximity to study site, study criteria, and target population; individuals identified in this manner will be provided the study's IRB-approved outreach material and, if interested in participating, will be connected to the study coordinators.

12. INFORMED CONSENT

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the UCSD Institutional Review Board responsible for oversight of the study. Written informed consent will be obtained from the subject from a member of the study staff. At the time potential subjects contact us regarding the study, any questions they may have will be answered by a member of the study staff. If the potential subject is still interested in participating, a clinic visit will be scheduled. The subject will be informed of the time that needs to be allotted for their first visit in which the informed consent will be administered.

Individuals unable to speak English will not be excluded from participating in a study. The approved informed consent and any subsequent versions will be translated into Spanish and on a case by case situation any other language that is deemed necessary. The translated informed consents will be submitted to the IRB for approval. The consent process will include a qualified translator in the subject's native tongue. If a qualified UCSD translator is not available the Cyrom Language Line will be utilized as they have certified medical interpreters. The interpreter will sign and date at the end of the approved informed consent unless the Cyrom interpreter is utilized. In this situation, the study staff member involved in the consent process will document translator's name, ID#, and date of the translation at the end of the approved informed consent.

The informed consent will describe the purpose of the study, the procedures to be followed, and the risks, and benefits of participation. This information will be explained to the study subject in a face-to-face setting by the individual consent the subject. Subjects will be encouraged to ask questions throughout the consent process and encouraged to discuss their participation with trusted advisors, such as family members, close friends, etc. Subjects will be allotted sufficient time to consider whether or not to participate in the research study. After allowing the potential subject time to read the informed consent the study staff and/or investigator will answer and address any questions or concerns the subject may have. Once all questions and concerns have been addressed and the subject wishes to participate, they will be asked to sign the informed consent.

Also, during the consent process, the Health Insurance Portability and Accountability Act (HIPAA) Authorization

will be addressed. A copy of the consent and HIPAA Authorization form as well as the Notice of Privacy Practices booklet will be given to the subject.

13. ALTERNATIVES TO STUDY PARTICIPATION

Subjects may decide not to take part in this study. The alternative to participating in this study is to receive counseling on HIV prevention, testing on sexually transmitted infections and HIV infection and obtain PrEP medication from a primary care doctor.

14. POTENTIAL RISKS

Participation in this study may involve some added risks or discomforts. These include:

***Risks of Truvada*:** Truvada is a combination of two antiretroviral medications: tenofovir disoproxil fumarate and emtricitabine. Truvada is categorized in a class of drugs called nucleoside reverse transcriptase inhibitors (NRTI). These drugs may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects.

Risks of Tenofovir Disoproxil Fumarate (TDF, Viread):
The following side effects have been associated with the use of tenofovir:

- Kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas
- Lactic acidosis, a buildup of lactic acid, which causes the blood to become more acidic.
- Shortness of breath
- Low phosphate, a chemical in the blood
- Allergic reaction, which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, body aches, shortness of breath, or a general feeling of illness.
- Changes in bone growth and strength were seen in study animals given tenofovir. Bone thinning has been seen in adults and children taking tenofovir.
- Upset stomach, vomiting, gas, loose or watery stools
- Dizziness
- Abdominal pain
- Lack of energy
- Rash
- Generalized weakness
- Depression
- Headache
- Liver problems. If you are developing liver problems, you may have one or more of the following symptoms:
  - Yellowing of the skin or whites of your eyes,
  - Dark urine,
  - Pain on the right side of your stomach,
  - Loss of appetite, upset stomach or vomiting,
  - Pale colored stools,
  - Itchy skin.
- **Muscle pain** and **muscle weakness**
- **Sleeping** problems

Risks of Emtricitabine (FTC, Emtriva):
The following side effects have been associated with the use of emtricitabine:

- Changes in the liver, which could mean liver damage
- Lactic acidosis (which may make you feel weak, tired, have unusual muscle pain, trouble breathing, nausea, vomiting, feel dizzy or have a fast or irregular heartbeat)
- Increased creatine phosphokinase (CPK), which could mean muscle damage
- Inflammation of the pancreas
- Headache
- Dizziness

- Tiredness
- Inability to sleep, unusual dreams
- Loose or watery stools
- Upset stomach (nausea) or vomiting
- Abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Skin darkening of the palms and/or soles
- Increased cough
- Runny nose
- Increased triglycerides or fats found in the blood

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.

Privacy and Confidentiality: Although we will make every effort to protect the subject's privacy and confidentiality, it is possible that the subject's status could become known to others. This could cause problems between the subject and the subject's family and/or community and could cause the subject to be discriminated against.

Risks of drawing blood: Participants may experience temporary discomfort from the blood draws. The needlesticks may cause local pain, bleeding, bruising and swelling, as well as lightheadedness, dizziness and rarely, blockage of the vein, fainting and/or a local infection.

Risks of Genital Swab and CVF aspiration: There may be some mild discomfort associated with insertion of genital swabs and CVF aspirator, similar to inserting a tampon. The discomfort will stop as soon as the tests are completed.

Text messaging adherence reminders: Receiving text message reminders to take medication may induce feeling of stigma or intrusions of privacy or confidentiality.

Drug Resistance: If a participant becomes HIV-infected while using Truvada, she may develop resistance to Truvada and other drugs in its class.

Sexually Transmitted Infections (STIs): Participants may experience some anxiety or embarrassment when being tested for sexually transmitted infections. If found to have a sexually transmitted disease, an appropriate referral for treatment will be made to one of several free public health clinics.

Testing for Infectious Disease/Reporting Requirements: There may be a chance that a participant will be diagnosed with HIV and/or HBV infection. The study staff will talk about options and provide referrals of doctors and/or facilities that can provide treatment for HIV and/or HBV infection if a participant found to be infected with HIV and/or HBV. The diagnosis of HIV and/or HBV may result in earlier treatment and/or prevention of many complications from the illnesses.

Awareness of a diagnosis of HIV and or HBV may have serious personal or social consequences. Some of these consequences include possible difficulty obtaining health insurance or employment and difficulty traveling to some foreign countries.

If someone is infected with hepatitis B (HBV) and are using Truvada, there have been cases in which individuals have experienced a flare of HBV with liver injury when this medication is stopped. If someone is diagnosed with HBV it will be confirmed that they will be able to continue to have treatment for HBV after study otherwise they will not be allowed on study.

Risks of Pregnancy while taking PrEP: Through the course of the study, participants could become pregnant if they are not using contraceptive methods (e.g., condoms, birth control pill) to prevent pregnancy. PrEP is not contraindicated in pregnancy but:

- It is not known if Truvada will cause harm to fetuses.
- It is not known if Truvada may cause babies to be born early or dead.
- It is not known if Truvada may cause babies to be sick or have birth defects.
- A recent study found significantly lower bone mineral content in newborns whose mothers took tenofovir, one of the components of Truvada, while pregnant compared with infants without tenofovir exposure. Those mothers were HIV-infected. It is not known if this lower bone mineral content will affect children's development over the long-term.

Should participants become pregnant over the course of the study, they will be asked to sign an additional consent form to allow continued follow up of the pregnancy and outlines the risks of taking PrEP while pregnant. They will be referred to a reproductive health specialist at UCSD.

Risks of Pregnancy: The risks of these medications to an unborn baby or nursing child are unknown. Most of the information that we have on TDF/FTC in pregnant women comes from follow-up of women who are being treated for HIV infection where there is a general consensus that HIV infected women should remain on Truvada to protect the mother and her fetus. In PrEP trials, a limited number of pregnancies have had exposure to oral and vaginal preparations of tenofovir and/or emtricitabine. During these trials, no health problems have been associated with PrEP use by women in pregnancy or for their children. However, the long-term safety of PrEP taken by HIV-uninfected women after fetal (during pregnancy) or infant (during breastfeeding) exposure has not yet determined. If a participant is pregnant, she cannot be in this study. If a participant thinks that she has become pregnant during the study, she must tell the study doctor immediately. If a determination of pregnancy is made during the study, the participant will be referred to obstetrical care and request to track their pregnancy and report the outcome including that of the participant's infant to the IRB. Participants should be counselled and monitored by their own doctor. Neither the study Sponsor, The University of California, or its Investigators will be responsible for providing routine medical care relating to the participant's pregnancy. The study will discontinue TDF/FTC as soon as it is aware of pregnancy unless there is a safety issue to discontinuation. If the mother is at high risk of acquiring of HIV during her pregnancy that would put her and her fetus in imminent danger and she can not acquire TDF/FTC outside of study the study PI may decide to continue TDF/FTC in consultation with the obstetrical provider to protect the mother and fetus. Once there is no longer risk, the mother or can acquire TDF/FTC through their insurance the study will no longer provide drug.

Female participants must also refrain from egg donation and in vitro fertilization during study and until at least 30 days after the last dose of study drug.

Participants who do not wish to get pregnant should protect themselves or their partner from becoming pregnant before, during, and after the study with use of effective methods of birth control. The study doctor will need to document what type(s) of birth control participants are using. If the participant becomes pregnant the study doctor will tell participants about the possible risks to their unborn child and options available to them. A separate consent form will be used to consent the participant to continue to be followed through the study and for pregnancy outcome including any premature termination, that must be reported to the Sponsor.

Risks of Email Communications: There are limitations to the confidentiality of email communications. Participants will be told not include any sensitive health information via email. The study team will include minimal information in study visit reminder emails if they choose to receive them.

Other Risks: Since this is an investigational study, there may be other unknown risks that are unforeseen or at this time cannot be predicted. They will be told of any significant new risks.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Laboratory: The UCSD AVRC laboratory performs complete specimen processing, receipt of shipments, and storage needed for clinical research. This includes phlebotomy, centrifugation, aliquoting, rapid freezing at -70^0, and preparation for distribution and shipping. A system, designed to continuously monitor the freezers, provides documentation of storage temperatures and conditions notifies AVRC personnel if temperatures fall below

designated criteria. The laboratory is staffed by four certified phlebotomists who are trained, certified and experienced in all International Air Transportation Association (IATA) Dangerous Goods procedures and regulations. The lab staff are also phlebotomy licensed. Specimen receipt and repackaging takes place in a 200 square foot laboratory site which contains a Level 2 biosafety hood, low and high speed refrigerated centrifuges, a refrigerator, and a -70^0 freezer for temporary storage of plasma, CSF and other samples.

All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA, the sponsor, or the UCSD IRB.

Phlebotomy will be performed by experienced phlebotomists.

UCSD Antiviral Research Center (AVRC): The AVRC, which occupies space on the first and second floors of a 36,000 square foot, 3-story building has over 55 research staff and contains offices for nine full-time faculty investigators (in UCSD's Division of Infectious Diseases), six Infectious Disease Fellows, two postdoctoral mathematicians, and nine research nurses. More than 5,000 research visits per year are conducted at the AVRC, including HIV counseling and testing, examination of research patients, 12-24 hour pharmacokinetic studies and infusions, specimen collection, processing, and banking, as well as data entry and analysis. The AVRC facility also includes a lobby and waiting area (approximately 200 sq. ft.), 8 examination rooms, one consultation room, a clinical laboratory, research pharmacy, 2 conference rooms, a data management center and two medical records libraries.

Family Health Centers of San Diego (FHCSD): Family Health Centers of San Diego is a non-profit community health center. In 2012 and 2013, FHCSD was the largest provider of healthcare to uninsured patients in the nation. The mission of FHCSD is to provider caring, affordable, high-quality healthcare and supportive services to everyone, with a special commitment to low income and medically underserved individuals. With a full- and part-time staff of more than 1200, FHCSD currently 38 locations throughout San Diego County, including 21 primary care clinics (three are Mobile Medical Units) that provide healthcare services at 33 locations including local schools, substance abuse treatment facilities, homeless shelters, and public housing sites), six dental clinics, four behavioral health facilities, comprehensive HIV services, and a safety-net dedicated pharmacy. Participants will be seen at the FHCSD TNC 4th Avenue facility in North Park.

Los Angeles LGBT Center: The Health and Mental Health Services Department includes a Mental Health Program with individual and group counseling provided by licensed clinicians and psychiatrists; an HIV treatment clinic with 2900 patients, 90% male and 10% female; a Primary Care Clinic with 1,000 patients where PrEP is being prescribed. As noted earlier, there is Transgender Health Program providing primary trans-care and hormone therapy to over 650 patients; and the Sexual Health and Education Program (SHEP), provides HIV and STI testing/treatment for 14,000 unique individuals during 27,000 screening and treatment visits annually. The SHEP population is approximately 78% MSM/bisexual, 15% heterosexual, 1% lesbian, 2% transgender, and 4% other/gender queer. SHEP clients are 7% Asian, 9% African American, 62% White, 10% more than one race, 11% other and about 35% of the clients identify as Latino, generally reflective of our geographic location. SHEP provides 20,000 HIV tests annually, with a 2.4% positivity rate overall. 10% of new positive diagnoses are acute infections. There are 2,380 cases of gonorrhea diagnosed annually with 11% positivity rate of tests performed; 2240 cases of chlamydia with a 9.75% positivity rate; and 480 cases of syphilis with a positivity rate of 2-3% (SHEP diagnoses 25% of the early syphilis in LA County.) In addition to HIV and STI testing and treatment, SHEP provides PEP (2,200 intakes annually), linkage to substance use and mental health services, and linkage to HIV care.

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 6 month intervals during the

remainder of study conduct.

Positive STI and HIV Diagnoses: Subjects diagnosed with a positive STI will be referred to their medical provider for treatment. If subject does not have a provider, they will be referred to the public health clinic where treatment will be provided.

If a subject tests positive for HIV during the study, additional blood tests will be performed to evaluate HIV viral load, CD4 count, and presence of drug resistance. Study staff will work with the subject to find appropriate HIV care.

In compliance with California state law, study staff will report names, contact information, and treatment records to the public health department if a subject tests for HIV, chlamydia, gonorrhea, or syphilis.

Pregnancy: Any participant 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.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

A Confidentiality Certificate from the U.S. Department of Health and Human Services (DHHS) has been applied for and will be available for review once approved.

The AVRC research staff has undergone the CITI Biomedical Human Research, and Good Clinical Practice (GCP) training along with the HIPAA training.

The research staff will protect Patient Protected Health Information (PHI) or other Personal Identification Information (PII) of any individual in general, obtained from as part of the University or Healthcare or other work-related records, for whatever purpose, as private and confidential, and will make every effort to safeguard such information from unauthorized access or dissemination. Steps in place to protect this information are outlined below (Data Security).

Consent Process/Study Visits: For confidentiality purposes the consent process and exams will be conducted in an exam room by one of the study staff members. The laboratory procedures will be done in the blood draw room or an exam room by an experienced phlebotomist.

Data Security: Any data collected as part of this study that is stored at the AVRC and/or is transferred via the internet will follow our data security process as outlined below.

In the following we provide a summary of the key features pertinent to this project to protect data.

- An anonymous participant identification number is used for all data collection, recording and submission to the project database.
- Data that contain any participant identifiers (e.g., name or contact information) other than the unique identifier are password protected and accessible only to staff members whose job requires knowledge of such data.
- Laboratories are instructed not to disseminate any participant identifiers in any communications with, or data submissions to, any other AVRC collaborators. Any data transfer over the Internet uses encryption.
- Data transfer and all Web-based utilities use secure access (user and server authentication, 128-bit SSL encryption). This type of encryption is the same as is used for Web-based transactions that involve credit cards or Web banking.
- No personal health information will be transferred through the iTab system, including reminders and responses. All references to PrEP will be kept generic (eg “meds”). In the event of the phone being lost or stolen, participants will report immediately to study staff and have service to that phone discontinued.

Research Laboratory Specimen Identification Policy: All research laboratory specimens leaving the AVRC to

an outside laboratory will be de-identified.

Procedures:

1. The Lab Manager will create a study specific AVRC internal lab requisition. The requisition will be saved and accessible via the AVRC internal computer system's shared drive.
2. Each research nurse will access and print the study specific requisition(s) via the shared drive.
3. Each research nurse will then complete the study specific requisition with the subject's name, DOB, medical record number (MR#), PID, AVRC number and study week.
4. The requisition will then be delivered by the research nurse to the AVRC lab.
5. The AVRC laboratory staff will then complete the appropriate form for the corresponding laboratory to which the specimen will be sent, using two coded identifiers, the subject's PID number (in the name field) and AVRC number (in the medical record number 's field)
6. The AVRC laboratory staff will prepare and label specimen tubes using the same two coded identifiers, the subject's PID number (in the name field) and AVRC number (in the medical record number's field). No personal health identifiers will be included on the specimen label (i.e., no name, initials, DOB, MR#, etc).
7. Prior to the blood draw, the phlebotomist will verbally verify the subject's name and DOB. The phlebotomist will confirm the coded specimen tube(s) identifiers with the coded form identifiers.
8. Coded specimens are transported to the appropriate lab either by AVRC staff or shipped via FedEx, under IATA regulations.
9. All study specific completed AVRC internal lab requisitions will be retained in a locked and secured area for a period of six months and thereafter shredded.

All stored Samples are accessible only to the AVRC laboratory personnel and the appropriate study members. Samples are stored under the coded identifiers as detailed above frozen and in freezers equipped with locks until they are shipped to the central laboratory under contract with the sponsor. The freezers are located in the AVRC and CTF building behind locked doors with cypher or keypad entry.

The stored samples are shipped as outlined above and are then secured under the sponsor's SOPs for storage of human biological samples.

17. POTENTIAL BENEFITS

Taking part in this study may benefit the subject, but no guarantee can be made. They may receive no benefit from this study. However, the information the Investigators obtained from this study may help others who are at high-risk for acquisition of HIV.

18. RISK/BENEFIT RATIO

Taking part in this study may benefit the subject, but no guarantee can be made. They may receive no benefit from this study. However, the information the Investigators obtained from this study may help others who are at high-risk for acquisition of HIV. Therefore, it is the opinion of the investigators that the benefits outweigh the risks.

19. EXPENSE TO PARTICIPANT

There is no cost to subjects for the study-related clinic visits, procedures, examinations, or laboratory tests in this study.

20. COMPENSATION FOR PARTICIPATION

Subjects will receive $25 after completion of their screening visit and $50 after completion of their Baseline visit and weeks 12, 24, 36 and 48 study visits for their travel and/or any inconvenience they may experience as a result of their participation in this study. Subjects that elect same-day PrEP will be compensated $50 after completing the in-clinic visit and $25 for completing both sets of questionnaires. Participants may choose to complete both sets in-clinic or complete one set in-clinic or one set at home. Subjects will also receive $10 for every study-initiated Interim Visit completed. Subjects will not receive compensation for visits that are not completed and will not receive compensation for subject-initiated Interim Visits.

Subjects will be provided additional travel stipends at each study visit based on the average round-trip commute time between the subject's residence and the study clinic. Subjects will be provided $5 per 20 minutes (rounded up) of commute, up to a maximum of $50. Commute time will be assessed during pre-screening.

Subjects enrolled into Sub-study IV will receive an additional $25 for completion of their Baseline and an additional $25 for completion of their Week 24 visit. Subjects may receive a maximum $50 for participating in the sub-study.

Family Health Centers of San Diego (FHCSD) The Night Clinic (TNC) will be reimbursing their participants with Target gift cards in lieu of cash. The gift card amounts will reflect the compensation amounts described above.

Participants who take part in the Post-Week 48 extension will receive $50 compensation plus travel stipend for visits after Week 48. Participants may receive a maximum of $100 for participating in the week 48 extension visits.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Drs. Sheldon Morris, Constance Benson, Ajay Bharti, Jill Blumenthal, Maile Karris, Scott Letendre, Susan Little, Davey Smith and Gabriel Wagner currently have privileges at UCSD Medical Center in the Department of Medicine, Division of Infectious Disease and are licensed and certified by the State of California to perform all the medical procedures discussed in the protocol at UCSD. In addition to having privileges with UCSD Medical Center, Drs. Susan Little and Davey Smith have privileges at the VA Medical Center.

Dr. David Moore is the co-Investigator and is a clinical psychologist in the UCSD Department of Psychiatry.

Joel Trambley, M.D. is an infectious disease specialist in San Diego and site PI for the Family Health Centers of San Diego. He will work with site coordinators to implement the study at Family Health Centers.

Robert Bolan, M.D. is an infectious disease specialist in Los Angeles and site PI for the Los Angeles LGBT (LALBGT) Center. He will work with site coordinators to implement the study at LALGBT.

Helene Le and Joseph Lencioni will serve as the regulatory contacts for this study. They will have access to the HRPP webpage.

The staff research associates Leah Burke, Jordan Silva, and Karen Chow at the AVRC will be involved with the consent process and study visit procedures.

All AVRC nurses (NP: Aurora Verduzco and RNs: Alina Burgi and Steven Hendrickx) are licensed by the State of California. Prior to the study opening at the AVRC, one of the study nurses will be assigned to the study and provide any back up to the staff research associates. The lead study nurse will provide in-service necessary to the other AVRC nurses who will be here back-up when the main study nurse is absent due to illness or vacations.

Deedee Pacheco, DeLys Brooks, Christopher Houston, Rebecca Gonzalez, and Ernesto De Leon Marquez will perform all lab duties for this study.

Leticia Muttera, PharmD and Niamh Higgins, PharmD, licensed by the State of California, will serve as the investigational pharmacists for this study and are responsible for accounting and dispensing the study drug.

Eric Ellorin, MAS will serve as the project manager for this study.

The PI, co-PIs, and all study staff at the AVRC have completed the required UCSD research training to include CITI Human Subjects and GCP training along with the UCSD IRB HIPAA tutorial.

22. BIBLIOGRAPHY

1. Milam J, Richardson JL, McCutchan A, Stoyanoff S, Weiss J, Kemper C, et al. Effect of a brief antiretroviral adherence intervention delivered by HIV care providers. Journal of acquired immune deficiency syndromes. 2005;40(3):356-63.
2. Richardson JL, Milam J, McCutchan A, Stoyanoff S, Bolan R, Weiss J, et al. Effect of brief safer-sex counseling by medical providers to HIV-1 seropositive patients: a multi-clinic assessment. AIDS. 2004;18(8):1179-86.

3. Marks G, Richardson JL, Crepaz N, Stoyanoff S, Milam J, Kemper C, et al. Are HIV care providers talking with patients about safer sex and disclosure?: A multi-clinic assessment. Aids. 2002;16(14):1953-7.

4. Richardson JL, Milam J, Stoyanoff S, Kemper C, Bolan R, Larsen RA, et al. Using patient risk indicators to plan prevention strategies in the clinical care setting. Journal of acquired immune deficiency syndromes. 2004;37 Suppl 2:S88-94.

5. Liu H, Miller LG, Hays RD, Wagner G, Golin CE, Hu W, et al. A practical method to calibrate self-reported adherence to antiretroviral therapy. Journal of acquired immune deficiency syndromes. 2006;43 Suppl 1:S104-12.

Please refer to Section 15.0 References of the Protocol for a complete list of references for this study.

Sub-study IV

1. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. The New England journal of medicine. 2010;363(27):2587-99. Epub 2010/11/26. doi: 10.1056/NEJMoa1011205. PubMed PMID: 21091279; PubMed Central PMCID: PMC3079639.

2. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. The New England journal of medicine. 2012;367(5):399-410. Epub 2012/07/13. doi: 10.1056/NEJMoa1108524. PubMed PMID: 22784037.

3. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. The New England journal of medicine. 2012;367(5):423-34. Epub 2012/07/13. doi: 10.1056/NEJMoa1110711. PubMed PMID: 22784038.

4. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2012;367(5):411-22. doi: 10.1056/NEJMoa1202614. PubMed PMID: 22784040.

5. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2015;372(6):509-18. doi: 10.1056/NEJMoa1402269. PubMed PMID: 25651245; PubMed Central PMCID: PMC4341965.

6. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Science translational medicine. 2011;3(112):112re4. Epub 2011/12/14. doi: 10.1126/scitranslmed.3003174. PubMed PMID: 22158861; PubMed Central PMCID: PMC3483088.

7. Cottrell M, Yang K, Prince HM, Sykes C, White N, Malone S, et al., editors. Predicting Effective Truvada PrEP Dosing Strategies With a Novel PK-PD Model Incorporating Tissue Active Metabolites and Endogenous Nucleotides. HIV Research for Prevention; 2014; Cape Town, South Africa.

8. Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS research and human retroviruses. 2013;29(2):384-90. Epub 2012/09/01. doi: 10.1089/aid.2012.0089. PubMed PMID: 22935078; PubMed Central PMCID: PMC3552442.

9. Zheng JH, Guida LA, Rower C, Castillo-Mancilla J, Meditz A, Klein B, et al. Quantitation of tenofovir and emtricitabine in dried blood spots (DBS) with LC-MS/MS. Journal of pharmaceutical and biomedical analysis. 2014;88:144-51. doi: 10.1016/j.jpba.2013.08.033. PubMed PMID: 24055850; PubMed Central PMCID: PMC3842403.

10. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. The Lancet infectious diseases. 2014. doi: 10.1016/S1473-3099(14)70847-3. PubMed PMID: 25065857.

11. Kashuba AD, Gengiah TN, Werner L, Yang KH, White NR, Karim QA, et al. Genital Tenofovir Concentrations Correlate With Protection Against HIV Infection in the CAPRISA 004 Trial: Importance of Adherence for Microbicide Effectiveness. Journal of acquired immune deficiency syndromes (1999). 2015;69(3):264-9. doi: 10.1097/QAI.0000000000000607. PubMed PMID: 26181703; PubMed Central PMCID: PMC4505741.

23. FUNDING SUPPORT FOR THIS STUDY

This protocol is designed and funded by the California HIV/AIDS Research Program (CHRP, PR15-SD-021). Funding dates are from 04/01/2016 to 06/30/2020. The financial contact for this study is Michael Duszynski. He can be reached at (619) 543-8889.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not Applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not Applicable.

26. IMPACT ON STAFF

The AVRC is an HIV/AIDS research facility. The nurses and other study personnel assigned to this study are funded by the clinical trial agreement.

27. CONFLICT OF INTEREST

None of the investigators listed in Section 21 above has received any monetary support therefore no conflict of interest exists for the finding of this study.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not Applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not Applicable.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable. In order for a subject to be eligible for this study they must not be cognitively impaired (see item 7 under Section 10—Inclusion Criteria) and must be able to communicate effectively with the study staff; therefore, the subjects enrolling/participating in this study will have the ability to:

1. Understanding, i.e., the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, as well as the risks and benefits of participating versus not participating;
2. Appreciation, i.e., the ability to appreciate the significance of the disclosed information and the potential risks and benefits for their own situation and condition;
3. Reasoning, i.e., the ability to engage in a reasoning process about the risks and benefits of participating versus alternative, and
4. The ability to express a choice about whether or not to participate.

If for any reason, the study staff finds that the subject does not understand, appreciate, have reasoning ability and/or cannot express his/her choice to participant in the study, the subject will not be enrolled and provided with the options that may be available to them.