BIOSTATISTICS
RESEARCH CENTER

CCTG 595

A Multicenter, Randomized Study of Text Messaging to Improve Adherence to PrEP in Risky MSM

Statistical Analysis Plan

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1 Introduction

This document describes the statistical analysis plan (SAP) for the CCTG595 clinical trial.

2 Study Design

CCTG595 is a controlled, open-label, two-arm, randomized (1:1) clinical demonstration project to determine if the use of a text message based adherence intervention (iTAB) improves retention and adherence to PrEP compared to standard of care (SoC) PrEP delivery.

The study is expected to enroll a total of 400 subjects. Eligible subjects will include HIV-uninfected men who have sex with men (MSM) and male to female (M to F) transgender individuals who have sex with men at least 17 years of age and who have a recent history of high risk transmission behavior. All subjects will start PrEP with TDF+FTC fixed dose combination given once daily. Subjects will be randomized 1:1 to either the iTAB text messaging adherence reminder intervention with SoC or the SoC alone arm. The randomization will be stratified by clinic site. Subjects placed into the iTAB intervention arm will recieve a personalized, automated texting system to maintain adherence and retention. Both groups will receive access to PrEP in accordance with standardized comprehensive methods of prescribing, risk reduction counseling, adherence counseling, and clinical assessments that include safety monitoring, as well as HIV and STD screening. The study will continue for 48 weeks after randomization of the last participant (up to about 2.5 years).

3 Study Objectives

3.1 Primary Objective

To compare adherence to fixed dose TDF/FTC between subjects randomized to receive SoC plus text message reminders versus SoC, when used for pre-exposure prophylaxis among MSM at high risk for HIV acquisition.

Hypothesis

MSM and transgender M to F having sex with men with high risk of HIV acquisition randomized to the iTAB intervention will have higher adherence to TDF/FTC for PrEP over 48 weeks compared to MSM that have comprehensive SoC alone.

3.2 Secondary Objectives

1. To determine factors associated with poor adherence/lost to PrEP in study participants. Factors will include demographics, ongoing substance use, untreated mental illness, socioeconomic status, low health/HIV and system literacy, fear of disclosure and non-English language.

2. To determine the rate of HIV seroconversion in PrEP users and compare the iTAB to SoC arms for number of new infections as a proportion at 48 weeks and end of the study.

3. To measure acquisition of other sexually transmitted infections (STIs); the proportion of subjects with any new STI at any site will be compared between the iTAB to SoC arms at 48 weeks and end of the study.

4. To evaluate changes in risk behavior after initiation of PrEP (risk compensation) comparing baseline to subsequent visits for number of HIV positive/unknown status partners and any unprotected anal intercourse with an HIV positive/unknown status partner.

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

4 Subject Disposition

4.1 Participant Flow Summary

Tables will summarize the following, by site, by study arm, and overall.

- The number of subjects screened
- The number of subjects screening failed
- The number of subjects randomized
- The number of subjects completed week 48 visit
- The number of subjects completed study
- The number of subjects prematurely discontinued study

Reasons for screening failure and premature discontinuation will be summarized by frequency and category for reason. Listings will also be provided.

4.2 Evaluation of Premature Discontinuation from Study

Proportions of subjects prematurely discontinued the study will be compared between the study arms using Fisher's exact test. The numerator will be the number of subjects who marked other than 'complete the study' as the primary reason in the Termination form. The denominator will be the number of subjects who were randomized.

Time to premature discontinuation will be summarized overall, and by study arm using the method of Kaplan and Meier. The cumulative probablity of premature discontinuation will be estimated overall and by arm, with 95% confidence interval. Log-rank test will compare time to premature discontinuation between randomized arms.

The survival indicator will be defined (1=early discontinued the study; 0=completed the study). The event time and censoring time will be defined from the baseline date to the termination date indicated in the Termination form.

5 Evaluation of Demographics and Baseline Characteristics

Tables will summarize the study population at baseline, overall and by study arm. Descriptive statistics will be presented as N, mean, standard deviation, minimum, 25th Q, median, 75th Q, maximum for continuous variables; frequency tables (row, column percentages) will be used for categorical variables. Statistical comparisons will be performed between randomized arms using Wilcoxon Rank Sum Test (for continuous variables) or Fisher's exact test (for categorical variables). The following variables will be examined at baseline:

- Age
- Race/Ethnicity (White, Black, Hispanic, Other)
- Education
- Household average monthly income
- Inclusion criteria
- STI status
- Language (English vs Other)
- Substance use (SCID screen)
  - Any drug use reported other than alcohol and marijuana
  - Meth use
- AUDIT score
- DAST score
- Sexual Compulsivity Score (SCS)
- HIV literacy score

6 Evaluation of Primary Objective

The primary objective of the study is to compare the adherence to PrEP during the 48-week study period between the iTAB intervetion group and the SoC group.

The primary analysis will be conducted on the modified intent-to-treat (mITT) population (i.e. randomized subjects who started PrEP).

Primary Adherence Endpoint

The primary adherence endpoint will be a binary endpoint (Yes/No) based on DBS samples from two visits (week 12 visit and the last on-drug visit over the 48 weeks). Both visits should have a detectable TFV-DP level >719 fmol/punch (consistent with taking four or more doses per week) to be considered adherent. If the last on-drug visit was at week 12 (i.e. the subject had only one DBS sample), adherence will only be determined by that sample. If a subject discontinued study before week 12 (i.e. had no DBS samples at all), the subject will be considered non-adherent.

Additional Secondary Adherence Endpoints

- Self-reported Adherence: a binary composite endpoint of continued on PrEP and >=90% self-reported adherence to TDF/FTC over 48 weeks. The endpoint will be defined yes if 14 or 15 out of 15 days were reported 'adherent' on the 3-day recall on the clinical assessment form collected at w4, w12, w24, w36, and w48. Note if a subject discontinued the study or missed any visits before w48, those visits will be considered not adherent in the calculation.
- a continuous version of the self-reported adherence measure: defined as percent days that were reported adherent based on the clinical assessment form. In the case where the adherence measure is missing (either due to the subject discontinued PrEP, or missed visit, or other reasons), two approaches will be applied.
  - treat the missing as 'not adherent'. This assumes the worst case (i.e. assume all the missing is related to adherence).
  - ignore the missing. This assumes the best case (i.e. assume all the missing is not related to adherence).
- FTC Adherence: a binary endpoint of having four of four detectable qualitative FTC plasma concentrations (measured at w12, w24, w36, and w48) over 48 weeks. Detectable FTC is defined as a quantitative level of >=0.35 ug/ml consistent with taking a dose in past 24 hours. Note missing will be treated as not detectable.
- Similar outcome as the primary endpoint where we will use the cut-off of >=1246 fmol/punch consistent with taking seven doses per week.
- Proportion of subjects on PrEP at week 48.

Descriptive Analysis

Descriptive analysis will look at self-reported adherence, FTC adherence and TFV-DP adherence measures by visit. Continous outcome will be summarized with N, min, Q1, median, Q3, and max, by study arm and overall. Binary endpoint will be summarized with frequency tables, by study arm and overall. Wilcoxon rank sum test will be used for comparison for continuous outcome; Fisher's exact test will be used for binary outcome.

Statistical Inference

A logistic regression model will be performed to compare the adherence over 48 weeks between the two groups. The model will include baseline factors (refer to the baseline variable list) as covariates if they are found unbalanced between the study arms (with $p<0.1$) and also univariately associated with the outcome ($p<0.15$). Interactions between each of the covariates and study arm will also be assessed individually. Significant interactions ($p<0.05$) will be included in the final model.

7 Evaluation of Secondary Objectives

7.1 Secondary Objective 1

To determine factors associated with poor adherence/lost to PrEP in study participants. Factors will include demographics, ongoing substance use, untreated mental illness, socioeconomic status, low health/HIV and system literacy, fear of disclosure and non-English language.

This objective will be assessed along with the primary objective analysis. The final primary multivariable model will be able to answer this question.

7.2 Secondary Objective 2

To determine the rate of HIV seroconversion in PrEP users and compare the iTAB to SoC arms for number of new infections as a proportion at 48 weeks and end of the study.

Number and proportion of subjects with HIV-seroconversion at 48 weeks will be summarized by study arm and overall. Fisher's exact test will be used for comparison. Same analysis will also look at the rate of seroconversion during the whole study period.

7.3 Secondary Objective 3

To measure acquisition of other sexually transmitted infections (STIs); the proportion of subjects with any new STI at any site will be compared between the iTAB to SoC arms at 48 weeks and end of the study.

Any new STI will be defined as positive results from Gonorrhea (GC) or Chlamydia (CT) at any site or positive syphillis RPR result with titer $>$1:4 based on the STI form collected after baseline visit.

Sensitivity analysis will also be performed looking at STI by testing as well as self-reported STI (outside diagnosis) based on the clinical assessment form.

7.4 Secondary Objective 4

To evaluate changes in risk behavior after initiation of PrEP (risk compensation) comparing baseline to subsequent visits for number of HIV positive/unknown status partners and any unprotected anal intercourse with an HIV positive/unknown status partner.

Descriptive summaries will be provided by visit (at w4, w12, w24, w36, and w48). Wilcoxon signed rank test will be used to compare the number of HIV positive/unknown status partners at each follow-up visit to the baseline visit. GEE model will be used to assess the change in risk behavior over time.

8 Evaluation of Safety Measures

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

9 Software

Statistical software R (version 3.1.1) will be used *http://www.r-project.org*.