MPYA: Monitoring Pre-exposure Prophylaxis for Young Adult Women

Statistical Analysis Plan

Version 2.0
November 4, 2019
NCT02915367

Kathy Thomas, Study Statistician
University of Washington

Jessica Haberer, PI
Massachusetts General Hospital/Harvard Medical School

Jared Baeten, PI
University of Washington

Contents

Introduction

This statistical analysis plan (SAP) details the statistical procedures to address the Primary and Secondary Objectives for the MPYA study. New versions of the SAP will be issued to document updates to the plan. It is expected that subsequent versions of the SAP will include statistical procedures for appropriate Tertiary Objectives as well.

Study Objectives and Summary

Protocol title:	Next generation real-time monitoring for PrEP adherence in young Kenyan women
Short title:	Monitoring Pre-exposure Prophylaxis for Young Adult Women (MPYA)
Design:	Two site, open-label, randomized prospective study
Study arms:	Randomization 1:1 with half to receive daily SMS reminders with the option of switching to SMS reminders only as triggered by missed doses; the other half will receive no SMS reminders.
Population:	Sexually active young women 18-24 years old at high risk for HIV infection who are interested in taking PrEP and have access to personal cellphone.
Sample size:	Approximately 314 women (157 per arm). Up to 350 women may be enrolled.
Follow-up:	2 years per woman, at 1 and 3 months and quarterly thereafter.
Study sites	• Thika, Kenya • Kisumu, Kenya
Primary objective (Aim 1):	Use the next generation Wisepill device in a cohort of young HIV-uninfected Kenyan women initiating PrEP to a. Measure real-time adherence b. Determine the impact of SMS reminders on adherence (daily or triggered)
Secondary Objective (Aim 1):	Use dried blood spot (DBS) tenofovir-diphosphate levels from the same cohort, to examine the same questions as primary objective.
Tertiary Objectives (Aim 2)	Determine the technical function, acceptability, cost, and validity of the next generation Wisepill device coupled with SMS reminders • Feasibility of Wisepill monitoring and SMS reminders • Acceptability of Wisepill monitoring and SMS reminders • Ease of use, health care associated costs, and cost effectiveness of Wisepill monitoring and SMS reminders

(Aim 3) Triangulate Wisepill adherence data with weekly assessment of HIV risk behaviors and perceptions (starting at 6 months) to measure prevention-effective adherence

- Validity of Wisepill monitoring compared to tenofovir concentration in DBS
- Quantified prevention-effective adherence (defined as adherence during periods of risk for HIV acquisition without other forms of HIV prevention)

General Analytic Considerations

Data sources

Data are to be derived from electronic data entry of questionnaire and clinic data into REDCap, as well as data from the Wisepill devices, data indicating SMS message delivery, and, starting 6 months into follow-up, SMS survey results. SAS datasets are created by the statistical team from these datastreams, for use in programming reports and analysis.

Test size and confidence levels

Analyses, including the primary analysis, will be based on two-sided α=0.05 level tests and 95% confidence intervals (CIs). No adjustment will be made for multiple comparisons.

Study size and Power

With 314 enrolled participants, expected mean individual adherence of 70% in the control arm, standard deviation of 30%, and 10% loss-to-followup, the study will provide 80% power using a 2-sided α=0.05 to detect a difference of 10% in mean individual adherence between the two groups.

Exposure and Outcome Definitions

Aim 1 exposure

- Randomization arm
    - Intervention arm for the participant, as assigned at randomization (regardless of receipt of SMS messages, i.e., intention-to-treat).

Aim 1 outcomes

- Wisepill adherence (pill taking)
    - whether bottle was opened on a given day; defined for all days after PrEP was initiated and participant was eligible for PrEP and for which Wisepill device was functioning
- Tenofovir-diphosphate levels in dried blood spots (DBS).
    - Tenofovir detection (Y/N)
    - Tenofovir level, a continuous variable, “not detected” is assigned the value of half the lower limit of detection.

Aim 1 time periods

- From PrEP initiation through the 6 month visit, to assess early use.
    - Precedes initiation of weekly SMS surveys to be sent to participants from 6 months onwards.

- From PrEP initiation to end of follow-up, to assess longer term use.

Aim 1 time interval exclusions

- "Eligible for PrEP": No exclusions other than intervals in which participant was on a safety-related PrEP hold.
- "On PrEP": Exclude intervals participant did not pick up PrEP, whether on a safety-related PrEP hold or any other reason.

Analysis Cohorts and Datasets

In the definitions below, a *cohort* refers to a particular set of participants and a *dataset* defines the time (or time intervals) contributed by participants in a cohort.

- **Screened cohort –** all participants with a screening CRF marked complete. If screened more than once, the final screening attempt will be retained for analysis.

- **Enrolled cohort –** subset of screened, who were enrolled and randomized, excluding any participant terminated from the study when subsequently found to be ineligible at the time of randomization.

    - **Enrolled dataset –** analysis set of all baseline and follow-up data contributed by each participant in the enrolled cohort, regardless of compliance to PrEP

- **Wisepill cohort –** subset of enrolled cohort who provided at least one day of data from a working Wisepill device after initiating PrEP.

    - **Wisepill dataset** – analysis set of all baseline data and follow-up Wisepill data contributed by each participant in the enrolled cohort, regardless of compliance to PrEP. This is dataset excludes days with a nonfunctioning Wisepill device

    - **Wisepill On PrEP dataset** – analysis set of all baseline data and follow-up Wisepill data contributed by each participant in the enrolled cohort, limited to intervals when the participant had begun PrEP and was not on a study drug interruption (i.e., had picked up PrEP from the pharmacy), excluding days with a nonfunctioning WIsepill device. The periods of study drug interruption are determined by the INT CRF recorded start and stop dates of study drug interruptions for any reason.

- **DBS cohort** – subset of enrolled cohort who provided at least one DBS specimen with tenofovir level results after initiating PrEP.

    - **DBS dataset** – analysis set of all baseline data and DBS tenofovir testing results contributed by each participant in the DBS -cohort, regardless of compliance to PrEP.

Interim Monitoring

The DSMB will be responsible for review of operational, endpoint, and other data, including unblinded data, to assess the relative safety and relative effects of the interventions during the trial and monitor the overall conduct of the clinical trial.

Early in protocol enrollment, one or more trial integrity reviews will be performed. Later, one or more formal interim analyses will be performed, to review data relating to relative effects of treatment of the trial outcomes. Both types of review will include overall conduct and patient safety.

The DSMB will provide recommendations about stopping or continuing the trial. The timing of formal interim analyses is yet to be determined. No formal stopping rules have been established.

Analyses

Baseline Data

Recruitment will be described for screened cohort including reasons for ineligibility among those screened.

Enrollment & Demographics by arm will be described for enrolled cohort. Summary statistics (e.g., frequencies, percentages, means, medians, inter-quartile range, minima and maxima) that are appropriate to the measurement scale will be used to describe baseline demographic, behavioral, medical history and contraceptive use history data per tables developed prior to first interim analysis of data. No formal statistical testing will be performed to compare distributions of baseline characteristics between randomized method groups.

Participant Disposition and Retention

The numbers of participants screened, enrolled, and randomized to each regimen will be tabulated by site and by arm. A flow diagram will be provided which presents the numbers and percentages of participants contributing to the Primary Evaluable cohort and retention at each expected study visit. For any participant excluded from the cohort, the diagram will provide reasons for exclusion. For retention:

- "Expected visit" is defined as a visit for which the visit window has closed. If the window had not yet closed, but the participant had attended the visit, the visit is counted as both expected and attended. For participants who die, visit windows closing after a participant's death are excluded.
- "Attended visit" is defined as an attended visit in the Participant Visit Summary (PVS) CRF.

PrEP Use and Drug Interruptions

Numbers of participants in the enrolled cohort who are eligible for PrEP and receiving PrEP, overall and at each specific visit, will be described. Numbers of participants with study drug interruptions, whether for safety reasons or participant preference ("opt out") will be described.

- "Eligible for PrEP" is defined as not on a study drug interruption due to possible seroconversion, renal problems, drug-related AE, breastfeeding, or Site Investigator decisions.
- "Received PrEP" is defined as "participant taking PrEP after this visit" on SUM CRF
- Drug interruptions
    - "Safety-related" = due to possible seroconversion, renal toxicity, AE, breastfeeding or Site Investigator decision.
    - "Participant opt-out" = due to pregnancy, participant opt-out or other.

- Percent of participants with drug interruption will be calculated out of those who initiated PrEP.
- Time on drug interruption calculated from reported interruption start date on INT CRF until PrEP restart date on INT CRF or visit cut date.
- Percent of all study time on drug interruption calculated from time of PrEP initiation until termination or visit cut date.
- Percent of study days with nonfunctioning Wisepill device, among those eligible for PrEP.

The Intervention: SMS Adherence Reminders

To describe the integrity of the intervention, within those randomized to the intervention the number of SMS reminders received as a proportion of those expected will be presented.

Safety

Study-Related Social Harms

Number of study-related social harms will be presented, both as number of events and as number of participants ever experiencing a study related social harm, overall and by arm.

Serious Adverse Events

Number of SAEs will be presented, both as number of SAEs and as number of participants ever experiencing am SAE. Includes reported adverse events graded 4 or 5. This will be presented overall, and by arm.

HIV-1 Seroconversions

Number of HIV-1 seroconversions, person-years, and HIV-incidence will be presented and seroincidence calculated by arm. Although expected to be underpowered for a formal statistical comparison, we will compute a hazard ratio comparing time to HIV seroconversion, using a Cox proportional hazard model; if data are too sparse for the Cox model to run, we will use an exact Poisson regression model instead.

Pregnancies

The number of women becoming pregnant will be presented by arm, with pregnancy incidence, and descriptive statistics of the number remaining on PrEP after becoming pregnant.

- "Participants exposed to PrEP" will be defined as any WisePill opening last menstrual period thru end of pregnancy (or last pregnant observation).
- "Participants continuing PrEP" will be defined as those who indicated plan to take PrEP when enrolling in the pregnancy sub-study.

Protocol Deviations

Protocol deviations will be summarized in frequency tables by site and treatment regimen.

Primary Objective (Aim 1): Determine the impact of SMS reminders using Wisepill device

Co-primary analyses: Adherence in first 6 months

Endpoint	Wisepill adherence (pill taking) in the first 6 months
Cohort	Wisepill
Dataset	Wisepill
Exposure	Randomized arm

Descriptive statistics: Wisepill adherence as % of days with openings, overall, and by arm, will be described, as well as descriptive summaries of individual adherence, including mean, median, and IQR.
Inferential statistics: Wisepill adherence will be statistically compared by arm as rate of pill taking using a Poisson model. The dataset for the model will be structured so that each record = one person during one quarter, with number of events = the number of days a pill was taken, and time = number of days eligible for PrEP. The covariate of interest will be assigned randomization arm, adjusted for study quarter and for site. We will use robust standard errors (generalized estimating equations) methods for the Poisson model, to adjust standard errors for repeated records per person. The model will provide estimates of the incidence rate ratio (IRR), describing the increase in rate of pill taking which is associated with randomization arm. If the variance of the outcome is found to be larger than that expected for a Poisson model (i.e., if individual adherence is overdispersed compared to a Poisson distribution), a negative binomial model will be used instead, which is able to model the increased dispersion.

Co-primary Analysis: Adherence while On PrEP, in first 6 months

Endpoint Wisepill adherence (pill taking) in the first 6 months
Cohort Wisepill
Dataset Wisepill On PrEP
Exposure Randomized arm
Descriptive and Inferential Analyses will mirror methods above.

Adherence throughout follow-up

Endpoint Wisepill adherence (pill taking) throughout follow-up
Cohort Wisepill
Dataset Wisepill
Exposure Randomized arm
Descriptive and Inferential Analyses will mirror methods above, except that the models for statistical comparison will include adjustment for time since enrollment. Pooled data will be used to determine what time categories are reasonable for adjustment considering the relationship of adherence and time (e.g., 0-6m, 7-12m, 13-18m, 19-24m).

Adherence while on PrEP, throughout follow-up.

Endpoint Wisepill adherence (pill taking) throughout follow-up
Cohort Wisepill
Dataset Wisepill On PrEP
Exposure Randomized arm
Descriptive and Inferential Analyses will mirror methods above for adherence throughout follow-up.

Secondary objective (Aim 1): Determine the impact of SMS reminders using biomarker

Adherence by tenofovir in dry blood spots (DBS), in first 6 months

DBS specimens are collected at quarterly visits. A random sample of 15% of study visits will be sent for tenofovir-diphosphate levels testing. Tenofovir levels are not expected to be available until the end of the study, at which point analysis can take place.

Endpoint Tenofovir-diphosphate levels in DBS in first 6 months
(a) Detected (Y/N, binary outcome)

(b) Level (continuous), where if not detectable, value is assigned as half the lower limit of detection.

Cohort DBS
Dataset DBS
Exposure Randomized arm

Descriptive statistics: For dried blood spots collected in the first 6 months of follow-up and while the participant was eligible for PrEP, descriptive summaries will be produced, overall, and by arm, including (a) proportion of DBS at each visit and overall with tenofovir detected, and (b) mean, median, and IQR describing continuous tenofovir levels at each visit, and overall. For overall levels, each participants' individual mean levels will be summarized with mean, median, and IQR over all participants. Separately, we will provide these same descriptive summaries but limited to dry blood spots collected while participant was "On PrEP".

Inferential statistics: (a) Tenofovir detection will be statistically compared by arm using a modified Poisson model with outcome = detection, covariate of interest = assigned randomization arm, adjusted for study quarter and for site, with robust standard errors to handle repeated measurements on each woman and modify Poisson model for use with a binary endpoint; this model will provide estimates of prevalence ratios (PRs), describing the increase in prevalence of detectable tenofovir which is associated with randomization arm. As with our primary analyses, we will use a negative binomial model if appropriate. (b) Continuous tenofovir levels will be compared by arm using a linear mixed model with outcome = tenofovir level, covariate of interest = assigned randomization arm, adjusted for site, and with random effect for participant to appropriately adjust standard errors of parameter estimates for correlated levels in repeated measurements from the same participant.

Adherence by tenofovir in dry blood spots (DBS), throughout follow-up

Endpoint All available tenofovir-diphosphate levels in DBS

(a) Detected (Y/N, binary outcome)

(b) Level (continuous), where if not detectable, value is assigned as half the lower limit of detection.

Cohort DBS
Dataset DBS
Exposure Randomized arm

Descriptive statistics: descriptive statistics will mirror methods for tenofovir in DBS in first 6 months but will provide data for all months with DBS collected, up to 24m.

Inferential statistics: will mirror methods for detection and levels in the first 6 months except that adjustment for time will be added to each model. Choice of form for the time variable will be driven by relationships seen between time and tenofovir detection (or levels, as appropriate).

Tertiary objectives

(Aim 2) Determine technical function, acceptability, cost, and validity of the next generation Wisepill device coupled with SMS reminders

This work will be undertaken by Ruanne and her students and statistical methods are not described here.

- Feasibility of Wisepill monitoring and SMS reminders
- Acceptability of Wisepill monitoring and SMS reminders

- Ease of use, health care associated costs, and cost effectiveness of Wisepill monitoring and SMS reminders

(Aim 3) Triangulate Wisepill adherence data with weekly assessment of HIV risk behaviors and perceptions to measure prevention-effective adherence

We will define prevention-effective adherence as Wisepill adherence during periods of risk for HIV acquisition (i.e. days participant had sex per SMS surveys), without other forms of HIV prevention (i.e., condom use per SMS surveys)

Descriptive statistics: Prevention-effective adherence will be described (% of days taking Wisepill out of days at risk) at each study visit, and overall, summarizing individual level mean, median, and IQR for prevention-effective adherence. Data will also be presented by study arm.

(Aim 3) - Validity of Wisepill monitoring compared to tenofovir concentration in DBS

We will provide descriptive statistics of Wisepill monitoring vs. tenofovir concentration by assigning DBS concentrations into reasonable categories and describe % pills taken in past 30 (?) days per Wisepill within each category.

Initial:

Adherence was categorized as high (>85% or 6+ doses/week; >1,050 fmol/punch), moderate (57-85% or 4-6 doses/week; 700-1,050 fmol/punch), and low (<57% or <4 doses/week; <700 fmol/punch) for electronic monitoring and DBS, respectively.

Relaxed:

Adherence was categorized as high (4+ doses/week; >700-fmol/punch) and low (<57% or <4 doses/week; <700 fmol/punch) for electronic monitoring and DBS, respectively.

We will also compute the Spearman correlation coefficient between continuous DBS tenofovir concentration levels and continuous proportion of days in the prior 30 days that the participant took a pill according to the Wisepill data.