HIV self-testing to improve the efficiency of PrEP delivery

JiPime-JiPrEP Study

Statistical Analysis Plan

Confidential

Version 4.3, 28 March 2022
NCT03593629

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1. Introduction

This document (Statistical Analysis Plan, SAP) describes the planned analysis and reporting for the **HIV self-testing to improve the efficiency of PrEP delivery (i.e., JiPime-JiPrEP) study**, a joint collaboration between the University of Washington and the Jomo Kenyatta University of Agriculture and Technology (R01MH113572, MPIs: Mugo/Ngure). It includes specifications for the statistical analyses and tables to be prepared for the final study reporting.

The planned analyses described in this SAP will be included in future manuscripts. Note, however, that exploratory analyses not necessarily identified in this SAP may be performed to support the analysis. All post-hoc or unplanned analyses which have not been delineated in this SAP will be clearly documented as such in the final study reporting, manuscripts, or any other document or submission.

2. Study rationale

Pre-exposure prophylaxis (PrEP) and HIV-1 self-testing are new and powerful HIV-1 prevention tools; delivering these strategies will require approaches that are time- and cost-efficient, for patients, care providers, and the health care system. In a highly innovative study bringing these two new tools together, we propose to use HIV-1 self-testing to reduce the frequency of clinic visits for persons taking PrEP, and we will evaluate the effectiveness and safety of our approach using a randomized, non-inferiority trial among women and men initiating PrEP in Kenya. We hypothesize that using HIV-1 self-testing to replace frequent clinic visits for persons on PrEP will not reduce PrEP adherence or continuation of use, will be highly acceptable to patients and providers, and will be associated with reduced health system costs.

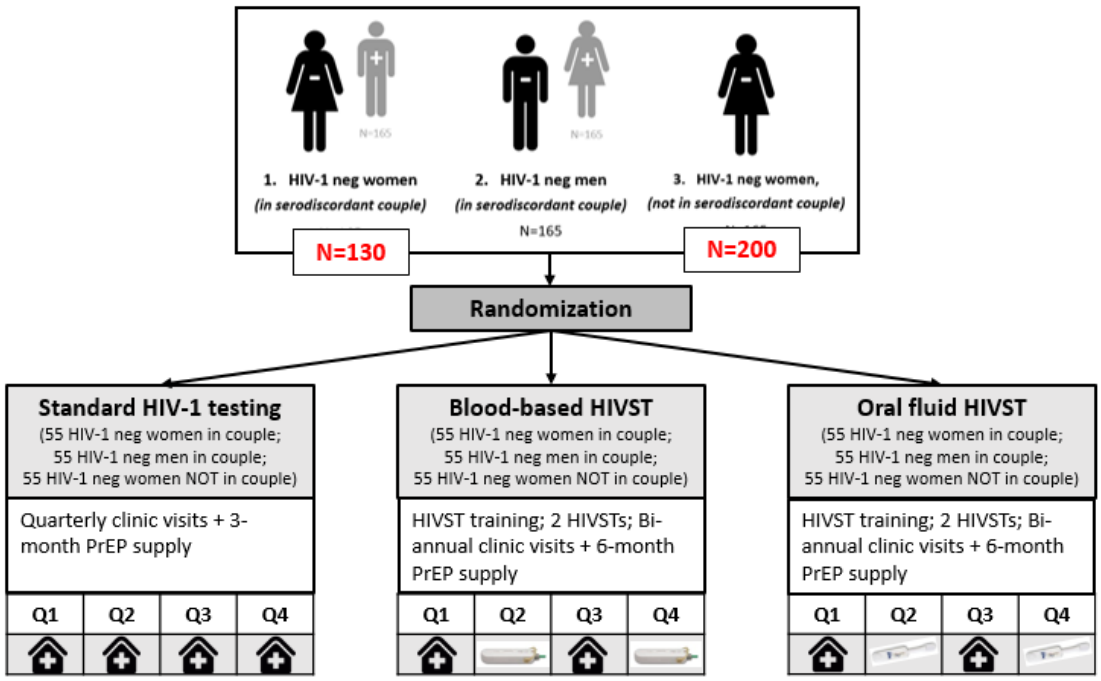
3. Study overview and objectives

3.1. Study overview

Protocol title:	HIV self-testing to improve the efficiency of PrEP delivery
Short title:	JiPime-JiPrEP [test yourself-PrEP yourself]
Design:	This study is a randomized non-inferiority trial
Study arms:	*Intervention:* Reduced clinic visits (6-monthly) with HIV-1 test + HIV-1 self-tests (either oral-fluid or blood-based) and a 6-month PrEP supply *Standard-of-care:* Standard clinic visits (3-montly) with HIV-1 test + 3-month PrEP supply
Randomization:	1:1:1 intervention (blood): intervention (oral fluid): standard-of-care
Population:	women and men who recently initiated PrEP (<1 month), in 3 groups: 1. HIV-1 uninfected men in a serodiscordant couple 2. HIV-1 uninfected women in a serodiscordant couple

	3. HIV-1 uninfected women at HIV-1 risk, not in a serodiscordant couple
Sample size:	495 in total* • 165 HIV-1 uninfected men in a serodiscordant couple • 130 HIV-1 uninfected women in a serodiscordant couple • 200 HIV-1 uninfected women at HIV-1 risk not in a serodiscordant couple ** The enrollment numbers for HIV-1 uninfected women in and not in a serodiscordant couple were adjusted due to challenges in enrolling HIV-1 uninfected women in a serodiscordant couple and to gain additional information on PrEP use in HIV-1 uninfected women not in a known serodiscordant couple – a priority population for HIV-1 prevention services.*
Follow-up:	6 and 12 months (all participants) + 3 and 9 months (standard-of-care only)
Study site:	Single PHRD clinic (Thika, Kenya)
Primary objective:	We will test the use of HIV-1 self-testing to decrease the frequency and burden of clinic visits for PrEP while resulting in equivalent adherence and HIV testing.
Secondary objectives:	We will test whether the use of HIV-1 self-testing affects recent abuse by a sexual partner, the prevalence of depression, participants' self-efficacy, HIV-1 risk-related sexual behaviors, PrEP disclosure, and HIV testing preferences, compared to standard-of-care PrEP delivery (a 3-month PrEP drug supply).

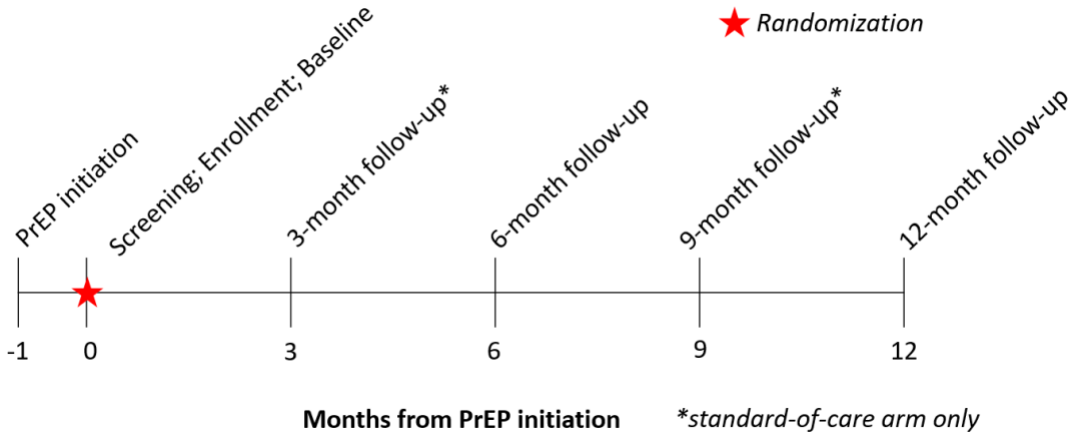
3.2. Study design



3.3. Eligibility criteria

Inclusion criteria	Exclusion criteria
• Age >= 18 years • HIV-1 uninfected (rapid test) • Not currently enrolled in other trial • Taking PrEP (1 month) and planning to continue • Willing to be randomized to one of the study arms	• Unable to provide written informed consent • Contraindication to use TDF+/-FTC/3TC

3.4. Study visits



4. Study endpoints

We have registered all primary and secondary trial outcomes on ClinicalTrials.gov (ID: NCT03593629)

4.1. Primary objective outcomes

4.1.1. Primary

The primary objective will be tested using three primary outcomes: 1) HIV-1 testing, 2) persistence in refilling PrEP, and 3) PrEP adherence (all measured at 6 months). We selected the 6-month measurements for our primary outcome measurements because for participants in serodiscordant couples, their sexual partner might have achieved HIV-1 viral suppression by 6 months, as which time there may no longer be a need for the HIV-1 uninfected partner to continue using PrEP.

In order to include all randomized participants when analyzing primary endpoints, we will impute those not contributing a response at the 6 month time point as not achieving the outcome (i.e., we will impute missing data = "fail" for each outcome). This means that those who do not return to study visits (are not "retained" at the study visit) or for other reason do not contribute a response, are counted as not achieving the outcome.

Retention window (6 months): While most participants return for follow-up close to the scheduled 6-month visit date, operationally the scheduling window for this visit opens 2 weeks prior this scheduled visit date and closes 2 weeks before the next scheduled visit date (at 270 days post enrollment for participants in the SOC arm and at 360 days post enrollment for participants in the HIVST arms). For the purposes of analysis, we will use follow-up visits assigned as 6-month visits by study staff (using the guidelines above) for our primary analysis. Additionally, we will analyze an "on-time retention" window, defined as less than 21 days post the scheduled 6-month visit date. While the "on-time retention" window is less inclusive, it has the benefit of being the same window in both intervention and control groups.

HIV-1 testing[1]:	Any self-reported HIV-1 testing (in-clinic tests and home tests, if applicable), between the enrollment and 6-month visit (binary outcome = yes/no, denominator = all randomized subjects, missing = no).
Persistence in refilling PrEP[1]:	The proportion of enrolled participants (binary outcome = refilled/not refilled, denominator = all randomized subjects, missing = not refilled) that return to the clinic and refill their PrEP medication, measured using clinic electronic dispensing data.
PrEP adherence[1]:	Adherence to PrEP will be measured by concentrations of tenofovir diphosphate (TFV-DP) in a 3 mm punch from a dried blood spot by liquid chromatography tandem mass spectrometry (LC-MS/MS) at the participant's 6-month visit. We will measure PrEP adherence using DBS samples in two ways: • [Primary]: Any detection of TFV-DP (above the limit of quantification) (binary outcome = yes/no, denominator = all randomized subjects, missing = not detected) • [Secondary]: Concentration of TFV-DP ≥700 fmol (binary outcome = yes/no, denominator = all randomized subjects, missing = not detected)

[1]We will measure these outcome for both the as-assigned" retention and "on-time" 6-month retention windows (described above) and assume missing = fail.

4.2. Secondary outcomes

We will additionally test whether, compared to SOC PrEP delivery (a 3-month PrEP drug supply), the delivery of a 6-month PrEP drug supply + HIVST affects the primary outcomes (described above) when evaluated at 12 months. We will also measure the effect of the interventions on other secondary outcomes, including: recent abuse by a sexual partner, the prevalence of depression, participants' self-efficacy, HIV risk-related sexual behaviors, PrEP disclosure, and HIV testing preferences at 6 and 12 months.

For the secondary outcomes that are the same as the primary (e.g., HIV-1 testing, persistence in refilling PrEP, and PrEP adherence), we will measure the outcomes in the two different retention windows (described in section 4.1.1), and assume missing = failure. For the secondary outcomes that are unique from the primary outcomes, we will use both 6- and 12-month measurements and will not restrict any analyses to the 'on time' windows and will not impute missing values as failures.

If PrEP is discontinued by the treating clinician for safety reasons (but not adherence reasons), follow-up thereafter will be censored, since the subject will not be able to be assessed for adherence to PrEP.

HIV-1 testing[1]:	1. Any self-reported HIV-1 testing (in-clinic tests and home tests, if applicable), past 6 months 2. Two or more self-reports of HIV-1 testing between the enrollment and 12-month visit (binary outcomes = yes/no, denominator = all randomized subjects, missing = no).
Persistence in refilling PrEP[1]:	1. The proportion of enrolled participants that return to the clinic and refill their PrEP medication, measured using clinic electronic dispensing data, at their 12-month visit. 2. The proportion of enrolled participants that return to the clinic and refill their PrEP medication, measured using clinic electronic dispensing data, at both their 6- and 12-month visits. (binary outcomes = refilled/not refilled, denominator = all randomized subjects, missing = not refilled)
PrEP adherence[1]:	[See definition in primary outcomes sub-section]
HIV-1 incidence:	The proportion of participants (binary outcome) that test HIV-1 positive since trial enrollment (we expect this to be very low due to our small sample size, especially considering that all participants are prescribed PrEP). We will assess prevalence of genotypic HIV-1 drug resistance among any seroconverters.

Recent abuse, by sexual partner:	The proportion of participants (binary outcome) that self-report verbal, physical, or emotional abuse by a sexual partner.
Prevalence of depression:	The proportion of participants (binary outcome) that report depressive symptoms. Determined using the Patient Health Questionnaire-9 item (PHQ-9) depression scale. A 0-27 point scale where scores 10 or greater can be categorized as likely depression.
Self-efficacy:	Measured using the General Self-Efficacy Scale (GSE), which is correlated to emotion, optimism, work satisfaction, to measure self-efficacy. The scale ranges from 10-40 points - higher scores indicate more self-efficacy (continuous outcome).
Number of sexual partners:	Self-reported number of sexual partners in the past month (numeric outcome).
Inconsistent condom use:	Measured by asking participants how many times they had sex in the past month and how many times a condom was used. If condoms were not used every time, condom use was categorized as inconsistent (binary outcome).
PrEP disclosure:	The proportion of participants (binary outcome) that report that at least one other person (besides one's main sexual partner in serodiscordant couples) is aware they are taking PrEP.
HIV-1 testing preferences:	Participants report their preference for HIV testing from the following options: blood-based HIV-1 self-testing, oral-fluid HIV-1 self-testing, and HIV testing at a standard health care clinic (categorical outcome).

[1]These outcomes (same as the primary, but measured at 12 months) will be measured at 12 months only.

5. Sample size justification

5.1. Original sample size calculation

Primary analyses: The trial will be powered for the primary adherence outcome (measured using any detection of TFV-DP in dried blood spots) at 6 months. Based on our prior work in HIV-1 serodiscordant couples and women at HIV risk, we estimate ~80% among those seeking to initiate PrEP will achieve blood levels consistent with high PrEP adherence. Thus, if PrEP adherence is 80% in both the standard of care and self-testing arms, with 10% loss-to-follow-up, a one-sided 95% confidence interval (common for non-inferiority trials), and a 10% non-inferiority margin, the planned sample size of N=495 (N=330 HIVST arms, N=165 SOC arm) provides 80% power. A 10% non-inferiority margin has been chosen as an important reduction in PrEP use that might be tolerated in order to gain programmatic efficiency through HIV-1 self-testing. Counting those LTFU as nonadherent means all participants randomized contribute.

Sub-group analyses. We planned for three sub-group analyses with: 1) HIV-1 serodiscordant couples (including 165 men and 130 women, 295 participants in total), 2) women (including 130 in serodiscordant couples plus an additional 200 women at risk, 330 women in total), and 3) women outside of serodiscordant couples (including 200 women at risk). The sub-analyses in serodiscordant couples and in all women will have 80% power to rule out a 12% decrease in PrEP adherence (i.e., a slightly greater non-inferiority margin).

We recognize that women outside of serodiscordant couples (N=200) may face unique adherence challenges and less frequent follow-up could be truly inferior to quarterly follow-up; thus, we also plan a superiority analysis for these women. In this analysis, we will have 80% power to detect a decline in PrEP adherence from 80% to 66% (14% lower) with self-testing.

5.2. Sample size re-calculation

Primary analyses: The primary adherence analysis has been redesigned to impute those LTFU as nonadherent, so that all participants randomized will contribute to the analysis. With a 10% non-inferiority margin, if PrEP adherence is 80% in both the standard of care and self-testing arms, our total sample size of N=495 will provide 83.6% power to rule out a greater than 10% decrease in adherence. However, counting those missing as nonadherent will likely lead to <80% considered adherent. If 70% are adherent in each arm, we will have 74% power to rule out more than a 10% difference. While power <80% is not ideal, the trade-off of including all participants in the analysis is an important consideration in this implementation science study.

Sub-group analyses. We have revised our plan to use the same clinically important non-inferiority margin of 10% for the subgroups. Power is not high when limited to any one subgroup, as is common in a clinical trial powered for analysis in the entire study population: if we assume PrEP adherence is 80% in SOC, to rule out a 10% decrease in PrEP adherence we will have 65% power among HIV-1 serodiscordant couples (N=295), 69% power among all women (N=330) and 51% power among women outside of serodiscordant couples (N=200). If we assume PrEP adherence is 70% in SOC, power will be 55% among HIV-1 serodiscordant couples, 59% among all women. and 43% among women outside of serodiscordant couples. Among the women outside of serodiscordant couples (N=200), we will also have 80% power to detect a decline in PrEP adherence from 80% to 59.8%, or from 70% to 48.4%.

6. Randomization and masking

6.1. Randomization

Randomization details. A list of sequential randomization assignments will be prepared for each study population: 1) HIV-1 uninfected men in HIV-1 serodiscordant couples, 2) HIV-1 uninfected women in HIV-1 serodiscordant couples, and 3) HIV-1 uninfected women at-risk for HIV-1 who are not in disclosed HIV-1 serodiscordant couples. Randomization will occur in a 1:1:1 fashion to: 1) blood-based HIV-1 testing at home (2 test kits distributed at each clinic visit) and in-clinic follow-up visits (including in-clinic testing) every 6 months, 2) oral-fluid HIV-1 testing at home (2 test kits distributed at each clinic visit) and in-clinic follow-up visits (including in-clinic testing) every 6 months, or 3) HIV-1 testing at in-clinic follow-up visits (including in-clinic testing) every 3 months (standard-of-care).

Randomization list. The randomization list was prepared using variable-sized blocks by a UW statistician and is stored in a password-protected electronic file on a UW server. The randomization list consists of a unique identifier for each study population and participant (see Section 7.2), together with the assignment to study arm.

Randomization implementation. Randomization will be done at the enrollment visit, which will occur approximately one month after the participants have begun taking PrEP. At the time of randomization, participants will open on opaque randomization envelope, given to them by a study pharmacist, that has their study arm assignment inside.

6.2. Masking

This study is unmasked. To minimized implementation bias, we have implemented procedures that standardize participant contact across the study arms:

Follow-up period	Standard-of-care arm	HIV self-testing arms
3-month	★	--
6-month	★	★
9-month	★	--
12-month*	★	★

-- **DO NOT** contact participants because they do not have a scheduled visit

★ Standard clinical procedures for reminding individuals of their appointment: Call one day after missed scheduled visit date then repeat seven days after the first call. An alternative contact, as listed in the locator form, will be called during the second week (after the repeat call made 7 days after the first attempt to contacting participant) if participant fails to answer phone calls from the clinic.

*At 12-months, if participants do not returned for their scheduled clinic visit after standard contact procedures have been implemented and 3 months have passed, we will note this and engage in more

intensive efforts to follow-up with this participants (including home visits) so that we can collect end-line data (including a DBS sample) from participants.

7. Data collection

7.1. Database

All quantitative data will be collected electronically in face-to-face interviews with trained Thika HIV-1 counselors, clinicians, and pharmacists. We will use CommCare (Dimagi, Cambridge, USA), an electronic data collection platform, to collect the quantitative data and will upload this data to CommCare's secure server daily. A team of data experts in both Thika and Seattle will monitor the data as it is coming in, and Seattle team will generate weekly data quality reports that will be shared with the Thika team for review and feedback.

7.2. Participant identifiers

Participant identification numbers have the following format: **53-18-XXX-Y-Z**.

53	Thika site code
18	Protocol number
XXX	Sequential digits, specific to participant groups: • **001-300** = HIV-1 negative men in serodiscordant couples • **301-600** = HIV-1 negative women in serodiscordant couples • **601-999** = HIV-1 negative women not in serodiscordant couples
Y	Specifies participant group: • **1** = HIV-1 negative men in serodiscordant couples • **2** = HIV-1 negative women in serodiscordant couples • **3** = HIV-1 negative women not in serodiscordant couples • **4** = HIV-1 positive women in serodiscordant couples • **5** = HIV-1 negative man in serodiscordant couple
Z	Check digit, a random number: **1-9**

8. Statistical considerations

8.1. Missing data

For all primary outcomes (e.g., HIV-1 testing, persistence in PrEP refilling, and PrEP adherence) we will assume that missing equals failure; for participants not retained in the relevant 6-month (or 12-month) retention windows described in section 4.1.1, the response will be considered

missing (and therefore failure). As a potential sensitivity analysis, we may impute missing outcomes using information gleaned through extensive follow-up of participants who miss their 12-month PrEP visit and phone-based surveys conducted during the periods of COVID-19 lockdown, and controlling for potential confounders in our analyses.

8.2. Multiple comparisons

An alpha of 0.05 will be used for the primary analyses and pre-specified secondary analyses. For pre-specified secondary analyses, we will report both the p-value and the number of pre-specified analyses performed.

8.3. Analysis sets

Data sets. Data sets for analysis will be produced by Katrina Ortblad, Dorothy Mangale, and Ashley Bardon. They will be .dta or .csv files containing a single header line whose variable names match those coded in CommCare. All missing values will be coded using "999". Codes for categorical variables (e.g., 0 for "No" and 1 for "Yes") will be used instead of character strings whenever possible.

Data codebook. A detailed codebook will be prepared, containing for each variable the form from which the variable derived, the text of the question, and all possible values for that variable with their coding. All codes and character strings representing categorical factors will be defined in the codebook.

9. Interim monitoring

The study will be monitored by a Data Scientific and Monitoring Board (DSMB) approximately every six months. The project director and statistician will generate both an open and closed report (statistician only) that will be shared with the DSMB prior to the meeting. The DSMB will give recommendations based on the report and accompanying presentation, and all recommendations and meeting minutes will be reported to the UW and Kenyan IRBs.

10. Data analysis

10.1. Overview of data analyses

Analyses. All analyses comparing randomization arms will be by intention-to-treat. The primary comparison will be self-testing versus clinic testing; the two self-testing modalities will be analyzed together (versus SOC in-clinic testing) because we hypothesize that the effect on

adherence and other outcomes relates to the use of self-tests and frequency of follow-up, not the self-test modality.

Model adjustments. Models comparing randomized arms will include study arm as the primary predictor in the model, and will adjust only for study population (male in partnership, female in partnership, or female not within partnership). Supplemental, adjusted analyses also will be performed where potential confounders are found to differ at baseline. Potential confounders considered will be based on our prior work assessing correlates of PrEP use: demographics (e.g., gender, age, educational level), sexual behaviors (e.g., condom use, outside partnerships), medical status (e.g., depression), and beliefs (e.g., risk perception, PrEP efficacy). Models containing more than one time point (e.g., 6 month and 12 month data in one analysis) will adjust for time point.

Significance. Significance will be assessed using a two-tailed test at the 0.05 level.

10.2. Baseline characteristics

Baseline characteristics will be described by study arm and study population. These will include demographic variables, HIV-1 testing history, sexual behaviors, and history of intimate partner violence.

10.3. Analysis of primary objective outcomes

To test the study's primary objective we will evaluate non-inferiority of the combined HIVST groups against SOC, for each of the primary objective outcomes: 1) self-reported HIV-1 testing, 1) persistence in refilling PrEP, and 3) PrEP adherence (any detection of TFV-DP in DBS samples) at 6 months. At 6 months, we will measure these outcomes using two different retention windows: 1) "as-assigned" retention and 2) "on-time" retention. If participants are not retained in care (i.e., the outcome is missing when visit is restricted to the specific retention window), then we will impute the outcome as described in *section 4.1,* describing primary endpoints.

The proportion of participants with each outcome in each of the retention windows will be described by randomized group. Our hypothesis is that the combined HIVST groups will be non-inferior to the SOC group for each of the specified primary objective outcomes. Statistical comparison will be a one-sided non-inferiority comparison, using a binomial regression model with identity link to estimate the risk difference (RD) for the outcome in the HIVST arm compared to SOC. If we encounter problems with model convergence, we will instead use a linear regression model (Gaussian errors and identity link) modified with robust standard errors to allow valid inference in the context of misspecification of the error structure as Gaussian rather than binomial. If the one-sided 95% CI for the RD (HIVST – SOC) excludes values below -10%, then the results will be interpreted as showing that the HIVST groups were non-inferior to SOC. If the 95%

CI includes values below -10%, then HIVST is not non-inferior. We will test different retention windows in various sensitivity analyses, including a sensitivity analysis where outcomes are not restricted to different retention windows.

(SOURCE: Naimi AI, Whitcomb BW. Estimating risk ratios and risk differences using regression. *American Journal of Epidemiology.* 2020; 189(6):508-510)

Secondary outcomes consisting of the same outcomes as above, but applied to the 12 month visit, will be conducted using the same methods as the primary outcomes at 6 months. Additionally, we will conduct secondary analyses that compare primary outcomes for individuals in each arm vs. each other arm.

10.4. Analysis of secondary outcome variables

<u>*Binary outcomes*</u> (*HIV-1 incidence, recent abuse by a sexual partner, prevalence of likely depression, inconsistent condom use, PrEP disclosure*). We will report the proportion of participants reporting these binary outcomes by randomized group and use a binomial regression model with identity link to estimate the RD and two-sided 95% CI for each outcome in the HIVST arm compared to SOC at 6 and 12 months.

<u>*Continuous outcomes*</u> (*self-efficacy, number of sexual partners*). We will report means, medians, and interquartile ranges by randomized group for these continuous outcomes, and use multivariable linear regression models, adjusting for the corresponding baseline measure (self-efficacy, number of sexual partners), to estimate effect size estimates as differences in means and two-sided 95% CIs at 6 and 12 months.

<u>*Categorical outcomes*</u> (*HIV-1 testing preference*). We will report the proportion of participants reporting the preference for clinic-based HIV-1 testing versus HIVST (combining the preferences for oral-fluid and blood-based HIVST), and also report the proportion of participants reporting the preference for oral-fluid versus blood-based (combining the preferences for clinic-based and blood-based HIVST) HIV-1 testing. We will report these proportions by randomization groups and use a binomial regression with identity link to estimate RDs and two-sided 95% CIs at 6 and 12 months.

10.5. Sub-group analyses

The following populations and sub-groups that are planned for analysis for any of the primary or secondary outcomes described above include:

- Participants in HIV-1 serodiscordant couples (N=295)
- Women (including those both in and not in HIV-1 serodiscordant couples) (N=330)
- Women not in HIV-1 serodiscordant couples (N=200)
- Age (<30 years & ≥30 years)
- Pre-COVID-19 period (pre 3/28/2020) & Post-COVID-19 period (post 3/28/2020) (exploratory)*
- Participants in HIV-1 serodiscordant couples who continue to be at risk for HIV acquisition at 12 months (exploratory)**

*We will compare data pre- and post-emergence of COVID-19 with time-varying covariates to understand if COVID-19 modifies the effect of the intervention on study outcomes. Since all participants had completed enrollment prior to the onset of COVID-19 in Kenya (3/28/2020), we will just look at the differences for the pre- and post-COVID-19 periods at 6 and 12 months. Because almost all participants had completed their 6-month follow-up visits when COVID-19 emerged in Kenya, we will likely be underpowered to measure differences between these sub-groups at 6 months.

**We will conduct this sub-group analysis only at month 12. In this sub-group analysis, we will exclude women not in HIV-1 serodiscordant couples and participants who have discontinued PrEP due to any of the following reasons (following Kenya standards for PrEP discontinuation): the participant is no longer in an HIV-1 serodiscordant partnership, the participant's HIV-positive partner has initiated and sustained ART for >6 months, or the participant's HIV-positive partner has achieved HIV viral suppression.

For the sub-groups above, the same models described above will be used at 6 and 12 months. The same non-inferiority margin of 10% will be used. Given that subgroup analyses do not have strong power, any failure to show non-inferiority in a subgroup will be considered in the context of the estimated RD and the point estimate and CI for the overall RD in the trial.

10.6. Sensitivity analysis

We will conduct a sensitivity analysis among participants in HIV-1 serodiscordant couples at 12 months to evaluate the effect of the intervention on the secondary outcomes defined above, as well as PrEP discontinuation due to a change in HIV risk following Kenya standards for PrEP discontinuation. In this analysis, we will categorize all secondary outcomes as having been achieved for participants who have self-reported discontinuing PrEP at 12 months for any of the following reasons: the participant is no longer in an HIV-1 serodiscordant partnership, the participant's HIV-positive partner has initiated and sustained ART for >6 months, or the participant's HIV-positive partner has achieved HIV viral suppression. We will report the proportion of participants reporting these binary outcomes by randomized group and will use a

binomial regression model with identity link to estimate the RD and two-sided 95% CI for each outcome in the HIVST arm compared to SOC at 12 months.

Adverse Events

The total number of adverse events will be reported by arm, by grade. The proportion of participants with the following events will be compared using a Fisher's exact test:

- Physical violence, assault, or abuse
- Non-physical harassment or assault
- Unintentional or unauthorized disclosure of HIV status
- HIV self-test kit misuse (e.g., incorrectly using the HIV self-test kit)
- Suicidal thoughts or ideation
- Death

Serious adverse events (including any instance of violence, suicidality, or death) will be reported to the DSMB within 24 hours, including a report of the circumstances surrounding the adverse event. The randomization arm of the participant will be communicated from Katherine Thomas (the study statistician) to the DSMB.

All serious and non-serious adverse events will be included in interim and final monitoring reports.

11. Changes to the SAP after unblinding

A summary of changes that have been made to the SAP after unblinding is presented below. All changes are in bold.

Date: Versions	Change(s)	Reason for Change(s)
15 Dec 2021: Version 4.0 to version 4.1	**Page 14 of 18 (Section 10.4, Analysis of secondary outcome variables)** was updated to indicate that risk differences will be presented for the secondary analysis outcome variables instead of relative risks and that the effect size for each secondary outcome variable would be estimated at two timepoints: months 6 and 12. We also clarified that 95% CIs for these outcomes will be two sided**.**	We have revised the effect size estimates for secondary variables to present risk differences to be consistent with the primary outcome estimates. We have also revised the analyses to estimate separate effect sizes for months 6 and 12, as we predict that the outcomes at these timepoints are not correlated and will actually be different. Kenyan guidelines recommend that people in

		serodifferent partnerships discontinue PrEP after their HIV-positive partner has been on ART for at least 6 months. Therefore, we predict that many people will discontinue PrEP for this reason by month 6, and outcomes at month 12 will likely be different. Additionally, we have clarified that the 95% confidence intervals for these effect size estimates will be two-sided, as these analyses are not intended to establish noninferiority of the intervention as our primary outcome comparison does.
	Page 7 of 18 (Section 4.2, Secondary outcomes) was revised to update the definition of PrEP adherence at 12 months for participants in an HIV-1 serodiscordant couple. These participants will not be counted as adherent to PrEP at 12 months if they discontinue PrEP because their HIV-positive partner has initiated and sustained ART for >6 months.	We have revised the secondary outcome definition for PrEP adherence at 12 months, as we do not anticipate that the intervention will have an effect on HIV-positive partners' ART adherence; therefore, we anticipate PrEP discontinuation due to this reason will be equally distributed across study arms since the number of participants in HIV serodiscordant partnerships is the same for each study arm. Instead, we will discuss the potential limitations of our analyses when we present the findings, and we have added a subgroup analysis and a sensitivity analysis to better understand the effect of the intervention on PrEP discontinuation.
	Page 15 of 18 (Section 10.5, Sub-group analyses) was updated to include an additional exploratory analysis among participants in HIV-1 serodiscordant couples who continue to be at risk for HIV acquisition at 12 months.	In this subgroup analysis, we will exclude singly enrolled women and participants who discontinue PrEP at 12 months due to no longer being in an HIV-1 serodiscordant partnership or if their partner has sustained ART for >6 months or achieved viral suppression. This analysis will evaluate the true association between the intervention and PrEP refilling and

		adherence by removing the effects of partners' behaviors on HIV risk.
	Page 15 of 18 (Section 10.6, Sensitivity analysis) was updated to include a sensitivity analysis among HIV-1 serodiscordant couples in which all secondary outcomes at 12 months among those who have discontinued PrEP following Kenya guidelines (i.e., due to no longer being in an HIV-1 serodiscordant partnership or if their partner has sustained ART for >6 months or achieved viral suppression) will be classified as having been achieved.	This sensitivity analysis was added to determine if the effects of the intervention change when discontinuing PrEP due to a reduction in HIV risk is also counted as a success.
12 Jan 2022: Version 4.1 to version 4.2	**Page 7 of 18 (Section 4.2. Secondary outcomes)** was revised to change the definition of the secondary outcome of 'persistence in refilling PrEP at 12 months' to reflect the same measure at 6 months. The definition was changed from 2 outcome measures: (1) Any PrEP refill in past 6 months and (2) Two or more PrEP refills between enrollment and 12-month visit.	We've changed the definition of this measure back to the definition of the variable from an earlier version of the SAP, which was the correct definition. We have also added an additional outcome measure to determine the persistence in PrEP refilling at both 6- and 12-month visits.
28 Mar 2022: Version 4.2 to version 4.3	**Page 14 of 18 (Section 10.4. Analysis of secondary outcome variables)** was revised to also report means for each continuous outcome and to remove the language about mixed linear regression models.	We have fixed two errors that were discovered for the analyses of continuous outcomes.