Sustainable East Africa Research in Community Health (SEARCH) Collaboration

Statistical Analysis Plan for Dynamic HIV Choice Prevention at Antenatal Clinics in Phase A of SEARCH-Sapphire

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1. Study Overview

In Phase A of SEARCH-Sapphire (NCT04810650), we are conducting an individually randomized controlled trial to evaluate the effect of Dynamic Choice HIV Prevention (DCP) delivered to women recruited from antenatal clinics (ANC) on biomedical HIV prevention coverage in rural Kenya and Uganda. Details of the trial design and procedures can be found in the corresponding Study Protocol. Analyses plans for qualitative outcomes and cost-effectiveness outcomes are available elsewhere. Power calculations are given in the Appendix.

In brief, from April-July 2021, we enrolled 400 participants who were currently or anticipated being at risk of HIV. These participants were randomized to the DCP intervention or the standard-of-care using a stratified random block design. The stratification factors were country and pregnancy status, and the random block sizes were 2 and 4. The randomization list was generated by an independent researcher.

The DCP intervention includes choice of HIV prevention product (oral pre-exposure prophylaxis [PrEP] or post-exposure prophylaxis [PEP]), choice in HIV testing, choice in service location, and provider training on patient-centered care. Follow-up is over 48 weeks.

The primary objective is to evaluate if the DCP intervention improved biomedical HIV prevention coverage, defined as the proportion of the follow-up where the participant self-reported using PrEP or PEP. Secondary endpoints include biomedical covered time during periods of self-assessed HIV risk (compared between randomized arms) as well as coverage and uptake of the DCP intervention components (within intervention arm only).

2. Population and Characteristics

The population of interest is persons aged 15+ years who are seen at ANC and report current or anticipated HIV risk, as assessed via the country-specific Ministry of Health screening tools or self-assessment.

To characterize measurement of this population, we will provide a participant flow diagram (i.e., a CONSORT diagram). Overall and stratified by trial arm, we will summarize the baseline characteristics, including age, country, marital status, occupation, HIV risk criteria, alcohol use (any in prior 3 months), mobility (nights away in the past 3 months), pregnancy, and any prior use of PrEP or PEP in the past 6 months. We will categorize age in “younger” if aged 15-24 years.

3. Endpoint Measurement and Definition

At week-24 and week-48 of follow-up, surveys will be administered to assess HIV risk, possession of PrEP pills, possession of PEP pills, use of PrEP (any doses taken), and use of PEP (any doses taken). The assessment is by month and covers the prior 6 months. We will visualize these data with heatmaps and describe changes in product use over time and by self-reported risk.

The **primary endpoint of biomedical HIV prevention coverage** (a.k.a., biomedical covered time) is the proportion of follow-up where the participant reports taking PrEP or PEP. Thereby, this endpoint has a minimum of 0% (no use) and a maximum of 100% (full coverage). Persons contribute follow-up time when they respond to a survey. Persons who fail to complete both week-24 and week-48 surveys are missing in the primary analysis. Persons with incident HIV infection are assumed not to be covered during the period prior to seroconversion.

Using these data, we will also define the following **secondary endpoints**:

- Biomedical covered time at-risk, where follow-up is restricted to months of self-reported risk
- Possession covered time, defined as the proportion of follow-up where the participant reports having or receiving PrEP or PEP pills
- Possession covered time at-risk
- Use/possession ratio, defined as the proportion of follow-up with PrEP or PEP pills where the participant reports taking them
- Use/possession ratio when at-risk

4. Evaluation of the SEARCH DCP Intervention Effect

We will assess the Dynamic Choice Prevention intervention effect with targeted minimum loss-based estimation (TMLE), which improves precision and power by adaptively adjusting for baseline outcome predictors.[1–5] Here, we will use **TMLE with Adaptive Pre-specification** to flexibly control for baseline covariates, while maintaining Type-I error control and accounting for the randomization scheme.[6–8] Using 10-fold cross-validation, we will chose the optimal approach for estimating the outcome regression (i.e., the expected outcome given the randomization arm and adjustment covariates) and the known propensity score (i.e., the conditional probability of being randomized to the intervention given the adjustment covariates). Specifically, we will select the combination of estimators (adjustment variables + approach) that minimizes the cross-validated variance estimate.

Our pre-specified, candidate adjustment variables consist of pregnancy status at enrollment, age, country, use of PrEP/PEP in the 6 months before enrollment, and nothing (i.e., unadjusted). Our pre-specified, candidate learners consist of generalized linear models (GLMs) adjusting for a single variable (beyond the intervention indicator), stepwise regression, multivariate adaptive regression splines (MARS), and the arm-specific mean outcome.

Primary effect estimates will be for the study sample and on the **difference scale**: $1/n \sum_{i=1}^{n}[Y_i(1) - Y_i(0)]$, where $Y_i(1)$ denotes the counterfactual outcome for participant *i* under the intervention and $Y_i(0)$ denotes the counterfactual outcome for participant *i* under the control.[9–11] Secondary comparisons will be on the ratio scale.

We will test the **null hypothesis** that the intervention did not change biomedical covered time with a two-sided test at the 5% significance level. We will also report point estimates and 95% confidence intervals for each effect measure and the arm-specific outcomes. Standard error estimation will be based on the estimated influence curve, and statistical inference will follow from the Central Limit Theorem (i.e., using the standard normal distribution).[1]

Secondary analyses: To assess the robustness of these findings, we will repeat these analyses using the unadjusted effect estimator. We will also repeat these analyses using TMLE to adjust for missing endpoints.

Subgroup analyses: We will repeat these analyses within strata defined by country, pregnancy status at enrollment, age group, alcohol use, and use of PrEP/PEP in the 6 months before enrollment. In subgroups with fewer than 41 participants, we will limit the

candidate estimation approaches to main terms adjustment for a single covariate or the simple mean and use leave-one-out cross-validation. To further understand effect heterogeneity, we may conduct variable importance measures (i.e., unadjusted and adjusted predictor analyses) with TMLE.

Secondary endpoints compared by arm: We will implement analogous analyses to evaluate the intervention effect on biomedical covered time at-risk, possession covered time (overall and at-risk), and use/possession ratio (overall and at-risk).

Validation of self-report: Since the primary and key secondary study endpoints rely on self-report, we will objectively measure adherence using drug levels in small hair samples collected among participants reporting any PrEP or PEP doses taken in the past 30 days. Overall and by arm, we will report the number and proportion of these participants with detectable tenofovir levels (>0.002 ng/mg) in their hair at week-24. Using a two-sample test, we will formally test the null hypothesis of equal proportions between arms. We may repeat these analyses at week-48.

Additional descriptive analyses: Overall and by arm, we will report the number and proportion of participants who withdrew, died, or seroconverted. We will provide seroconversion narratives and may test the null hypothesis of the HIV incidence rate is the same between arms through Poisson regression with person-years-at-risk as offset.

5. Intervention Implementation

Within the intervention arm, we will describe coverage and uptake of the DCP intervention at baseline (week-0), week-4, week-12, week-24, and week-36:

- Visit coverage: number and proportion who attended study visits
- Choice of prevention product: number and proportion who selected PrEP, PEP, condoms, or nothing
- Choice of HIV testing: number and proportion who selected a self-test or rapid HIV test
- Choice of service location: number and proportion who selected to have visits at clinic or at an out-of-facility location (e.g., home)

All metrics will exclude persons who died, withdrew, or seroconverted by that week of follow-up.

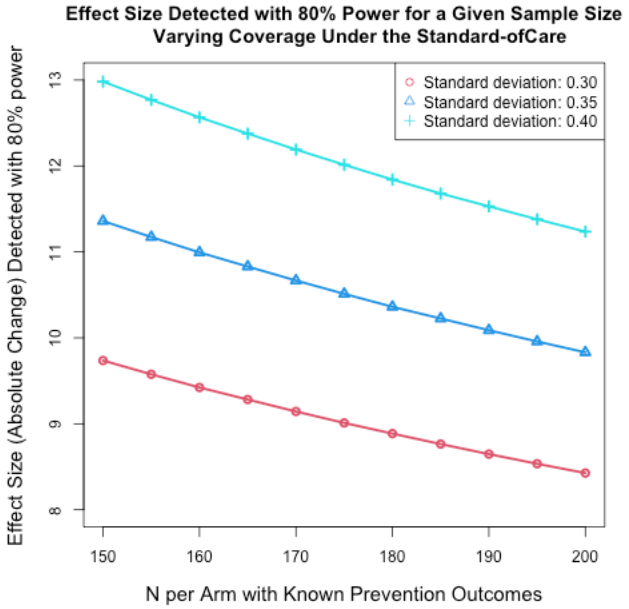
We will also characterize ever use of DCP intervention components over follow-up. We may also report on reasons for product changes, barriers to care, plans to address

those barriers, and utilization of the phone hotline. We will report these metrics overall and within key subgroups.

Appendix: Power calculations

Sample size and power calculations were based on a two-sample t-test with *power.t.test* function in *R*.[12] We expect these calculations to be conservative, because of the precision gained through stratified randomization and covariate adjustment during the analysis.

We estimated 200 participants/arm would provide 80% power to detect at least a 10% absolute increase in biomedical HIV prevention coverage, assuming a standard deviation of 0.3. As shown in the following Figure, even with 25% attrition (from 200 to 150 participants/arm) and higher than expected variability (e.g., standard deviation=0.40), these calculations suggest we would be well-powered to detect at least a 13% absolute increase in prevention coverage.



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