STATISTICAL ANALYSIS PLAN

Improving HIV prevention among heterosexual cisgender men seeking STI services in sub-Saharan Africa: examining the benefits, acceptability, and associated costs of a systems-navigator-delivered integrated prevention package

HPTN 112, Protocol Version 2.0

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1. LIST OF ABBREVIATIONS AND ACRONYMS

Term/Abbreviation	Definition
DBS	Dried blood spot
DSMB	Data and Safety Monitoring Board
GEE	Generalized estimating equation
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IDI	In-depth Interview
IND	Investigational new drug
INT	Intervention
ITT	Intent-to-treat
KS	Key stakeholders
LAI	Long-acting injectable
MCAR	Missing completely at random
PP	Per-protocol
RD	Risk difference
SAP	Statistical Analysis Plan
SMC	Study Monitoring Committee
SN	Systems Navigation
SOC	Standard of Care
STI	Sexually Transmitted Infection
TFV-DP	Tenofovir-diphosphate
TLFB	Timeline Follow-back

2. INTRODUCTION

This statistical analysis plan (SAP) details the statistical procedures that address the primary study objectives specified in Protocol HPTN 112: Improving HIV prevention among heterosexual cisgender men seeking STI services in sub-Saharan Africa: examining the benefits, acceptability, and associated costs of a systems-navigator-delivered integrated prevention package. A description of secondary analyses is included. New versions of the SAP will be issued to document updates and changes in the plan. Any meaningful changes or additions to this SAP (e.g. in response to protocol amendments or violations of assumptions underlying pre-planned analyses) will be documented in section 15 of the SAP. Analysis plans for secondary analyses not anticipated prior to study completion will be developed as separate documents.

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Formal interim monitoring will not be implemented in the study due to the short enrollment window and limited follow-up period and considering the minimal risk of the intervention to participants. The Study Monitoring Committee (SMC) will review summary information related to safety, study conduct, and preliminary endpoints, but those reports will not include any formal statistical analyses.

2.1 General Design Considerations

2.1.1 Purpose

To evaluate the potential benefit(s), acceptability, and associated costs of a systems navigator-delivered HIV prevention intervention in promoting and supporting persistent use of evidence-based HIV pre-exposure prophylaxis (PrEP) among heterosexual cisgender men receiving care for sexually transmitted infections (STIs) in Lilongwe, Malawi.

2.1.2 Design

Single site pilot effectiveness-implementation hybrid type 1 trial.

2.1.3 Population

The study population will consist of the following participation types:

1. HIV seronegative heterosexual cisgender males seeking STI services who have accepted PrEP services.

2. Other key stakeholders relevant to systems navigation program implementation. Work related to this population is entirely qualitative and will not be addressed in this SAP.

2.1.4 Study Size

Approximately 200 heterosexual cisgender males, presenting as HIV-seronegative and initiating PrEP (followed prospectively) and approximately 15 other key stakeholders.

2.1.5 Study Duration

The proposed study duration is 15 months (65 weeks), including up to 39 weeks for participant recruitment. Seronegative participants will be on study for at least 26 weeks, and up to 52 weeks depending on the date of enrollment.

The visit window schedule is included in the following table.

Visit	Target Visit Day	Target Visit Window	Target Visit Window Days	Allowable Visit Window
Eligibility Determination	--	--	Up to 7 days before enrollment	--
Enrollment	Day 0	--	0	0
Week 13	Day 91	-21/+21	Day 70 – 112	Day 70 – 153
Week 26	Day 182	-21/+21	Day 161 – 203	Day 154 – 244
Week 39 (optional)	Day 273	-21/+21	Day 252 – 294	Day 245 – 336
Week 52 (optional)	Day 365	-21/+21	Day 344 – 386	Day 337 – 427

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2.1.6 Study Location

The study location will be Bwaila STI Clinic, Lilongwe, Malawi.

2.1.7 Study Regimen

Systems navigation integrated into PrEP services delivered at an STI clinic in promotion of persistent effective PrEP use – either daily oral, 2-1-1 event driven, or injectable.

Navigators will:

- Conduct brief counseling (and risk-focused) sessions,
- Conduct POC STI testing,
- Assess barriers of PrEP use, and trace persons who default from PrEP care to facilitate PrEP re-engagement, offering PrEP "restart" kits as appropriate.

2.2 Study Objectives and Endpoints

2.2.1 Primary Objective(s)

- To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among heterosexual cisgender men seeking STI clinical services in Lilongwe, Malawi at 26 weeks.
- To assess acceptability and barriers of implementing a systems-navigator delivered HIV prevention package among key stakeholders in the clinic and heterosexual cisgender men initiating PrEP at STI clinics.

2.2.2 Secondary Objective(s)

- To assess feasibility of a future randomized controlled trial.

2.2.3 Exploratory Objective(s)

- To assess prevention-effective PrEP use among heterosexual cisgender men initiating PrEP at STI clinics.
- To assess PrEP modality preferences among heterosexual cisgender men initiating PrEP at STI clinics.
- To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among heterosexual cisgender men seeking STI clinical services in Lilongwe, Malawi, at 39 and 52 weeks.
- To quantify costs and resources necessary to develop and integrate a systems-navigator delivered HIV prevention package into an urban STI clinic, informing future cost-effectiveness model development.

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- To perform exploratory laboratory assessments that may include evaluation of factors related to HIV infection or other STIs); characterization of HIV in participants who acquire HIV; characterization of the host response to antiretroviral drugs; and evaluation of virologic, pharmacologic, or STI-based laboratory assays.

- To evaluate event-driven PrEP drug concentrations within the context of TLFB reported PrEP use and sex acts.

- To explore the perceived and experienced PrEP related stigma and potential influence of perceived gender norms on PrEP persistence among heterosexual cisgender men initiating PrEP at the STI clinic.

2.3 Randomization

Participants are enrolled and randomized after being initiated on PrEP (within 7 days of starting). They will be randomized to the intervention or standard of care arms in a 2:1 ratio. Randomization will be stratified by age (15-25, >25), and a permuted block design will be used to ensure balanced treatment assignments within each stratum. Age-based stratification was elected due to expected differences in effect of intervention and base-case PrEP persistence among younger compared to older cisgender men. A 2:1 randomization was opted for to facilitate evaluation of acceptability outcomes, which are only examined among persons randomized to the intervention arm.

2.4 Blinding

Not applicable for this protocol.

2.5 Sample Size and Power

A total of approximately 200 HIV seronegative PrEP initiating participants will be enrolled in approximately 39 weeks and followed for at least 26 weeks but up to 52 weeks. An overall retention rate of 90% will be targeted. As a pilot study, the sample size is chosen to provide reasonable precision for assessing the primary endpoints and informing future studies. A 2:1 randomization to intervention and SOC was chosen to maximize the ability to assess acceptability of the intervention.

Based on previous studies, we expect persistent PrEP use under SOC is 40% at 26 weeks. The targeted difference in persistent PrEP use at 26 weeks between the intervention and the SOC arm is 15%-35%. This is a pilot study seeking to rapidly evaluate indication of an effect signal that would suggest potential benefit of systems navigation to inform a future larger study. Our sample size, selected to quickly enroll and answer this important and timely knowledge gap, will be sufficient to identify a minimum detectable RD of 0.22 assuming 80% power and 5% alpha level, and RD of 0.25 assuming 90% power and 5% alpha level.

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

3.1.1 Intent-to-treat (ITT)

All participants who are randomized, HIV-uninfected at enrollment, and without major enrollment violations (including those who are HIV-positive at enrollment or duplicate enrollees) will be included in

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the primary ITT analysis dataset. Primary analysis follow-up data will include study time through the first 26 weeks (target window) of study participation.

3.1.2 Intervention (INT)

The ITT cohort subset to those randomized to the intervention arm.

3.1.3 Persons Living with HIV (PLHIV)

All participants who are randomized and determined to be HIV-positive at enrollment. These participants are transferred to the seroconverter schedule (described in Protocol Version 2.0, Appendix III) and are required to complete visits at Week 13 and Week 26.

3.2 Statistical Analysis Issues

3.2.1 Subgroups

Important participant subgroups are:

- Age: 15 – 25, >25
- Baseline chosen PrEP modality (LAI, daily oral, or event-driven)
- Any STI (syphilis, gonorrhea, or chlamydia) at enrollment: any or none

3.2.2 Missing Data

Data may be missing due to participant dropout, participant nonresponse, late/missed visits, or failures in data collection. In general, the last category (failures in data collection) is quite rare in HPTN trials. Further, it is common to assume that such data are missing completely at random (MCAR)[1] and so will not bias results. However, participant dropout, nonresponse, or missed visits are unlikely to be MCAR and so attention must be paid to the potential for bias if there are high levels of missing data for these reasons. Here we discuss the approaches we will take for analyses in the presence of missing data.

PrEP persistence during the first 26 weeks (one of the primary endpoints) is defined as adherence to any PrEP modality through 26 weeks. The main reasons for missing adherence data are missed study visits (for daily oral PrEP and event-driven PrEP) or seroconversion/dropout. Note that for LAI, PrEP adherence is defined as receiving on-time injections at PrEP visits as documented in the PrEP visit cards and is always measured.

In the primary analysis for PrEP persistence, participants with any missing adherence data during the first 26 weeks (due to late/missed study visits for daily oral PrEP and event-driven PrEP, or seroconversion/dropout) will be classified as non-persistent. This strategy belongs to the *composite variable strategies* in the International Council for Harmonization (ICH) E9 (R1). Note that missingness in the 30-day Timeline Follow-Back (TLFB) assessments is not included in this classification and is handled separately, as described below.

An exception to the composite variable approach arises in cases of incomplete 30-day TLFB data. Note that missing values in the 30-day TLFBs can lead to incomplete PrEP adherence data for participant periods under prescribed event-driven PrEP. It is inappropriate to define participant periods as non-adherent solely because some information in the 30-day TLFBs is unknown. To address this, if feasible

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we will first use multiple imputation to fill in missing values for the following daily variables:

a. Whether sex occurred

b. Whether a condom was used

c. Whether PrEP was taken that day

d. Whether PrEP was taken before sex

Imputation will be restricted to periods under prescribed event-driven PrEP. Predictors in the imputation model will include age, education, presence of STIs, and information from the 30-day TLFB in the last study visit (if available).

Imputation will proceed in stages (if feasible):

1. Impute missing values for whether sex occurred on each day using available covariates.

2. For condom use and PrEP taken before sex, impute missing values only on days when sex is reported or imputed to have occurred. On days without sex, these variables will be treated as structurally missing and excluded from implementation.

3. For PrEP taken that day, impute missing values on all days, regardless of whether sex occurred.

If this daily-level approach proves infeasible due to convergence issues or poor predictive performance, we will use an alternative approach based on Multiple Imputation of Aggregated 30-Day TLFB Variables (if data proves feasible). In this alternative, we will summarize each 30-day period into counts or proportions (e.g., number of sex acts, proportion with PrEP coverage) and apply multiple imputation at the period level using the same set of predictors. If there is insufficient TLFB data to do any kind of imputation, we will exclude time periods with attended visits but missing TLFB from our assessment of persistence.

Historically, HPTN trials have had good retention of participants and we expect that to be the case for this trial. The rate of missing any adherence data due to missed study visits (i.e., adherence data missing at either the week 13 or week 26 visits) will be summarized by study arm. If these rates are low and similar between arms, we will not conduct additional sensitivity analyses. However, if the rate of missing any adherence data due to late/missed study visits exceeds 10% or differs meaningfully between arms (>5%) in a way that could affect the primary outcome, we will perform sensitivity analyses using multiple imputation. Baseline data and longitudinal adherence outcomes up to week 26 will be used to develop the imputation model, with standard errors adjusted according to Rubin's method.

The missing data strategy will be applied to the endpoints for uptake of "re-start" kit. In other words, in our primary analysis, those with missing data will be considered to not have used the "re-start" kit. Sensitivity analyses using multiple imputation will be conducted if the missing rate exceeds 10% if there is sufficient data. Note these endpoints will be evaluated among those in intervention arm only and to whom the "re-start" kit is distributed through end of study participation.

Missing data strategies for other primary endpoints are outlined below. The endpoints for engagement with system navigators do not have missing data. Self-report endpoints (e.g. acceptability) may also be subject to participant nonresponse, which will be analyzed using a complete case approach. However, if non-response is high (>10%) then we may perform sensitivity analyses using multiple imputation..

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4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

4.1 Interim Analyses

Not applicable for this protocol.

4.2 SMC Reports

Monitoring reports will be provided to the HPTN Study Monitoring Committee (SMC) approximately every 6 months. The content of these reports will be developed by the protocol team, but will generally include the following information:

Open Report

1. Screening
2. Accrual
3. Baseline demographic characteristics of enrolled participants
4. Baseline chosen PrEP modality
5. Baseline self-reported HIV risk behavior
6. Engagement with system navigator, among the intervention arm
7. Disposition
8. Retention
9. Loss-to-follow-up, withdrawal, termination, product holds, death
10. Protocol deviations

Closed Report

1. PrEP modality switch, aggregated over study arm
2. PrEP persistence through Week 26, aggregated over study arm
3. Uptake of “re-start” kit among those whom it is distributed, among participants randomized to intervention arm
4. HIV incidence rate, aggregated over study arm

4.3 DSMB Reports

Not applicable for this protocol.

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5. GENERAL ANALYSIS METHODS

The mean, median, standard deviation, quantiles, and range will be calculated for continuous variables. For categorical variables, the counts and proportions will be reported. Z-tests will be used to compare endpoints between arms, as appropriate.

6. TRIAL PARTICIPANT DISPOSITION

6.1 Disposition of Participants

A flow chart may be generated to describe the disposition of participants. The number of participants screened, screened out (with reasons for exclusion), enrolled, randomized, allocated to each study arm, HIV-positive at enrollment, reasons for discontinuation from follow-up (with reasons for discontinuation), and the number of participants with available data at each follow-up visit (categorized by target and allowable windows), and those included in the primary efficacy analysis will be summarized. Note, prior to screening, all potential participants have been informally pre-screened by a clinic PrEP nurse and prescribed PrEP, and there may be no screened out participants.

6.2 Treatment Exposure

Not applicable for this protocol.

6.3 Protocol Deviations

A table or listing will be used to describe protocol deviations by participants in this study. These may include deviations such as participants who were inappropriately enrolled (e.g. participants who receive the intervention despite being assigned to control). For duplicate enrollments, all duplicate entries have been excluded. In one instance where a participant attempted to enroll three times, both the duplicates and the original enrollment were excluded (i.e. the participant was terminated and fully removed from the ITT analysis set due to a major enrollment violation). The number and proportion of participants enrolled in the ITT Cohort who complete each scheduled visit (categorized by target and allowable windows) will be tabulated, by arm and overall.

7. BASELINE DATA

A table will be generated to describe demographic and other relevant baseline characteristics, both overall and by arm. The characteristics may include age, education level, employment, income, marital status, number of sex partners in the past 3 months and past 12 months, STIs (any, syphilis, gonorrhea, chlamydia), preferred type of PrEP, type of PrEP initiated, , transactional sex, intended PrEP use (time), PHQ-2, GAD-7, evaluation of substance use, , PrEP awareness/use history, violence questions (from the psychosocial context form), healthcare engagement, and technology access.

8. EFFICACY/EFFECTIVENESS ANALYSES

8.1 Primary Objective – Efficacy

To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among heterosexual cisgender men seeking STI clinical services in Lilongwe, Malawi at 26 weeks.

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8.1.1 Primary Endpoints

The primary endpoints are described by the following attributes:

1. Population: HIV seronegative heterosexual cisgender males seeking STI services at Bwaila STI clinic who have accepted PrEP services.

2. Endpoint: Persistent PrEP use across all three modalities (LAI, daily oral, or event-driven PrEP), where persistence is defined as adherence to any PrEP modality throughout the 26 weeks period, comparing proportions in intervention and control arm participants. PrEP persistence (as a binary yes/no) will be the primary endpoint for this analysis. See below for details on how the endpoint is defined.

3. Treatment of interest: Systems navigation integrated into PrEP services delivered at an STI clinic in promotion of persistent effective PrEP use - either daily oral, 2-1-1 event driven, or injectable.

4. Handling of intercurrent events:

    a. Missed study visits (for daily oral and event-driven PrEP), study dropout, discontinuation of PrEP due to being deemed low-risk by nurses, or seroconversion: composite-variable strategy (see Section 3.2.2).

5. Summary measure: mean difference between two arms.

Definition of endpoint: PrEP persistence through Week 26 is defined as PrEP adherence at both the Week 13 and Week 26 visits (where the time frames covered by visit-level adherence assessments differ by PrEP modality). PrEP adherence is defined as:

a) LAI: receiving on-time injections (+/- 7-day window for the first injection and +/- 14-day window thereafter through week 26 visit (visit date when available, otherwise target visit date is used*). Specifically, these windows are based on the expected injection dates documented in the participant's PrEP visit cards and validated using the interval from the previous injection date. After the initial two loading doses (4 weeks apart), subsequent injections are expected every 56 days (8 weeks).

   For example, if a participant receives on-time injections at week 0, week 4, week 12, and week 20, they would be considered adherent throughout the 26 weeks period, as this schedule provides continuous coverage through week 26. In general, a participant will be considered adherent at a given time point if it falls within the target window of 8 weeks + 2 weeks from their previous injection.

   * Since LAI injection records are the only means used to determine adherence, a missed study visit (or a visit outside the target visit window) does not preclude a participant from adherence. In cases where a study visit is missed (or occurs outside the target study window), a participant with on-time injections through target visit date is considered adherent.

b) Daily oral: having protective PrEP concentration detected at designated follow-up visits (target window), based on intraerythrocytic TFV-DP collected as DBS (TFV-DP concentrations ≥ 900 fmole/punch, roughly corresponding to ≥ 4 doses/week will be classified as adherent).

c) Event-driven: consistently correct event-driven PrEP (2+1+1) during the past 30 days, assessed through self-report of PrEP use and sex acts at study follow-up visits, and intraerythrocytic TFV-DP concentrations. Specifically, adherence is defined as all condomless sex acts covered by

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2+1+1 PrEP protection based on TLFB [5], and intraerythrocytic TFV-DP concentrations that exceed the expected level in Table 1.

Below is an example illustrating how to classify adherence under the 2-1-1 event-driven PrEP dosing strategy.

- Suppose the first recorded condomless sex act in the 30-day period occurs on a Friday. The participant should have taken two pills at least 2 hours before sex on Friday, followed by one pill on Saturday (any time) and one pill on Sunday (any time).

- If condomless sex occurs on multiple consecutive days—say, Friday and Saturday—the participant should continue daily dosing until two days after the final day of sex. For example, if sex occurred on Friday, Saturday, and Sunday, they should take one pill each day through Tuesday.

- Now consider a case where the participant had condomless sex on Friday, Saturday, and Sunday, took daily doses through Tuesday, and then had sex again on the following Friday (five days after the last sex day). Because this is within seven days of the previous dosing sequence, they only need to take one pill to restart, and this dose does not need to be taken before sex. Any sex act occurring within seven days of the last PrEP dose does not require the two-pill loading dose.

- However, if more than seven days have passed since the last condomless sex act and PrEP dose, the participant would need to restart with two pills before sex, followed by the standard post-sex dosing.

Table 1: Intraerythrocytic TFV-DP concentrations that correspond to different number of protected events (condomless sex acts). For example, if a participant reports four protected events in the last 30 days, this assumes 16 doses were ingested in that timeframe. Therefore, one may expect, on average, 16/30 (53%) of the estimated daily dose value for TFV-DP which is ≥1600 fmol/punch; In this case, we would expect 53% of ≥1600 fmol/punch, or ≥850 fmol/punch. This approach comes with some assumptions: (i) A relatively constant rate of covered acts in the preceding 8 weeks; (ii) Linear pharmacokinetics of RBC TFV-DP, which is observed; (iii) Sample collection relatively close to the last covered act (~within a week).

Expected TFV-DP (fmol/punch) for F/TDF, using indirect method (50:50 extraction)	**Number of Events in the last 30 days**	**Expected tablets in the last 30 days (based on 2-1-1 dosing)**
≥ 900	≥ 5	≥ 20
≥ 850	4	16
≥ 650	3	12
≥ 450	2	8
≥ 200	1	4

An important consideration is that the three PrEP modalities follow different clinical evaluation schedules. LAI adherence is assessed based on injection dates using calendar time, while adherence for daily oral and event-driven PrEP is assessed using specimens collected at study visits, which may not align with calendar time (e.g., the week 13 visit may occur earlier or later than 13 weeks after enrollment, given target and allowable visit windows). To address this, in the primary analysis, adherence for daily oral and event-driven PrEP will be evaluated only if the visit occurs within the target window. Participants who miss the target window but attend during the allowable window or miss the visit entirely will be classified as non-adherent based on the composite variable strategy described in Section 3.2.2. In a sensitivity

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analysis, we will consider an alternative definition that includes adherence assessments from visits occurring within the allowable window.

In Figure 1 below, we provide some examples of PrEP modality pattens. For example, if a participant chooses daily oral PrEP throughout, then persistence is defined as having protective PrEP concentration at both week 13 and 26 visits. As another example, if a participant switches from daily oral PrEP to CAB at week 14, then persistence is defined as having protective PrEP concentration at week 13 and receiving on-time CAB injections afterwards. A person is defined as having a modality switch if they changed modalities before a visit that occurred in the target window, or the target visit date otherwise.

For switches between CAB and daily oral (scenarios d, e, h, and l), we consider two scenarios:

- For participants who have been on daily oral PrEP for a duration of at least 8 weeks prior to DBS collection (not necessarily immediately prior), we will use standard TFV-DP concentration thresholds to assess adherence. These thresholds reflect steady-state levels based on the most recent 8 weeks of use. Specifically, TFV-DP concentrations ≥900 fmol/punch in DBS—which correspond approximately to ≥4 doses per week—will be classified as adherent during the daily oral PrEP period.

- If a participant uses oral daily PrEP for less than 8 weeks since the previous study visit, one can adjust as follows (example below):

  Suppose a DBS sample collected 14 days after initiating F/TDF shows a TFV-DP concentration of 710 fmol/punch. Given a TFV-DP half-life of 17 days, this concentration represents approximately 43.5% of the expected steady-state level, calculated as $1 - e^{-(\ln 2)/17 \times 14}$=0.435. To estimate the steady-state equivalent, divide the observed concentration by 0.435: 710/0.435 = 1632 fmol/punch, leading to an interpretation of daily F/TDF dosing and adherent for the daily oral period.

- If a participant initiates daily oral PrEP less than 7 days before sample collection or their duration of daily oral PrEP use between visits is less than 7 days, it is challenging to accurately assess adherence over such a short period using DBS. If this occurs, these cases will be evaluated individually. However, our default strategy will be that if the duration of oral PrEP use is less than 7 days and not contiguous with a study visit, calculation of adherence will not incorporate information about what happened in that <7 day period.

Note: for scenario (d), adherence to daily oral PrEP cannot be reliably assessed for the period following week 13 if that period is too short (<7 days) to allow meaningful evaluation based on the DBS sample collected at week 26. In such cases, adherence during the post–week 13 period of presumed oral PrEP use cannot be assessed, which is equivalent to assuming persistence to be the same as that observed during the first 13 weeks for the purpose of the primary outcome or assuming adherence during that <7 day period for the purpose of analyzing visit-level adherence. If the duration of daily oral PrEP since the previous visit is more than 7 days, adherence will be assessed using the thresholds above depending on the total duration of daily oral PrEP use since the previous visit. If the duration is less than 8 weeks, the expected steady-state should be based on the total duration (not just the date of initiation).

For scenario f and g: Suppose a participant uses event-driven PrEP for 11 weeks (e.g., 2 weeks are covered by 30-day TLFB with two sex acts protected), then switches to daily oral PrEP for the final 2 weeks of the first 13-week period. In this case, we will apply the adjustment strategy described above—specifically, estimating the expected percentage of steady-state TFV-DP concentration based on the number of days on daily dosing and adjusting the measured concentration upward accordingly. We will not combine event-driven and daily oral PrEP adherence estimates, as TFV-DP accumulation follows linear kinetics, and additive interpretation of different dosing strategies is not appropriate.

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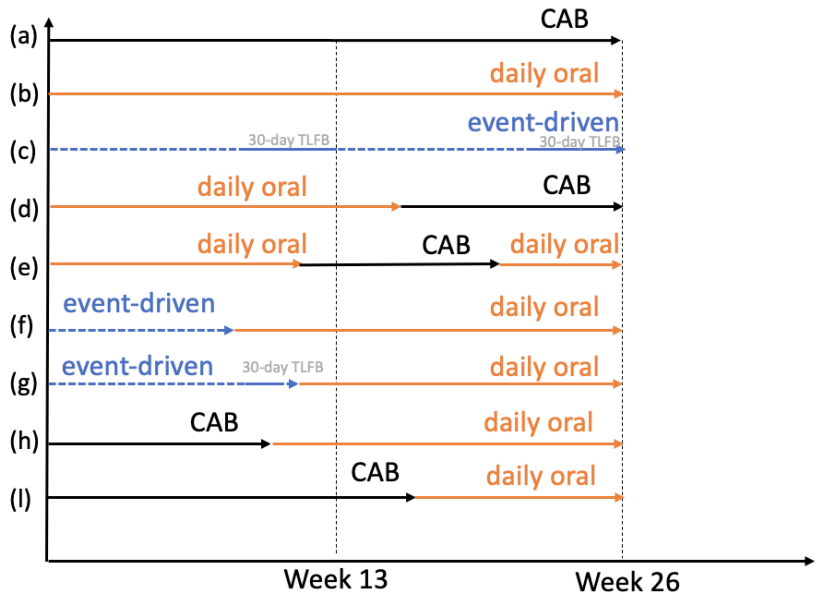


Figure 1. Examples of PrEP modality pattern

8.1.2 Hypothesis

H_0: PrEP persistence is equal across control and intervention arms.
H_a: PrEP persistence is not equal across control and intervention arms.

8.1.3 Population

ITT Cohort

8.1.4 Descriptive Analysis

The number and proportion of participants with PrEP persistence through week 26 will be presented overall, by arm, baseline PrEP modality, and their joint levels. Additionally, these will be presented based on the joint levels of study arm and PrEP modality switches during the follow-up period; however, this should be interpreted with caution, as modality switching is a post-randomization variable. To evaluate the potential impact, modality switching patterns may be visualized using Sankey diagrams, both overall and stratified by study arm. The proportions of participants who switched modalities, along with their reported reasons for switching, will be summarized and compared across study arms. Confidence intervals for the proportion of participants with PrEP persistence will be calculated using the binomial distribution.

The number and proportion of participants with PrEP adherence will also be summarized by arm and over time , or by baseline PrEP modality. For daily oral PrEP or event-driven PrEP, boxplots of intraerythrocytic TFV-DP concentrations may also be presented.

Note that some participants may have been adherent with PrEP but stopped PrEP only after being assessed as "low risk" by the study nurse. These individuals are distinct from those who independently discontinued PrEP by not returning for follow-up visits. We may summarize the proportion of participants who have been adherent with PrEP but stopped PrEP only after being deemed low risk, both overall and by study arm.

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8.1.5 Statistical Analysis

In accordance with intention-to-treat (ITT) principles, all participants in the ITT cohort are included, classified according to their randomized study arm. To estimate the difference in PrEP persistence rates between the intervention and control arms, we will use the g-computation method, a robust method for covariate adjustment method in estimating the treatment effect (Ye et al. 2023; FDA 2023). Specifically, we will fit a logistic regression model, adjusting for arm, age strata used in randomization, and baseline PrEP modality. We will then average the predicted probabilities for each treatment arm across all participants and finally calculate the difference between the two averaged predicted probabilities. This approach will generate a 95% Wald-based confidence interval, based on which we also have a two-sided test at the α=0.05 significance level.

8.1.6 Sensitivity Analysis

The primary analysis is to consider a binary endpoint indicating persistent PrEP use throughout the 26-week period, which indicates “perfect” persistence. We will conduct several sensitivity analyses to assess the robustness of our findings:

- We will define participants who stopped PrEP because they were deemed low-risk by the nurse as adherent and repeat the primary analysis.
- We will consider defining adherence to daily oral PrEP and event-driven PrEP using adherence assessments from visits occurring within the allowable window, rather than the target window used in the primary analysis.
- We consider the duration of PrEP adherence within the 26-week period in the ITT cohort. For instance, a participant prescribed daily oral PrEP who is adherent at the week 13 visit but not at the week 26 visit would have an adherence duration of 13 weeks. Similarly, for a participant receiving LAI PrEP with two injections, the adherence duration would be defined as lasting through the expected date of the next injection. The time with PrEP adherence is a continuous endpoint, with no need to account for censoring, as seroconversion and dropout are classified as non-adherence. As described in Section 8.1.5, the g-computation method will be applied using a linear model, adjusting for arm, age strata used in randomization, and baseline PrEP modality. We will then average the predicted outcome values for each treatment arm across all participants and finally estimate the difference in time with PrEP adherence in the two arms. This approach will generate a 95% Wald-based confidence interval, based on which we also have a two-sided test at the α=0.05 significance level.

8.2 Primary Objective – Acceptability

To assess acceptability and barriers of implementing a systems-navigator delivered HIV prevention package among key stakeholders in the clinic and heterosexual cisgender men initiating PrEP at STI clinics.

8.2.1 Primary Endpoints

The primary endpoints for engagement with systems navigators are described by the following attributes:

1. Population: HIV seronegative heterosexual cisgender males seeking STI services at Bwaila STI clinic who have accepted PrEP services. The analysis set includes participants in the intervention arm of the ITT cohort.

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2. Endpoints:

    a. Engaged by systems navigator within 7-days of enrollment visit (defined as any contact, i.e. text exchange, in-person communication).

    b. Status of engagement by systems navigator (no engagement, at least one attempted engagements but none successful, at least one successful engagement) after the initial engagement during the first 26 weeks following initiation of PrEP.

    c. Number of attempted and successful contacts (text, telephone call, home visit, other) with intervention arm participants made with systems navigators (number of contacts per participant) among those with successful engagements after the initial engagement during the first 26 weeks following initiation of PrEP.

3. Treatment of interest: Systems navigation integrated into PrEP services delivered at an STI clinic in promotion of persistent effective PrEP use - either daily oral, 2-1-1 event driven, or injectable.

4. Handling of intercurrent events: none.

5. Summary measure: mean for continuous endpoints, and proportion for binary and categorical endpoints.

The primary endpoints for uptake of self-test/pill pack ("re-start" kit) are described by the following attributes:

1. Population: HIV seronegative heterosexual cisgender males seeking STI services at Bwaila STI clinic who have accepted PrEP services. The analysis set includes participants in the intervention arm of the ITT cohort.

2. Endpoint:

    a. Self-report accepting PrEP "re-start" kit.

    b. Self-report ever use of "re-start" kits—defined as using an HIV self-test in conjunction with or prior to initiating the PrEP pill pack—among those accepted "re-start" kits.

    c. Self-report ever use of HIV self-tests among those accepted "re-start" kits.

    d. Self-report ever use of PrEP pill packs among those accepted "re-start" kits.

3. Treatment of interest: Systems navigation integrated into PrEP services delivered at an STI clinic in promotion of persistent effective PrEP use - either daily oral, 2-1-1 event driven, or injectable.

4. Handling of intercurrent events: Missed study visits, study dropout, or seroconversion: composite-variable strategy (see Section 3.2.2).

5. Summary measure: proportion.

The primary endpoints for acceptability and barriers among key stakeholders are described by the following attributes:

1. Population: key stakeholders, including participants enrolled as seronegative PrEP initiators and other key stakeholders. The analysis set includes participant key stakeholders in the intervention

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arm of the ITT cohort and other key stakeholders.

2. Endpoint: Acceptability based on quantitative surveys (participants enrolled as seronegative PrEP initiators only). Specifically, we will evaluate their responses to the acceptability questions at week 13 and 26:

    a. The system navigation intervention meets my approval.

    b. The system navigation intervention is appealing to me.

    c. I like the system navigation intervention.

    d. I welcome the system navigation intervention.

3. Treatment of interest: Systems navigation integrated into PrEP services delivered at an STI clinic in promotion of persistent effective PrEP use - either daily oral, 2-1-1 event driven, or injectable.

4. Handling of intercurrent events: none.

5. Summary measure: proportion for each category.

8.2.2 Descriptive Analysis

For binary endpoints, the number will be tabulated, its specified proportion will be calculated, with confidence intervals calculated under binomial distribution. For categorical endpoints, the counts and percentages of participants in each category will be presented. For continuous endpoints, its mean, median, standard deviation, quantiles, and range will be calculated. Analysis may be conducted overall and stratified by study visit.

In addition to the endpoints in Section 8.2.1, fidelity to intervention delivered by system navigators will be further summarized by the following indicators:

- Mean, quantiles, and range of the percentage of PrEP follow-up visits with SN contact on the same day.
- Proportion of participants with SN contact at over 80 percent of their PrEP visits.
- Among participants who indicated a preference for appointment reminders, the percentage who received them.
- Percentage of participants with a missed PrEP visit who had tracing attempted (by phone or in person).
- Percentage of PrEP visits at which STI specimens were collected on the same day.
- Among participants who were traced in person, the percentage of participants who were offered a restart kit (with a summary of reasons why the kit was not offered).

8.2.3 Statistical Analysis

No formal comparisons will be made for this endpoint.

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9. SAFETY ANALYSES

9.1 Adverse Events and Deaths

As the study only involves low-risk activities (recruitment activities; testing for HIV and STIs; questionnaires; support for linkage-to-PrEP; PrEP engagement, and PrEP adherence) and contains no biomedical intervention or clinical care (PrEP prescription or other medical treatment), and adverse event reporting and monitoring will not be undertaken. As such, adverse events will not be summarized.

9.2 Laboratory Evaluations

No safety analyses will be performed on laboratory findings as this study only involves low-risk activities.

9.3 Other Safety Measures

Not applicable for this protocol.

10. IMMUNOGENICITY ANALYSES

Not applicable for this protocol.

11. PHARMACOKINETIC ANALYSES

Not applicable for this protocol.

12. SECONDARY ENDPOINTS

12.1 Secondary Objective – Feasibility

To assess the feasibility of a future randomized controlled trial.

12.1.1 Endpoints

- Calendar time to enroll 200 participants.
- Proportion of participants retained at each eligible study visit. Specifically, this is the proportion of participants who had not terminated/died/lost/seroconverted to follow-up at prior to each visit (either date of visit if completed or end of allowable visit window if not completed).
- Proportion of participants who complete all study visits (categorized by target window or allowable window), as eligible based on date of enrollment, through 26 weeks, 39 weeks*, and 52 weeks*.
- Proportion of PrEP visits on the same day as study visits, possibly also by PrEP modality.
- Proportion of participants completing 30-day Timeline Follow-back (TLFB) at quarterly study visits.

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- Time to complete each study visit.
- Additional time (at PrEP visits) engaging with systems navigators (intervention arm only), as reported by the system navigators in the system navigator CRF.

* Among participants eligible for longer follow-up only. Participants enrolled in the first 13 weeks of recruitment will be followed for 52 weeks and those enrolled during the first 26 weeks of recruitment will be followed for 39 weeks. The remaining participants will be followed for 26 weeks total follow-up.

12.1.2 Population

ITT Cohorts

12.1.3 Descriptive Analysis

For binary endpoints, the number will be tabulated, and its specified proportion will be calculated. For continuous endpoints, its mean, median, standard deviation, quantiles, and range will be calculated. Time to complete study visit data was not collected consistently and will not be able to be summarized.

12.1.4 Statistical Analysis

No formal comparisons will be made for this objective.

13. STATISTICAL ANALYSIS CHANGES FROM PROTOCOL

Related to the secondary endpoint of “Time to complete each study visit”, time to complete study visit data was not collected consistently. As such, it will not be able to be summarized.

14. REFERENCES

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15. CHANGE HISTORY

Identify major changes. Only changes after version 1.0 approval need to be recorded. All final SAP versions should be whole numbers (i.e., 2.0, 3.0). Only include a history of changes for full version numbers.

Version		Affected Section(s)	Activity Description
Number	Effective Date		
1.0	07 July 2025	N/A	New document
2.0	Date of final signature	(1) All (2) Section 1 (3) Section 3.2.2 (4) Section 7 (5) Section 8.1.1 (6) Section 8.1.4 (7) Section 8.2.1 (8) Section 8.2.2 (9) Section 12.1.1 (10) Section 12.1.3 (11) Section 13	(1) Updated to latest SCHARP template. (2) RD added to abbreviations list. (3) Added language to address that imputation will be done if data proves feasible to do so. (4) Removed “history of prior PrEP use” as this was redundant. Removed “sexual orientation” as identifying as heterosexual was an inclusion criteria. (5) Added language to clarify by-visit endpoint. Added language to clarify how to handle when a participant switches from Oral PrEP to CAB depending on the length of time participant was on oral PrEP. Clarified language around visit windowing. (6) Language altered to reflect updated to TLF requests for the FSR. (7) Endpoints changed to be “self-reported” in alignment with protocol endpoints. (8) Added “on the same day” to clarify endpoint related to PrEP follow-up visits with SN contact. Changed language regarding systems navigator’s offering PrEP restart kits to be among those traced in person (a pre-requisite for offering). Changed tracing endpoint to be on the participant level as opposed to visit level (per pre-database lock PI request). (9) Removed duplicate “Proportion of participants completing 30-day Timeline Follow back (TLFB) at quarterly study visits”. Removed “(as recorded in diary of events)” from “Time to complete study visits” as we became aware this data is unavailable. (10) Removed variance as it was not requested. (11) Added acknowledgment that time to complete study visit data was not collected consistently, and this endpoint will be unable to be summarized.

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