DOT Diary Longitudinal Pilot: A Pilot Randomized Controlled Trial to Evaluate the DOT Diary Mobile Phone App among Young MSM in the US

Sponsored by:
National Institutes of Health, National Institute of Mental Health (NIMH)

Date:
April 5, 2019

Version:
4.0

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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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1.0 Background

In July 2012, the FDA approved pre-exposure prophylaxis (PrEP) with daily tenofovir disoproxil fumarate co-formulated with emtricitabine (TDF/FTC) for reduction of sexually acquired HIV infection. Nevertheless, a major weakness of this dosing strategy is the difficulty with adherence and persistence with daily dosing. Indeed, adherence to daily oral PrEP has been so low in a number of studies as to preclude assessment of efficacy in some populations,[1,2] and to under-estimate efficacy in others.[3] To date, the only real-time adherence methodology used in PrEP trials has been electronic medication containers such as MEMSCap and WisePill.[4,5] However, these devices do not directly confirm pill ingestion, can easily be defeated by extra openings without ingestion, and data have been lost by faulty transmission or loss of devices.[6-9] Pill counts are even more easily defeated, by pill-dumping. Although drug levels in blood have become the standard for estimating adherence, between-person variability in pharmacokinetics (PK) as well as practical and financial limits on the frequency of blood sampling prevent this approach from providing accurate day-to-day information on adherence. To accurately estimate biological efficacy in clinical trials, new methods are needed to confirm and track pill ingestion accurately over time. Software-based methods that leverage existing smartphones, do not require changes to the medication itself, and can be optimized based on participant behavior will facilitate real-time monitoring and feedback at the patient, site, and study levels. Together, these will ensure maximal adherence during trial conduct, and enable unbiased estimation of biological PrEP efficacy. Finally, an accurate and scalable adherence measurement tool that is used successfully in clinical trials has the potential to increase PrEP uptake and adherence in diverse clinical settings with high-risk populations.

In 2014, men who have sex with men (MSM) accounted for 70% of new HIV diagnoses in the United States, and MSM are the only US population in which new HIV infections are rising.[10] Black and Latino men are at particularly high risk, with HIV infection rates estimated to be 6.6 and 2.9 fold higher than among White men. Disparities in HIV prevalence increased in 2008-2011, and grew fastest in the youngest age groups.[11] Young MSM (YMSM) accounted for nearly 20% of the estimated HIV diagnoses nationwide and over 80% of new HIV infections among youth in 2014. Furthermore, Black and Latino YMSM accounting for 55% and 33% of HIV infections among YMSM, respectively.[10] Despite the promise of PrEP in preventing HIV acquisition among YMSM, PrEP uptake has been low in this vulnerable population. According to national prescription data, youth under 24 are the least likely to initiate PrEP, with only 9% of PrEP initiations in 2015 occurring in this age group.[12] In a recent national survey, only half of YMSM aged 15-24 had heard of PrEP, and 1.7% had ever used PrEP.[13] Demonstration projects also highlight challenges with PrEP uptake and adherence. In the US Demo Project of 550 MSM, only 20% were age 25 or under, and PrEP uptake was lower among younger, non-white, and less educated persons.[14] In multivariate analysis, the only independent predictors of adherence as measured by tenofovir diphosphate levels in dried blood spots were Black race (adjusted odds ratio, aOR 0.28, 95% CI 0.12-0.64) and enrollment in Miami (aOR 0.32, 95% CI 0.17-0.60).[15] Self-reported adherence, pill counts, and medication possession ratios did not completely explain the disparities in TFV-DP levels. Similar findings were seen in the ATN 110 study of YMSM aged 18-22, where PrEP uptake was only 16%, and PrEP adherence was lower among Black YMSM and declined overall during follow-up, particularly with less frequent visits.[16] Clearly, future PrEP studies must include sizeable numbers of African American, Latino, and young MSM, who are at high risk for HIV and may require timely adherence support, triggered by an accurate measure of adherence. Additionally, studies of on-demand (or 2-1-1) PrEP, in which 2 doses of TDF/FTC PrEP are taken in the 24 hours prior to sex, and 1 dose each taken 24 and 48 hours later, have demonstrated promise in a randomized study[refs] and

implementation programs[refs]. High adherence to this intermittent dosing regimen requires pre-planning and tracking of sexual activity in relation to pill-taking.

Because of its ability to ensure treatment adherence, directly observed therapy (DOT) has been used for decades both to measure and maximize adherence for treatment of tuberculosis infection,[17] and more recently has been used to ensure protocol-defined dosing in PrEP PK studies.[18] A number of studies have found DOT to be successful in improving adherence to antiretroviral therapy,[19-21] including in African American and Latino populations.[22,23] However, the cost and logistical complexity of DOT in large clinical trials can be prohibitive. AiCure has developed an automated system "Automated DOT® (aDOT)" that uses artificial intelligence (computer vision and machine learning) to visually monitor adherence to treatment. Data (dosing data and patient reported outcomes) are transmitted to a centralized, cloud-based, system for analysis and intervention. On the patient side, the aDOT application is downloaded onto a smartphone and works via the front-facing camera, confirming participant identity, the medication, and correct ingestion. Visual confirmation of intentional nonadherence (confirmed fraudulent behavior) triggers alert to study staff. The platform has the potential to combine the accuracy of in-person DOT with the convenience of real-time centralized data collection and monitoring. The AiCure platform has been used in drug development and population health settings.[24-26]

In the DOT Diary research project (PI: Buchbinder, R01MH109320-01), the AiCure aDOT smartphone app has been adapted for use in monitoring and supporting Truvada® PrEP use among YMSM through formative work (UCSF IRB Study 15-17436) and initially piloted in the DOT Diary Cheating Protocol (IRB Study 16-18933) among 40 participants. As part of this development work, a sexual diary has been integrated into the aDOT app to assist YMSM in understanding whether they are receiving protection from PrEP for individual sexual episodes, and when it is particularly important to take PrEP (e.g. after a sexual episode). Specifically, the sexual diary allows participants to track sexual encounters, sexual behaviors that occurred in each encounter, and rating characteristics of partners. Partner-specific information (e.g. ratings) entered by participants is stored on a secure server) but is not transmitted to the study team. The app provides a calendar displaying all days in which PrEP medication was taken, and all days in which sexual activity occurred, allowing participants to see coverage of sexual encounters with PrEP. Based on pharmacokinetic and pharmacodynamic data from prior PrEP trials, the app will also indicate the estimated level of protection achieved from PrEP (e.g. low, medium, high), and also provide personalized messages on the additional numbers of doses needed to maximize protection. Additionally we have been maximizing the acceptability and ease of use of the app through an 8-week DOT Diary Optimization Pilot Protocol (IRB Study 17-22864) among 20 YMSM in San Francisco and Atlanta.

In the next stage of app development and assessment, we will conduct the DOT Diary Longitudinal Pilot to assess the impact of the app on PrEP adherence as measured by pharmacokinetic measures of PrEP use (tenofovir diphosphate [TFV-DP] and emtricitabine triphosphate [FTC-TP] levels in dried blood spots [DBS]). We will also assess the concordance of TFV-DP and FTC-TP in DBS with adherence measured by DOT Diary, and the acceptability and ease of use of the app over a longer (24-week) period. This pilot study will allow evaluation and further refinement of the app in preparation for testing in a larger efficacy trial among YMSM at risk for HIV acquisition. We will conduct this pilot protocol among YMSM in Atlanta and San Francisco Bay Area, two metropolitan regions heavily impacted by HIV,[27] yet differing in sociodemographics, as well as in the availability and uptake of HIV prevention services, including PrEP. These diverse research locations will allow collection of data to inform app development among a broad group of YMSM.

2.0 Longitudinal Pilot Study Objectives

2.1 Primary Objectives

1. To assess the effect of DOT Diary on PrEP adherence as measured by TFV-DP in DBS among YMSM initiating PrEP
2. To evaluate the concordance of TFV-DP and FTC-TP in DBS with adherence measured by DOT Diary
3. To assess the acceptability and ease of use of DOT Diary over a 24 week period

2.2 Secondary Objectives

1. To assess PrEP coverage of sexual acts (prevention-effectiveness adherence) as measured by DOT Diary in the intervention arm
2. To evaluate the daily use of the DOT and diary components of the DOT Diary through 24 weeks of follow-up

3.0 Research Locations

The pilot study research activities will be implemented at two study sites, 1 in the Atlanta area and 1 in the San Francisco Bay area, in accordance with local approvals. These sites are the following:

- Bridge HIV, San Francisco Department of Public Health, San Francisco, California
- Emory University, Atlanta, GA

4.0 Study Population

This study is designed to enroll a diverse population of YMSM in the Atlanta and San Francisco Bay Areas. Although no restrictions are put on the racial/ethnic make-up of the study participants, sites will strive to enroll at least 50% African American or Latino YMSM into this study.

4.1 Inclusion criteria

- Self-identifies as a man
- Age 18-35 at enrollment
- Reports having insertive or receptive anal sex with a man or trans woman in the past 12 months and one or more of the following criteria in the past 12 months:
    - Any condomless anal sex outside of a mutually monogamous relationship with an HIV-negative partner
    - Two or more anal sex partners
    - Self-reported STI (gonorrhea, chlamydia, syphilis)
    - Having a known HIV-positive sexual partner
- HIV-negative as determined by a negative 4th generation HIV test at screening and negative test, per HIV testing algorithm in Study-Specific Procedures document (SSP), at enrollment.
- Willing to initiate PrEP
- Eligible to take PrEP

    - Creatinine clearance ≥60 ml/min as estimated by Cockcroft-Gault equation at screening
    - Hepatitis B surface antigen (HBsAg) negative
- Willing and able to provide written informed consent
- Able to read and speak English
- Smartphone ownership compatible with DOT Diary app
- Meets local locator requirements
- Lives, works or plays in Atlanta Metropolitan Area, San Francisco, Alameda, Marin, Contra Costa, Santa Clara, or San Mateo Counties

4.2 Exclusion criteria

- PrEP use within the past 4 months (PrEP naïve participants will be prioritized)
- Any reactive HIV test at screening or enrollment
- Signs or symptoms of acute HIV infection at screening or enrollment
- History of pathological bone fracture not related to trauma
- Taking nephrotoxic medications
- History of participation in the active arm of an HIV vaccine trial
- In a mutually monogamous sexual relationship with an HIV-negative partner for the past 12 months
- Unable to commit to study participation for 24 weeks
- Any medical, psychiatric, or social condition or other responsibilities that, in the judgment of the investigator, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.3 Recruitment

Participants will be recruited through a variety of strategies, including online and social media strategies (e.g. craigslist, Grindr and Facebook ads); distributing posters, flyers, and palm cards about the study; and direct outreach at local venues frequented by YMSM, including community based organizations, schools, churches, and community events. Those that express interest through advertisements will be followed-up with by study staff via phone and/or email, if preferred. In addition, former participants who have previously given consent to be contacted for future research may also be directly contacted for recruitment.

4.4 Co-enrollment Guidelines

Participants in this study will not be allowed to take part in other concurrent interventional research studies during their participation in this study; co-enrollment in observational studies may be allowable with approval of the protocol team. This is due, in part, to concerns about participant study burden, American Red Cross-mandated limitations on per-unit-time phlebotomized blood volumes, and confounding in the interpretation of the study data.

4.5 Participant Retention

Once a participant enrolls in the DOT Diary Longitudinal Pilot, the study site will make every effort to retain him for the entire follow-up period in order to minimize possible bias associated with loss-to-follow-up. Study site staff are responsible for developing and implementing standard operating procedures (SOPs) that reflect retention strategies necessary to achieve the retention goal of 90% at the final study assessment/visit. Components of such procedures may include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Collection of detailed locator information at the study Screening Visit and updating of this information at each subsequent visit, if necessary.
- Use of appropriate and timely visit-reminder mechanisms.
- Immediate and multifaceted follow-up for missed visits.

4.6 Participant Withdrawal

Regardless of the participant retention methods used, participants may voluntarily withdraw from the study for any reason at any time. The site investigator also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Team. Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site IRBs/ECs terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals from the study in participants' study records.

5.0 Study Design

5.1 Overview

This is a pilot study to assess the effect of DOT diary on PrEP adherence among YMSM, and to assess the acceptability and ease of use of the DOT Diary app in this population over a 24 week period. We will enroll up to 100 total participants (approximately 50 per city) who have not been on PrEP in the last 4 months (PrEP naïve participants are preferred) and are willing to initiate PrEP at the enrollment visit. Participants will be randomized 2:1 to receive (intervention arm) or not receive (control arm) the DOT Diary app at enrollment. Participants will return for follow-up visits at 6, 12, 18, and 24 weeks for safety assessments, pharmacologic measures of adherence (tenofovir diphosphate [TFV-DP] and emtricitabine triphosphate [FTC-TP]), study drug provision, and quantitative and qualitative acceptability assessments.

5.2 DOT Diary app

DOT Diary is a smartphone app designed to track participant adherence to oral PrEP use and sexual behaviors on a day-by-day basis. DOT Diary is built upon AiCure's HIPAA-compliant platform which uses artificial intelligence (computer vision and machine learning) to visually monitor adherence to treatment. Computer vision and neural networks confirm that the correct participant is presenting the correct medication and ingesting the medication. Real-time data (dosing data and patient reported outcomes) are transmitted to a centralized, cloud-based, system for analysis and

intervention. Data are presented to study personnel on a browser-based dashboard. Study personnel may switch on automated notifications (notifications are based on adherence thresholds). Study personnel receive weekly updates regarding participants. In addition to dosing data, the platform will automatically flag behavioral events for further review that may be indicative of a participant intentionally not taking the medication, or 'feigning' adherence. If deceptive behavior is confirmed by human review, study personnel are notified. On the participant side, the aDOT application is downloaded onto a smartphone and works via the front-facing camera. Dosing data are encrypted and stored, then transmitted to centralized servers; all protected health information (PHI) is encrypted and withheld from view on the dashboard.

To facilitate participant tracking of sexual encounters, a sexual diary has been integrated with the AiCure aDOT system to create the DOT Diary app. The sexual diary allows participants to track sexual encounters, sexual behaviors that occurred in each encounter, and rating characteristics of partners. Ratings characteristics are subjective items such as physical attributes, chemistry, personality, and overall; participants can rate each characteristic on a scale of 1-5 stars. These are features that were requested by participants in earlier formative work during app development to increase usefulness and acceptability of the app. Partner-specific information (e.g. ratings) entered by participants is not shared with the study team. Participants are instructed to only use nicknames for their partners and to not include any protected health information identifiers, such as phone number, date of birth, address, email address, etc. There are no fields in the sexual diary to record this type of identifier. The app will provide a calendar displaying all days in which PrEP medication was taken, and all days in which sexual activity occurred, allowing participants to see coverage of sexual encounters with PrEP. Based on pharmacokinetic and pharmacodynamic data from prior PrEP trials, the app will also indicate the estimated level of protection achieved from PrEP (e.g. none, low, medium high), and dosing needed to maximize protection. Participants will be provided information that these are estimates of protective levels, and that protection from PrEP is not 100%. Additionally, the app will provide summary data on doses taken, sex partners, and sexual activity in graphical form to promote participant insights and reflection about their pill-taking and sexual behaviors.

Although the data entered into the sexual diary is being stored on servers through AiCure, partner-specific information is only being stored for participant data back-up purposes and will not be accessed or used by AiCure for any purpose. Information about sexual encounters (excluding partner nickname and ratings) will be used for the data visualization summaries described in the previous paragraph as well as for data analysis by the study team.

5.3 Randomization

Participants will be randomized in a 2:1 ratio to the intervention (N=67) or control (N=33) conditions, using randomly-permuted blocks of randomly selected size 3 and 6, stratified by site (San Francisco, Atlanta). The randomization scheme will be generated and archived by the study statistician, and implemented in RedCap.

5.4 Provision of PrEP

Enrolled participants will be provided with PrEP in the form of daily oral FTC/TDF, dispensed in 30-pill bottles. Participants will be instructed to take one pill orally once

daily with or without food. The drug will be provided to ensure enough study drug until the next visit. A minimum of 2 bottles will be dispensed at the enrollment visit, and 1-2 bottles at follow-up visits to ensure the participant has adequate supply until the next study visit, accounting for potential missed visits and rescheduling. If participants experience difficulties in accessing PrEP for use after study participation due to insurance issues or lack of a health care provider willing to prescribe PrEP, PrEP medication may be provided to participants for an additional 3 months (3 bottles) to ensure continued access to PrEP in the post-study period.

5.5 Study Product Formulation, Content, and Storage

FTC/TDF is a fixed dose combination tablet containing 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF) in each tablet. FTC/TDF study tablets must be stored at 25°C, with excursions permitted to 15°C-30°C (59°F-86°F) (see USP Controlled Room Temperature). FTC/TDF tablets must be stored in the original container while at the site or site pharmacy. Each container is packaged with a child-resistant screw cap and contains a silica gel to protect the product from humidity.

FTC/TDF 200mg/300mg is available as Truvada®, a medication approved by the U.S. Food and Drug Administration (FDA) for treatment of HIV-1 infection and for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. Further information on Truvada® is available in the current package insert, which is located at http://rsc.tech-res.com/safetyandpharmacovigilance.

5.6 Study Product Supply and Accountability

Truvada® is manufactured and provided by Gilead Sciences, Inc. Truvada® will be shipped directly to the site per the Site-Specific Protocol (SSP). Sites will dispense study medication, either directly or through a site pharmacist, as described in their SSP. Procedures for storage and destruction of unused study products are described in the SSP.

5.7 Study procedures

An overview of the study visits and procedures schedule is presented in Table 1. Presented below is additional information on visit-specific study procedures. At all visits, locator information will be confirmed, and participants will be provided risk reduction counseling, condoms, and lubricant, and a stipend. At all visits, study staff will work with participants to establish continued access to PrEP after completion of the 24-week study; PrEP will be provided to participants for the duration of the study. Beginning at the enrollment visit, study staff will assist participants with PrEP navigation services, including referrals to local PrEP providers/clinics and linkage to PrEP navigators who can help evaluate insurance eligibility, facilitate coverage for PrEP medication and services, and assist with Truvada® medication and co-pay assistance programs, with the goal of having participants establish a source for ongoing Truvada medication by the end of the study.

Table 1: Study visits and procedures

	SCR[&]	ENR	Week 6	Week 12	Week 18	Week 24
Obtain informed consent	√					
Obtain demographic, risk data, cell phone compatibility for assessment of eligibility	√					
Locator information	√	√	√	√	√	√
Risk reduction counseling, provide condoms and lube	√	√	√	√	√	√
HIV 4th gen	√		√	√	√	√
Creatinine, RPR	√			√		√
Blood test: HbSAg	√					
HIV testing according to HIV testing algorithm in SSP		√				
Oral, rectal swabs for GC, CT	√			√		√
Urine for GC, CT	√			√		√
Medical history, limited physical examination†		√		*		*
Confirm eligibility criteria met		√				
Randomization		√				
Download app, provide instructions		I				
Dispense TDF/FTC		√	*	√	*	*
Observe first dose using DOT (clinic staff) and DOT Diary (app)		I				
Provide PrEP Basics, adherence counseling		√				
Assist with PrEP and benefits navigation		√	√	√	√	√
CASI: sexual behavior (baseline, week 12 and 24), DOT Diary use and acceptability (weeks 12 and 24)		√		√		√
DBS collection			√	√	√	√
DOT Diary exit qualitative interview[¥]						√
Provide stipend	√	√	√	√	√	√

[&]Screening visit must occur within 4 weeks of the enrollment visit
†Medical history and physical exam may be performed at screening and updated at enrollment per site preference
*if indicated
[¥]In a subset of participants
I = immediate intervention arm only

5.6.1 Screening Visit

Participants who express interest in participating in the study will be pre-screened by telephone or online, according to what is allowed at each site, to avoid unnecessary screening visits. The study will be briefly described in a pre-screening call or online, and those participants who remain interested will be scheduled for an in-person screening visit.

At the screening visit, study staff will verify that participants meet the eligibility criteria outlined above. All screening procedures will take place in a private room. Staff will review the informed consent form, including study purpose and design, to ensure that the potential volunteer understands the study and wants to participate. Staff will also review the AiCure Mobile App Authorization Form and offer a printed copy to all participants (this document is located in the DOT Diary app as well). Participants will then be asked to undergo a test of understanding to ensure that they understand the goals of the study, and understand the app and privacy safeguards. Participants who are eligible and demonstrate good understanding of the study may then be screened for the study, after signing the consent form. If the participant answers multiple questions on the test of understanding incorrectly, and is not able to explain the correct answers after additional counseling, the staff may elect to either decline to proceed with screening the participant, or ask the participant to return for an additional screening visit. If upon re-taking the test of

understanding at the follow-up visit, the participant still has multiple incorrectly answered questions, the participant will not be allowed to enroll.

After signing the informed consent, staff will ask the participant to complete a form collecting comprehensive locator information. The participant's blood will be drawn for HIV testing, creatinine, RPR, and hepatitis B surface antigen (HBsAg) testing. Urine and rectal/pharyngeal swabs will be collected for STI testing. Participants will also be provided risk reduction counseling, condoms, and lubricant. The participant will be provided a stipend for completion of screening procedures.

5.6.2 Enrollment visit

Participants who are eligible after screening will return to the clinic for an enrollment visit. All screening procedures must be complete within 4 weeks (28 days) of the enrollment visit. At the enrollment visit, HIV testing will be performed according to HIV testing algorithm in SSP. Participants will complete an online questionnaire via computer-assisted self-interview (CASI) that gathers data on baseline demographics, drug use and sexual behaviors, knowledge and use of PrEP, and experience using technology. Participants will also be provided risk reduction counseling, condoms, and lubricant. A study clinician will then perform a medical history and limited physical exam (this may be done at screening and updated at enrollment, based on site preference). Study staff will confirm participant eligibility and enroll the participant into the study.

Participants will then be randomized to receive the DOT Diary intervention immediately at enrollment (intervention arm) or PrEP alone (control arm) in a 2:1 ratio (see randomization procedures in Section 5.3). Participants who are randomized will be considered enrolled in the study. Participants in the intervention arm will be provided instructions to download the app on to their smartphone. Study staff will demonstrate how to use the DOT Diary app, and participants will complete the tutorial in the app and demonstrate taking their first dose of TDF/FTC using the app. Participants will also select a daily dosing time, and the app will be programmed to send the participant a daily text message or app notification at this time to take their pill and use the app. Participants will also set preferences regarding the sexual diary, including preferences regarding partner rating items. Staff will instruct participants to not include any personally identifiable information about partners in the sexual diary, such as real names or contact information. Staff will emphasize that partner nicknames should be used that help the participant identify the partner but are not easily identifiable to anyone else. For example, “Bob” or “Leather pants guy.”

All participants will be dispensed 3 bottles of TDF/FTC (90 pills) and provided the PrEP Basics handout and adherence counseling regarding importance of daily adherence to PrEP for maximal protection and strategies to integrate pill-taking into one's routine. The participant will be provided a stipend for completion of the enrollment visit.

All participants will receive a phone call check-in one week after PrEP initiation to inquire about any side effects or other problems experienced in taking PrEP and provide additional support, if appropriate. Staff will also ask all immediate intervention arm participants about any issues with using the DOT Diary app and provide assistance as needed.

5.6.3 Weeks 6 and 18

At the week 6 and 18 visits, participants will have HIV 4th generation testing and risk reduction counseling performed and their blood collected for DBS. Additional bottles of study drug will be distributed as needed to ensure the participant has adequate supply until the next study visit, accounting for potential missed visits and rescheduling. Participants who are using the app will be asked about any problems or issues with using the app and will provide assistance as needed.

Between all follow-up visits, study staff will reach out to participants by phone or text message in the event of prolonged non-use, multiple overrides of the device, or evidence of suspicious behavior per the *DOT Diary Panel Management and Participant Contact SOP*.

5.6.4 Weeks 12 and 24

In addition to the procedures described at the week 6 and week 18 visits, participants will have blood tests for creatinine, and RPR, as well as urine and oral and rectal swabs for GC/CT at the week 12 and 24 visits. Participants who test positive for STIs will be offered or referred for treatment per local clinic protocol; local guidelines for STI reporting will be followed. They will also complete a CASI assessing sexual and drug use behavior, use of the various components of DOT Diary and acceptability of the app (if they used the app in the past 12 weeks).

At week 12, participants will be dispensed 3 bottles of TDF/FTC (90 pills).

At week 24, up to 24 participants (12 at each site) will complete an exit in-depth interview with a member of the DOT Diary team trained in qualitative methods. The purpose of this interview is to elicit feedback from the intervention arm on their experiences using the app, acceptability and ease of use, any technical difficulties encountered, and how the app could be further improved. Participants will also be asked whether they thought data in the app accurately represents their pill-taking and sexual behaviors, as well as willingness to use the app in future studies of PrEP. Participants in both arms will be asked about their experiences adhering to PrEP, and what might have been helpful in ongoing adherence. Participants will be selected for interviews using purposive sampling based on level of engagement with the app, level of adherence as measured by the app, and to achieve diversity based on sociodemographics (e.g. age, race/ethnicity) and other characteristics. Interviews may also be conducted with control arm participants to learn what would have helped them in taking PrEP. Qualitative interviews may be conducted in-person or via video or phone to facilitate scheduling. All qualitative interviews will be audio-taped; portions or whole interviews may be transcribed if they are particularly informative.

As this is the final clinic visit, the participant will be thanked for his participation, and a notation will be made on whether he is interested in contact for future studies. If the participant has not yet established outside access to PrEP, study staff may dispense an additional 3 bottles of TDF/FTC to minimize gaps in PrEP coverage while they assist the participant in securing ongoing access to PrEP.

For the intervention arm, staff will instruct the participant to uninstall the DOT Diary app from their mobile device to remove any possibility of further data transmission. Staff will assist participants, as needed, in uninstalling the app.

After completion of the study, staff will also be asked to comment on how well the staff-facing interface worked for their interactions with participants, including suggestions for improving the interface or app.

5.6.5. 3-Month Post Study Check In

Participants will receive a phone call check-in three months after completion of in-person study visits to confirm whether they have been able to access PrEP outside of the study. Study staff will provide additional PrEP navigation as needed to connect participants to a local PrEP provider.

5.6.6 Microincentives

Microincentives are increasingly being used to support users for their time and effort in using assistive applications in clinical trials and real-world settings.[28] Participants in the intervention arm will be provided $0.50 each day the AiCure system is used for dosing. As participants in the control condition will not be using the AiCure system, they will be asked to track the number of steps they take each day using a fitness app on their smartphone and will be provided $0.50 each day they send a screenshot from this app via text message to a secure research portal. Participants may also choose a different activity to track each day (e.g. number of hours they slept the night before) and text this information to the study team in the same manner. Intervention participants will be reimbursed every 2 weeks via an electronic payment system linked to the DOT Diary app (based on use of the app during that 2 week period) or receive a lump-sum payment at their next study visit. Control participants will receive a lump-sum payment at their next study visit.

5.6.7 Toxicity Management

The site investigator has the discretion to hold TDF/FTC at any time if s/he feels that continued medication use would be harmful to the participant or would interfere with treatment deemed clinically necessary according to the judgment of the investigator. Clinical or laboratory abnormalities that require follow-up will be documented and the clinical provider will contact the participant to schedule an interim visit for follow-up and/or repeat laboratory testing. All participants reporting an adverse event will be followed clinically until the occurrence resolves (returns to baseline grade, defined as grade at enrollment) or stabilizes, or until an effective referral to local health care providers is accomplished.

5.6.8 Procedures for participants with suspected or confirmed HIV infection

The Protocol Team must be notified of any reactive HIV test result identified at any time after study enrollment. Individuals who have one or more reactive or positive HIV tests at Screening are not eligible to participate in this study. Furthermore, at Screening and Enrollment, individuals with any signs or symptoms consistent with acute (pre-seroconversion) HIV infection will not be enrolled. Participants who have any reactive or positive HIV test result after enrollment will stop TDF/FTC PrEP and will be referred immediately for HIV primary care and treatment per local clinic guidelines.

5.6.9 Interim contacts and visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study. All interim contacts and visits will be documented in a participant management system or participants' study records and/or applicable Clinical Research Forms (CRFs).

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff or wish to provide new contact information. Interim visits at which no data are collected are not documented on CRFs. Other interim contacts and visits may occur in response to Adverse Effects (AEs) experienced by study participants, or loss of study medication. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care. In the event of loss of study medication, additional TDF/FTC medication may be dispensed to the participant per the discretion of the site investigator, and the protocol team will be notified of this occurrence. If the participant's device is no longer working (lost, broken) or the app is not supported by the participant's device, the study site may supply a provisioned device with the app pre-installed for the participant to use for the remainder of the study.

5.6.10 Early termination of study participation

Participants may voluntarily withdraw from the study for any reason at any time. The site investigator may, withdraw participants before their scheduled termination visit to protect their safety or staff safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the OHRP and US FDA), or site IRB terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records. The week 24 visit procedures should be followed when possible, in the event that a participant chooses to withdraw early from the study.

5.6.11 Risks to participation

Phlebotomy
Venipuncture is sometimes associated with discomfort. Phlebotomy may lead to discomfort, dizziness, bruising, swelling, and rarely, an infection at the venipuncture site.

HIV and STI Testing
Examination and swabbing of the pharynx and rectum can be associated with discomfort. Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become worried or anxious while waiting for their HIV and STI test results. Individuals who learn that they have an STI or HIV infection may experience anxiety or depression related to their test results. Trained clinic staff will be available to help participants deal with these feelings.

Sensitive Questions
Participants will be asked questions about their sexual behavior that may make them feel uneasy. Participants do not have to answer any question that they do not want to and can

stop answering the questions at any time. Participants may also become embarrassed, worried, or anxious when being counseled about PrEP.

Confidentiality

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (e.g., because participants could become known as at "high risk" for HIV infection or be thought to be HIV-positive). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and communities. In addition, we are evaluating a mobile app that captures information about the participant's dosing of PrEP and sexual encounters with partners. Multiple measures have been taken in the app to protect participant confidentiality, including password protection of the app, and blurring and encryption of images prior to electronic transmission. However there is the possibility that this information could become known to others. Study data will be stored using password protected databases and double-locked cabinets will be used to store contact and consent forms, which will have participant identifying information.

HIV Resistance

It is possible that a participant who is taking PrEP and becomes infected with HIV during this study may develop viral resistance mutations to TDF/FTC. Multiple steps will be taken to minimize the risk of drug resistance. HIV testing will be performed at Screening and Enrollment, and then at every follow-up visit (every 6 weeks). Persons with acute viral syndromes that may reflect acute HIV infection will not be eligible for enrollment. If acute HIV infection is suspected after enrollment, the participant will undergo evaluation using tests described in the SSP Manual. These steps should minimize the risk of drug resistance occurrence by identifying HIV infection in its early stages and stopping TDF/FTC. If any participant becomes HIV-infected during the study and develops TDF or FTC resistance, an alternative treatment regimen could be used that is not impacted by resistance to these drugs.

TDF/FTC Side Effects.

TDF/FTC is a FDA-approved drug licensed for the indication of PrEP for HIV prevention. Risks and side effects related to TDF/FTC include the following:

- Gastrointestinal intolerance (such as nausea, abdominal pain, diarrhea, or vomiting)
- Flatulence
- Headache
- Sleep disturbance
- Rash
- Redistribution/accumulation of body fat. This has been observed in HIV-infected patients receiving combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. These effects are not expected in this study involving a brief exposure to antiretroviral drug.

Rare, but serious side effects include:

- Lactic acidosis/severe hepatomegaly with steatosis
- Renal impairment, including cases of acute renal failure and Fanconi's syndrome (renal tubular injury with severe hypophosphatemia)

- Increase in bone metabolism leading to osteopenia or osteomalacia
- Hypersensitivity reaction

5.6.12 Benefits to the subject or future benefits

As part of study participation, participants will be provided up to 9 months of free TDF/FTC PrEP and assistance with PrEP navigation to establish ongoing PrEP access. There may be benefits for future PrEP trials or PrEP use, if information gained results in an improved aDOT app.

6.0 Data management and analysis

6.1 Data management

CASI data will be collected online using Qualtrics and stored in password-protected databases. The aDOT app will require a unique log-in and password and secure connections will be utilized as a way to protect confidentiality. Participants will be assured that the information they provide will be managed with the highest standards of confidentiality. All study staff will be trained in Good Clinical Practice (GCP) and will have received additional training about maintaining confidentiality.

The AiCure smartphone app makes a real-time determination of whether the participant has properly administered their medication, providing reminders and encouraging following proper procedures to ensure medication ingestion as prescribed. Study participants will receive a medication reminder at a time within a predefined window. This notification reminds participants to take their medication dose while using the AiCure smartphone app. Participants will follow a series of prescribed steps in front of the front-facing webcam to visually confirm their ingestion of the medication. The application on the smartphone will make an automated determination of whether the patient has properly taken their medication at the prescribed time. There is no need for study personnel to review the administration, nor would study personnel need to be available at the time the participant takes their medication. The amount of guidance that the device provides to the participant is automatically reduced as the participant becomes more proficient at using the application.

Study personnel will have access to real-time data on a browser-based dashboard. Study personnel may switch on automated notifications (notifications are based on adherence thresholds) and will receive regular participant and site updates (dosing and intervention summaries, site performance data, and week on week adherence rates). In addition to dosing data, the platform will automatically flag behavioral events for further review that may be indicative of a participant intentionally not taking the medication, or ‘feigning’ adherence. If deceptive behavior is confirmed by human review, study personnel are notified. Based on the data, study staff will determine whether to follow up with a participant and select a method for intervention. If the intervention is conducted via the browser-based dashboard (by phone, SMS text, or request for in-clinic visit), the intervention will be logged. Intervention will consist of non-judgmental contact with the participant, such as asking if they are having trouble using the mobile app or taking their medication as directed. At the end of the study, all raw data logged on the AiCure platform will be distributed to study personnel for analysis.

On the participant side, after dosing is completed, video data are encrypted and transmitted to a secure centralized location for further analysis. Once received at the

centralized location, the data are then removed from the device (store and forward). The captured data and video are reviewable through a roles and rules restricted system ensuring privacy of the information, allowing access to the data by study team members at the research sites. Video data captured by the aDOT platform will only be available to AiCure personnel and will be analyzed for proper medication administration. Individuals outside the clinical sites will not know the identity of the study participants and will not have access to any medical or health records of the patients. Video data will be destroyed on or before January 1, 2021. The system is compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information.

Phone numbers of the participants may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with participants, including automated messaging from the aDOT platform and contact by study personnel or other monitoring personnel. At no time is the phone number visible to study personnel or monitoring personnel. Individuals outside the clinical sites will not be provided with participant names, nor will they be given access to participant medical records. Phone numbers will not be used by AiCure for any non-study purpose.

Partner nicknames and ratings entered in the sexual diary will be stored secure servers for back-up purposes only and will not be used for any purpose, including research. Clinical site staff will not have access to partner-specific information such as nickname or ratings.

Audio-recorded qualitative interviews at week 24 will be recorded onto digital media using a portable recorder that records directly into computer readable format and can be transferred from the recorder and stored in an encrypted volume that is then stored on a secure computer or burned on a DVD which will be stored in a locked cabinet. The data will be transferred via USB cable to a password-protected, encrypted volume created on a laptop computer. Only study personnel will have access to the password. A copy of the encrypted volume would be stored on secured servers at one of the research institutions for study team members at different research sites to access. The encrypted volume will be opened (mounted) only when it is being used for analysis purposes. At all other times, the encrypted volumes containing the data will remain closed (dismounted) and thereby encrypted. Because the data are stored in an encrypted format, the risk of unauthorized access is very low.

6.2 Statistical Analysis

6.2.1 Primary Objectives

The primary objectives of the study are:

1. *To assess the effect of DOT Diary on PrEP adherence as measured by TFV-DP in DBS among young MSM initiating PrEP*

   We will use GEE logistic models to estimate the average effect of assignment to DOT Diary on repeated TFV-DP levels ≥700 fmol/punch, which are consistent with taking 4-7 PrEP doses per week. In exploratory analyses, we will examine whether the between-group difference increases over time. We will also use analogous GEE linear models to estimate the effects of D2 on log-transformed TFV-DP levels, as well as GEE proportional odds models for an ordinal outcome defined as TFV-DP levels

consistent with <2, 2-3, and 4-7 doses per week, using cut-points determined by pharmacokinetic benchmarks established through directly-observed dosing.[29]

Minimum detectable effects (MDEs). We used data from the EPIC study to estimate the baseline level and intraclass correlation (ICC) of the repeated binary measures of DBS TFV-DP levels ≥700 fmol/punch as 60% and 0.69 respectively, and retention of 80% of participants at 24 weeks. Under these assumptions, we will have 80% power in 2-sided tests with a type-I error rate of 5% to detect average between-group differences in adherence of 23 percentage points.

2. *To evaluate the concordance of TFV-DP and FTC-TP in DBS with adherence measured by DOT Diary*

Validation of DOT will focus on concordance between aDOT-based assessments of PrEP adherence by the AiCure device with four DBS measurements:

a. We will use a pharmacokinetic (PK) model with parameters estimated in the DOT-DBS Study (NCT02022657) to calculate the expected TFV-DP levels when each DBS is obtained, based on the aDOT-based pattern of pill-taking over the previous 6 weeks. We will then estimate the correlation between these predictions and observed TFV-DP levels based on DBS, and scatterplot the two measures against each other, with a Lowess smooth. As an additional measure of concordance, we will estimate the proportion of 90% prediction intervals obtained from the PK model that include the measured DBS TFV-DP levels.
b. We will use aDOT records of pill-taking over the previous 4 and 8 weeks to estimate the average number of PrEP doses per week taken by each participant, then estimate concordance of aDOT- and DBS-based indicators for protective dosing of 4-7 doses/week, with 95% confidence intervals. The DBS indicator will be defined by TFV-DP levels ≥700 fmol/punch. We will also assess concordance of aDOT- and DBS-based measures of <2, 2-3, and 4-7 doses per week, using the Kappa statistic.
c. We will estimate concordance between an aDOT-based indicator for any PrEP use over the previous 48 hours with an indicator for detection of FTC-TP in DBS, again with 95% confidence intervals.

Margins of sampling error (MSEs). The expected sample of 240 DBS (an average of 3.59 from each of 67 participants, accounting for cumulative 20% loss to follow-up over 24 weeks) will allow us to estimate the concordance of paired binary measures within MSEs of 6.3-8.4 percentage points, depending on the sample concordance. MSEs for concordance of DOT results with detection of FTC-TP will be similar.

3. *To assess the acceptability and ease of use of DOT Diary over a 24 week period*

Acceptability and ease of use will be measured using the System Usability Scale (SUS) and Client Satisfaction Questionnaire (CSQ-8) adapted for use in the DOT Diary Longitudinal pilot.[30] Average values of our measures of acceptability and ease of use will be estimated with 95% confidence intervals.

MSEs. The estimated sample of 54 participants providing end of study data will allow us to estimate mean SUS and CSQ-8 scores within MSEs of 0.27 standard deviations (SDs).

6.2.2 Secondary Objectives

The secondary objectives of the protocol are:

1. *To assess PrEP coverage of sexual acts (prevention-effectiveness adherence) as measured by DOT Diary*

   We will estimate the probability of coverage of condomless receptive sexual acts in each period, with sexual acts treated as trials, and coverage as success. Confidence intervals will be obtained using GEE binomial models, with robust standard errors will be used to account for within-subject correlation as well as over-dispersion of the binomial outcome.

   MSEs. We also used EPIC data to estimate the average number of condomless receptive sexual acts per participant as ~7. Under this assumption, we will be able to estimate coverage probabilities within MSEs of 4-10 percentage points, depending on coverage levels and the ICC of coverage across episodes.

2. *To evaluate the daily use of the DOT and diary components of DOT Diary through 24 weeks of follow-up*

   We will estimate the average use of DOT and the diary, as proportions of days and weeks on study, respectively.

   MSEs. Proportions will be estimated within MSEs of 7-12 percentage points, depending on the sample proportions.

6.2.3 Qualitative Data analysis

Recordings of the in-depth interviews (IDIs) will be analyzed using MAXQDA software for qualitative analysis. The analysis team will include members at both San Francisco and Atlanta study site, as well as a representative from AiCure. Interviewers will complete a debrief report promptly following each interview to capture results relevant to the study objectives. Debrief reports will also include an assessment of whether the interview merits additional in-depth analysis. Debriefing reports have been shown to be of sufficiently high quality to use as a primary source.[31] Debrief reports and selected transcripts will be reviewed for emergent themes and results relevant to the study objectives. Team members will create summary reports based on this analysis for use in providing feedback and suggestions in achieving study goals, and to contribute to manuscript development. Debrief reports will be reviewed promptly in order to provide feedback and suggestions for subsequent interviews. The first two audio recorded interviews and resulting debrief report at each site will be reviewed by a member of the team at the other site in order to assure uniformity in interview approaches and information included in debrief reports.

7.0 Safety Monitoring and Adverse Event Reporting

7.1 Safety Monitoring and Clinical Data Review

A multi-tiered safety review process will be followed for the duration of this study. Close cooperation between the Protocol Chair, study site investigators, study coordinator, statistician, and other study team members will be necessary to monitor participant safety and to respond to occurrences of toxicity in a timely manner. The research team will have regularly scheduled meetings during the period of study implementation, and additional ad hoc calls will be convened if required.

The study site is responsible for continuous close monitoring and management of AEs. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the Protocol Team if unexpected concerns arise. The site will have SOPs describing methods for AE reporting and toxicity management to ensure that AEs are reported and managed in accordance with the protocol and for alerting the Protocol Team if unexpected concerns arise.

7.2 Adverse Event Definition and Reporting

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

As daily oral FTC/TDF for PrEP is a licensed medication, we will focus assessment of AEs on the known toxicity profile of the medication, including creatinine elevations / decreases in creatinine clearance, bone fractures / toxicity, and symptoms associated with a start-up syndrome (e.g. diarrhea, nausea, headache, abdominal gas). A targeted symptom review will be performed at each visit using a symptom checklist focused on symptoms associated with FTC/TDF. The severity of these symptoms will be graded according to the following scale in order to aid clinical management of symptoms.

GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Abnormal creatinine values will be graded according to the following scale:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline

Study participants will be provided a telephone number and contact information for an on-call clinician and will be instructed to contact the clinician to report any AEs as-needed. For life-threatening events, participants will also be instructed to seek immediate emergency care. At the time a laboratory AE requiring retesting or follow-up is identified, participants will be called back to the clinic if possible, and will be followed as deemed clinically appropriate. All participants reporting any AE assessed as related to FTC/TDF administration (see Section 7.3) will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

7.3 Assignment of Relationship to FTC/TDF

Relatedness is an assessment made by a study clinician of whether or not the event is related to the TDF/FTC administration. The relationship of all clinically relevant AEs to the FTC/TDF will be assessed per the clinical judgment of the investigator based on the package insert.

7.4 Reporting Requirements for this Study

The site investigator will report an adverse event to the local IRB if study staff determines it may qualify as a Serious or Unexpected Adverse Event that is assessed to be related to study product. An adverse event is defined as being unexpected if the event exceeds the nature, severity or frequency described in the current IRB Application including the protocol, consent form and prescribing information.

A serious adverse event (SAE) includes any AE that meets any of the following criteria:

- Result in death
- Are life-threatening AEs
- Require inpatient hospitalization or prolongation of existing hospitalization
- Result in persistent or significant disability/incapacity;

An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation,
- Due to an overdose of study medication, or
- Due to a deviation from the IRB approved study protocol

In addition, all SAEs will be reported to the Protocol Team within 72 hours of recognition by study staff.

7.5 Social Impact Reporting

Although the study site will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that a negative social impact may result (e.g. participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Negative social impacts from use of the app will also be monitored, such as unintended loss of privacy or confidentiality. A formal survey about positive and negative social impacts will be administered at week 12 and 24; however, participants will be able to report negative social impacts at all regular visits. In the event that a participant reports a negative social impact, every effort will be made by study staff to provide appropriate care

and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance. While maintaining participant confidentiality, the study site may engage its Community Advisory Board (CAB) in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

8.0 Laboratory Specimens and Biohazard Containment

8.1 Local Laboratory Specimens

Specimens will be collected for testing at the local laboratory. All testing will be done as part of standard of care except DBS. Local laboratory evaluations/procedures will include:

- HIV testing
- Serum creatinine for creatinine clearance
- HBV testing (HBsAg)
- Syphilis testing
- Urine GC/CT testing
- Oral and rectal GC/CT testing

US local laboratories must be certified under the Clinical Laboratory Improvement Amendments (CLIA-certified). Rapid HIV testing may be performed under a CLIA-waiver at the research clinic site.

The study site will adhere to standards of Good Clinical Laboratory Practice (GCLP), and local standard operating procedures for specimen management including proper collection, processing, labeling, transport, and temporary storage of specimens.

8.2 Dried Blood Spots (DBS)

Dried blood spot (DBS) specimens will be collected at the week 6, 12, 18, and 24 visits. Specimens will be frozen and batch shipped to the University of Colorado Pharmacology Laboratory for testing of TDF-DP and FTC-TP drug concentrations.

8.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the United States Centers for Disease Control and Prevention (CDC). All infectious specimens will be transported in accordance with United States Code of Federal Regulations (42 CFR 72).

9.0 Administrative Procedures

9.1 Training

Recruiters and staff who collect data will complete CITI, GCP, and Human Subjects training, and also a minimum of one hour of training on recruitment procedures, use of the DOT Diary app, and all study instruments. Trained qualitative interviewers will conduct the in-depth interviews and code the responses.

9.2 Confidentiality

All staff are required to sign an oath of confidentiality and receive annual training on maintaining confidentiality, privacy, and handling questions about study participants from friends, employees, and insurance companies. Study staff will discuss any privacy concerns the participant may have regarding the need to contact them, via phone or e-mail, and contact methods will be tailored accordingly. A participant's involvement in this study will not be divulged without the subject's written permission, except as necessary for monitoring by the sponsor and/or its contractors; other government and regulatory authorities, and/or the local IRBs.

Information collected from subjects will be handled in the most confidential manner possible. All data will be coded by a subject number. Personal identifier records will be kept in a password protected computer files and double-locked cabinet at the study site, and any forms with identifying information will be stored separately from other study data. Digital audio and video recordings will be encrypted and stored on password protected computers until destroyed. A Business Associates Agreement for HIPAA has been established with AiCure to ensure confidentiality and security of data stored by AiCure. Identifiable information transmitted to AiCure will not be used for any non-study purposes such as business or marketing. In case of hard drive failure, backup copies of video data will be stored for safekeeping as encrypted volumes. Transcripts of the recordings will be transcribed in such a way as to not have any identifying information present. Participation in study visits will take place in a private office. Questionnaires and surveys will not include any personal identifiers.

Participant phone numbers stored by AiCure will be destroyed at the end of the study and will not be used for any non-study purposes or by AiCure staff.

Each patient will assign and maintain their own password for access to the app and any data therein. Any patient-related data stored in the local device, including sexual history data, will be stored in an encrypted state at all times, and will be unencrypted only when access is requested after password confirmation by the user.

9.3 Informed Consent

The informed consent process will conform to local IRB consent standards. Informed consent will be written and obtained at the study site in a private room, before any study procedures are initiated. Potential participants will be given a copy of the informed consent form and the Experimental Subject's Bill of Rights, and a study staff member will offer to review the form with the participant, and answer any questions the participant may have. The informed consent will be witnessed by a member of the study staff. A copy of the signed form will be given to the participant and the original will be kept in a separate, locked file.

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