Full title:

DOT Diary Optimization Pilot Protocol

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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. However, 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.

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. Automated DOT (aDOT), using artificial intelligence with advanced features to detect diversion, combines the accuracy of in-person DOT with the convenience of real-time centralized data collection and monitoring. AiCure has developed a HIPAA-compliant smartphone app which uses artificial intelligence software to automate DOT. The system works through a webcam to automatically confirm that the right patient is taking the right medication at the right time, using security features to identify evidence for cheating; biometrics used to confirm patient identity also protect against duplicate enrollment and multiple registration of users with same or similar names. Medication adherence data are automatically transferred to a centralized cloud-based dashboard for real-time analysis. The AiCure platform has been pilot tested in a variety of clinical settings and populations, including patients with schizophrenia, attention deficit hyperactivity disorder (ADHD), and stroke.[24]

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). 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 not transmitted to the study team and remains on the phone in the password-protected app. 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.

In the next stage of app development, we will conduct the DOT Diary Optimization Pilot to identify areas of the app that require refinement to maximize the acceptability and ease of use of the DOT adherence monitoring app. We will assess overall acceptability and ease of use of the integrated DOT Diary (D^2) app over an 8 week period, elicit feedback on the dashboards used by staff to track PrEP adherence, and assess participant preferences for feedback on non-use or frequent self-reported dosing on the app. The goal of this pilot study will be to refine and optimize the app for further testing in a larger and longer pilot study 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,[25] 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 Optimization Pilot Study Objectives

2.1 Primary Objectives

1. To assess key attributes including acceptability and ease of use of DOT Diary over 8 weeks by MSM on PrEP and identify potential improvements to the app to maximize acceptability
2. To evaluate the quality of execution and persistence of use of the DOT and sexual diary components of DOT Diary by young MSM on PrEP over an 8-week period and identify potential improvements to the app to maximize quality of execution and persistence

2.2 Secondary Objectives

1. To assess participant preferences for feedback on non-use or self-reported dosing that over-rides the DOT Diary app
2. To assess situations and reasons for sub-optimal use of the app, for the purpose of app optimization
3. To get a preliminary assessment of overall PrEP adherence by tenofovir diphosphate levels in DBS among young MSM using the DOT Diary app

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 Atlanta and the San Francisco Bay Area. Although no restrictions are put on the racial/ethnic make-up of the study participants, sites will strive to enroll at least 70% African American or Latino YMSM into this study.

4.1 Inclusion criteria

- Self-identifies as a man
- Age 18-35 at enrollment
- Reports having 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 (not in 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 rapid 4th generation test at enrollment
- Currently taking PrEP or interested in initiating 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
- Meets local locator requirements
- Lives, works or plays in Atlanta Metropolitan Area, San Francisco, Alameda, Marin, Contra Costa, Santa Clara, or San Mateo Counties
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4.2 Exclusion criteria

- 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 8 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.

We will enroll approximately half of the participants who are already on PrEP (n=10) and half who are de novo PrEP users (n=10).

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 over the 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. This will include participants from prior PrEP studies.

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 Optimization 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 required 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 active review and updating of this information at each subsequent visit.
- 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 an optimization pilot study to evaluate and optimize the acceptability, ease of use, quality of execution and persistence of use of DOT Diary among young MSM on PrEP over an 8-week period, and to refine the app to maximize acceptability for longer periods of use (6 months or more) in future studies. We will enroll up to 20 total participants (approximately 10 per city) who are either taking PrEP or willing to initiate PrEP at the enrollment visit. All participants will be provided the DOT Diary app which will be downloaded on to their own personal smartphone and asked to use it over the 8-week study period. Participants will return for follow-up visits at 4 and 8 weeks for study drug provision (week 4 only) 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 software to automate directly observed therapy (aDOT). The system works through a webcam to automatically confirm that the right patient is taking the right medication at the right time, using security features to identify evidence for cheating, as well as biometrics to confirm patient identity and protect against duplicate enrollment and multiple registration of users with same or similar names. Medication adherence data are automatically transferred to a centralized cloud-based dashboard for real-time analysis. These data are encrypted and

stored, creating a real-time audit trail of every dosing; 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. Partner-specific information (e.g. ratings) entered by participants is not transmitted to the study team and remains on the phone in the password-protected app. 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%.

5.3 Provision of PrEP

Enrolled participants will be provided with PrEP in the form of daily oral FTC/TDF, dispensed in 30-pill bottles. Participants who are on PrEP will be asked to use the study supply, as this will eliminate issues with gaps in availability of medication. Participants will be instructed to take one pill orally once daily with or without food. The drug will be provided for 8 weeks (2 bottles total). Two bottles may be dispensed at the enrollment visit to the participant to ensure adequate supply between study visits. If participants experience difficulties in accessing PrEP 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) after study completion to ensure continued access to PrEP. Beginning at the enrollment visit, study staff will assist participants in securing ongoing access to PrEP, including providing linkages to local PrEP-prescribing providers/clinics and assisting participants with benefits and PrEP navigation.

5.4 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.

5.5 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.

5.6 Study procedures

An overview of the study visit 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 $50 stipend. At all visits, study staff will work with all participants to establish continued access to PrEP after completion of the 8-week study. Study staff will assist 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.

Table 1: Study visits and procedures

	SCR	ENR	Weeks 4	Week 8
Obtain informed consent	√			
Obtain demographic, risk data, cell phone compatibility for assessment of eligibility	√			
Locator information	√	√	√	√
Risk reduction counseling, provide condoms and lube	√	√	√	√
Blood tests (HIV 4th gen, creatinine, RPR)	√	√		√
Blood test: HbSAg	√			
Rapid 4th gen HIV test (fingerstick)		√		
Oral, rectal swabs for GC, CT		√		√
Urine for GC, CT		√		√
Medical history, limited physical examination†		√	*	*
Confirm eligibility criteria met		√		
Download app, provide instructions		√		
Dispense TDF/FTC: 1 month of pills (additional month can be administered at enrollment)		√	√	
Observe first dose using DOT (clinic staff) and DOT Diary (app)		√		
Provide PrEP Basics, adherence counseling		√		
Assist with PrEP and benefits navigation		√	√	√
CASI: sexual behavior (baseline, week 4 and 8), DOT Diary use and acceptability (weeks 4 and 8)		√	√	√
DBS collection			√	√
DOT Diary acceptability qualitative interview			√	√
Provide stipend	√	√	√	√

†Medical history and physical exam may be performed at screening and updated at enrollment per site preference

*if indicated

5.6.1 Screening Visit

Participants who express interest in participating in the study will be pre-screened by telephone, according to what is allowed at each site, to avoid unnecessary screening visits. The study is briefly described by telephone, and those participants who remain interested are scheduled for a 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. 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. Participants will also be provided risk reduction counseling, condoms, and lubricant. The participant will be provided a $50 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. An HIV 4th generation rapid test will be performed, and urine and rectal/pharyngeal swabs will be collected for STI testing. 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 be dispensed 1 bottle of TDF/FTC (30 pills). A second bottle may be dispensed to ensure the participant will have enough pills prior to his next visit. Participants will also be 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. Participants will also 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. The participant will be provided a $50 stipend for completion of the enrollment visit. One week after enrollment, study staff

will check-in with participants by phone to see if they are having any issues with using the app or experiencing any problems with taking PrEP.

5.6.3 Week 4

At the week 4 visit, participants will be dispensed 1 bottle of TDF/FTC pills (if not dispensed at enrollment) and complete a CASI assessing sexual and drug use behavior, use of the various components of DOT Diary, and acceptability of the app. Participants will have a medical history and limited physical exam based on symptoms, and their blood collected for DBS. Participants will also complete a qualitative interview to provide additional feedback on the acceptability of various components of the app and how they could be improved. Study staff will review the context and reasons for overriding the DOT component of the app, situations in which the app was particularly easy or difficult to use, and other contextual information to probe how the app might be improved for both acceptability and persistence of use. Participants will also be asked about their use of the diary component, including facilitators and barriers of diary use, communication about protection level, the interface of sexual practices and pill taking, and other contextual information to probe how the app might be further improved.

All qualitative interviews will be audio-taped; portions or whole interviews may be transcribed if they are particularly informative. Between follow-up visits, study staff will reach out to participants by phone or text message in the event of prolonged non-use or multiple overrides of the device. During the qualitative interview, participants will be asked to provide feedback about these contact attempts made by study staff to optimize communication. Based on this feedback and at the direction of the protocol team, the algorithm for follow-up with participants may be adapted during the trial, with the goal of optimizing these escalation algorithms by the completion of the pilot.

5.6.4 Week 8 visit

In addition to the procedures described at the week 4 visit, participants will have blood tests for HIV (4^{th} generation assay), creatinine, and RPR, as well as urine and oral and rectal swabs for GC/CT at the week 8 visit. 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. Participants will also complete a qualitative interview to obtain feedback on the app after 8 weeks of use. In addition to the topics discussed at week 4, participants will be asked about the acceptability and ease of use of the app overall and of different components of the app, 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. As this is the final 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.

After the week 8 visit is complete, staff will also be asked to comment on how well the staff-facing interface worked with each participant, including suggestions for improving the app.

5.6.5 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.

5.6.6 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.

5.6.7 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 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.

5.6.8 Early termination of study participation

Participants may voluntarily withdraw from the study for any reason at any time. The site investigator may, with the approval of the Protocol Team, 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 8 visit procedures should be followed when possible, in the event that a participant chooses to withdraw early from the study.

5.6.9 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 the week 8 visit. 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

5.6.10 Benefits to the subject or future benefits

Individuals may not experience any direct benefits by participating in the research. As part of study participation, participants will be provided up to 5 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 patients 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 a healthcare provider to review the administration, nor would a healthcare provider need to be available at the time the patient

takes their medication. The amount of guidance that the device provides to the patient is automatically reduced as the patient becomes more proficient at using the application.

After the device confirms proper medication ingestion, video recordings will be encrypted and transmitted to a secure centralized location for further analysis. Once received at the centralized location, the data is then removed from the provisioned device (store and forward). The captured data and video is 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 from the AiCure smartphone app will only be available to researchers 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, 2020. 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 patients may also be collected and stored in an encrypted manner. Storing the phone numbers will allow for direct communication with patients, including automated messaging from the Platform device and contact by healthcare providers or other monitoring personnel. At no time is the phone number visible to healthcare providers or monitoring personnel. Individuals outside the clinical sites will not be provided with patient names, nor will they be given access to patient medical records.

Audio-recorded qualitative interviews during study visits 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 key attributes including acceptability and ease of use over 8 weeks of use of DOT Diary by MSM on PrEP and identify potential improvements to the app to maximize acceptability

   Using CASI, we will assess acceptability and ease of use of the app overall and of different components of the app using the Client Satisfaction Questionnaire (CSQ-8), a validated assessment tool assessing various domains of the app with demonstrated high internal consistency across a number of studies,[48] and the System Usability Scale, *a validated 10-measure scale that assesses subjective usability of a system, as well as other measures of acceptability and ease of use of*

the app. Average values of our measures of acceptability and ease of use will be estimated with 95% confidence intervals. *Margins of sampling error (MSEs).* The proposed sample of 20 participants will allow us to estimate means within margins of sampling error (i.e., half widths of 95% confidence intervals) of 0.47 standard deviations (SDs). Areas of refinement of the app will be elicited through qualitative in-depth interviews and analyzed as described below.

2. To evaluate the quality of execution and persistence of use of the DOT and sexual diary components of DOT Diary by young MSM on PrEP over an 8-week period and identify potential improvements to the app to maximize quality of execution and persistence

   We will estimate the average use of DOT and the diary, as proportions of days and weeks on study, respectively. Frequency of use and time spent on different app components will be calculated. *MSEs.* Population proportions will be estimated within MSEs of 13-22 percentage points, depending on the sample proportions.

6.2.2 Secondary Objectives

The secondary objectives of the protocol are:

1. To assess participant preferences for feedback on non-use or self-reported dosing that over-rides the device
2. To assess participant perception of concordance between a review of app data and their actual pill-taking and sexual practices; including reasons for discrepancies
3. To get a preliminary assessment of overall PrEP adherence by tenofovir diphosphate levels in DBS among young MSM using the DOT Diary app

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. [26] Debrief reports and selected transcripts will be reviewed to 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. 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. Negative social impacts will be collected during 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
- 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 4 and 8 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 aDOT 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. 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.

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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