DOT Diary Longitudinal Pilot Statistical Analysis Plan

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Statistical Analysis Plan

Primary Objectives

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.[28] To help with interpretation of these results, retention in the study will at each 6-week visit will be reported. ***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.

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. ***First,*** 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-confirmed pattern of pill-taking over the previous 6 weeks, as assessed using aDOT-confirmed results. In sensitivity analyses, we will include self-reported pill-taking. 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***.*** ***Second,*** we will also use aDOT-confirmed 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. ***Third****,* 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.

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.[29] 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).

Secondary Objectives

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.

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. In the primary ITT analysis, participants will be included in the denominator through 24 weeks, regardless of dropout. In a per-protocol analysis, participants will be omitted from the denominator after dropout. ***MSEs.*** Proportions will be estimated within MSEs of 7-12 percentage points, depending on the sample proportions.

Subgroup analyses. Four pre-specified subgroup analyses will conducted in which interaction terms will be added to the primary GEE logistic models for protective DBS levels, to assess modification of treatment effects by 1. site; 2. age (categorized as <25 and 25+); 3. race/ethnicity, categorized as African American or Latinx vs White or other; and 4. prior PrEP use. Within-subgroup effect estimates will be presented only if the corresponding omnibus test for treatment-subgroup interaction is statistically significant at $P<0.15$, and results will be presented as exploratory.

Exploratory analyses of treatment effect mechanism. Standard per-protocol analyses focused on treatment effects among participants who are adherent to blinded placebo-controlled treatment are not feasible in a context where use of the app is directly tied to pill counts and DBS results. For the same reason, the design also precludes standard mediation analysis assessing treatment effects on the mediator as well as effects on the primary outcome before and after adjustment for the mediator. To better understand how any effect occurs, we will explore associations between aDOT-confirmed pill counts and time spent using the app overall, as well as time spent with the sexual diary, within the intervention arm. In addition, we will assess the relationships among sexual risk, as measured via the diary, pill counts, and DBS results.

Qualitative Data analysis. Recordings of the in-depth interviews (IDIs) will be analyzed using DeDoose 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.[30] 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.