Document:
Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

Sustainable East Africa Research in Community Health
(SEARCH) Collaboration

Statistical Analysis Plan for the
SEARCH "Dynamic Choice HIV Prevention" Extension Study including the Option of Long Acting Cabotegravir Injectable Suspension (CAB-LA) in rural Kenya and Uganda

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This document provides the statistical analytic plan (SAP) for the evaluation of the effect of the SEARCH Dynamic Choice HIV Prevention intervention, including the option of CAB-LA, on biomedical prevention coverage (primary outcome) as well as HIV incidence and biomedical prevention coverage during periods of self-reported HIV risk (secondary outcomes) in a randomized trial extension study in rural Kenya and Uganda (Clinicaltrials.gov: NCT05549726). The SAP was locked prior to unblinding and effect estimation.

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1. OVERVIEW OF TTHE SEARCH CAB-LA EXTENSION STUDY

This study is testing the hypothesis that a "Dynamic Choice HIV Prevention" intervention that offers participants CAB-LA, oral Pre-Exposure Prophylaxis (PrEP), or post-exposure prophylaxis (PEP) and the ability to switch between products over time using a patient-centered delivery approach will achieve higher prevention coverage for males and females ≥15 years of age and at risk for HIV infection acquisition, as compared to the country standardof-care (SoC). The current SoC for biomedical HIV prevention includes oral PrEP and PEP. This study is being conducted in rural western Uganda and rural western Kenya. The follow-up is over 48 weeks. Additional details of the study design, arms, and procedures can be found in the Study Protocol.

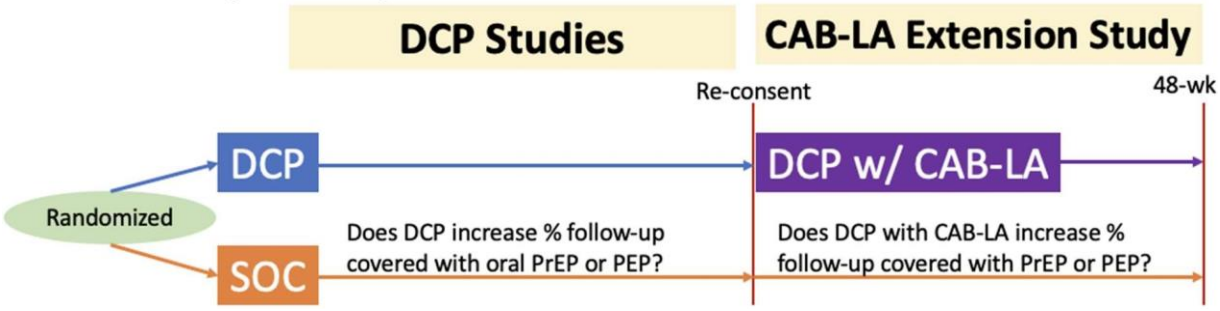
The primary objective is to evaluate the effect of the Dynamic Choice HIV Prevention intervention versus the SoC on biomedical HIV prevention coverage, defined as the proportion of follow-up time covered by either PrEP (oral PrEP or CAB-LA) or PEP. Secondary, pre-specified endpoints compared between arms and included in this SAP are coverage during periods of self-reported risk of HIV acquisition ("at-risk coverage") and HIV incidence. We additionally describe product use over time between arms. Analysis plans for other endpoints (e.g., implementation metrics and the change in endpoints before and after adding CAB-LA to the intervention) are available elsewhere. Power calculations and history of changes are given in the Appendix.

2. POPULATION AND CHARACTERISTICS

The study population is persons who were enrolled in the 3 randomized Dynamic Choice HIV Prevention trials that recruited from antenatal clinics, outpatient departments, and the community.[1–3] These trials were designed to evaluate the impact of the Dynamic Choice HIV Prevention intervention (offering choice between oral PrEP and

PEP as biomedical HIV prevention options) versus the SoC on biomedical HIV prevention coverage over 48 weeks (Figure 1).

Figure 1: Schematic of the CAB-LA extension study with abbreviations of DCP for Dynamic Choice HIV Prevention intervention and SOC for standard-of-care.



The Dynamic Choice HIV Prevention trials enrolled participants aged ≥15 years with current or anticipated risk to acquire HIV. Inclusion criteria for the CAB-LA extension study are 1) Prior enrollment in a SEARCH Dynamic Choice HIV Prevention trial, 2) HIV-negative by country-standard rapid HIV testing algorithm, and 3) Residence in the study region. In the extension, participants maintained their original randomization arm and are not blinded to the treatment arm. The primary statistician (LBB) will remain blinded to the treatment arm until the official unblinding of the study when the primary and secondary effect analyses, described in this SAP, are conducted. Additional details, including randomization procedures and eligibility for CAB-LA access among intervention arm participants, are in the Study Protocol.
To characterize participant flow from original randomization through measurement of the primary endpoint of the extension, we will provide a CONSORT diagram. To describe the study population, we will summarize participant characteristics at start of the extension, overall and by arm. These characteristics will include recruitment setting, country, sex, age, marital status, occupation, pregnancy (women only), circumcision (men only), and alcohol use (having 1+ alcoholic drink per week).

3. ENDPOINT DEFINITION AND MEASUREMENT

3.1. Biomedical HIV Prevention Coverage

The primary endpoint of this study is biomedical HIV prevention coverage, defined as the proportion of follow-up time covered by either PrEP (TDF/3TC or CAB-LA) or PEP. Thereby, this endpoint has a minimum of 0% (no use) and a maximum of 100% (full coverage). For oral PrEP and PEP, coverage is defined using self-report via a structured survey administered at 24 and 48 weeks of follow-up. Specifically, for each month of the prior 6 months, participants retrospectively report any use of oral PrEP (i.e., pill ingestion) and any use of PEP. For CAB-LA, coverage is defined through injection logs. Coverage from CAB-LA begins 3 days after an injection and continues for 67 days.

3.2 At-Risk Coverage

A secondary endpoint of this study is at-risk coverage, defined as the proportion of follow-up time that a participant reports being at risk of HIV acquisition during which they are covered by a biomedical prevention option. Product use over time will be defined analogously to the primary outcome. Self-reported risk of HIV acquisition will be assessed retrospectively via the structured survey administered at 24 and 48 weeks of follow-up.

3.3 Incident HIV Acquisition

A secondary endpoint of this study is incident HIV acquisition. HIV rapid antibody testing and HIV RNA testing (Cepheid GeneXpert Diagnostic System, Sunnyvale, California) will be performed at baseline, week-24, and week48. HIV testing is also available at the Ministry of Health clinics at all study sites. All participants with detectable HIV RNA and negative rapid antibody testing will have repeat antibody testing for confirmation of HIV diagnosis. All possible incident HIV infections will be reviewed by two HIV clinical experts blinded to the trial arm to determine if the participant meets the definition of confirmed incident HIV infection.

4. EVALUATION OF THE EFFECT OF THE SEARCH DYNAMIC CHOICE HIV PREVENTION INTERVENTION WITH CAB-LA

4.1. Primary Analysis: Effect on Biomedical HIV Prevention Coverage

The primary endpoint of biomedical HIV prevention coverage will be compared between arms with targeted minimum loss-based estimation (TMLE) to improve efficiency over the unadjusted effect estimator.[4–12] Briefly, TMLE combines estimates of the outcome regression (i.e., the conditional expectation of the outcome, given the intervention and

covariates) and the known propensity score (i.e., the conditional probability of the intervention, given the covariates) to obtain doubly-robust inference for the estimand of interest.
The primary analysis will adjust for recruitment setting (antenatal clinic, outpatient department, or community) in the outcome regression and adaptively adjust for additional baseline covariates to optimize precision, while preserving Type-I error control. Specifically, we will use Adaptive Pre-specification to select the candidate TMLE that maximizes empirical efficiency.[8,10,12] Using 10-fold cross-validation, we will select from the following prespecified candidates:

Outcome regression estimators: generalized linear models (GLMs) adjusting for a single covariate (beyond setting), main terms GLM, LASSO, or no further adjustment.
Propensity score estimators: GLMs adjusting for a single covariate, main terms GLM, LASSO, or no adjustment
Candidate variables: sex, age, alcohol use, mobility, or nothing

The primary analysis will estimate the marginal effect on the absolute scale (i.e., the difference in the average of the arm-specific outcomes). Secondary comparisons will be on the ratio scale. Standard error estimation will be based on the estimated influence curve, accounting for clustering from the community-based setting.[9,10,13–15] Statistical inference will follow from the Central Limit Theorem.[4] Specifically, we will create Wald-type 95% confidence intervals and test the null hypothesis of no difference in biomedical HIV prevention coverage with a two-sided test at the 5% significance level. We will also report point estimates and 95% confidence intervals for the arm-specific estimates.
In sensitivity analyses, we will assess the robustness of our findings by only adjusting for setting in the outcome regression as well as implementing the unadjusted effect estimator. We may conduct an additional sensitivity analysis adjusting for, instead of excluding, participants with zero follow-up. Additionally, we will evaluate the effect on coverage when restricting follow-up time to periods included in the structured survey administered to assess use of oral PrEP or PEP.
In additional sensitivity analyses, we will use data from the initial trials through the extension and apply TMLE to adjust for differences between participants who did vs. did not continue in the extension and participants who did vs. did not have their endpoint ascertained. See Section 6 for details.
We will repeat these analyses within subgroups defined by sex and age group (15-24 years vs. 25+ years) and apply the Bonferroni correction for multiple testing. To further understand effect heterogeneity, we may conduct variable importance measures (i.e., unadjusted and adjusted predictor analyses) with TMLE.
Prior to locking this SAP, we will conduct treatment-blind simulations to verify Type-I error control for all endpoints.[12]
4.2. Secondary Endpoint Analysis: Effect on At-Risk Coverage
We will implement analogous analyses to assess the SEARCH effect on coverage during periods of self-reported HIV risk. We will use the same approach for effect estimation, statistical inference, and multiple testing. We will conduct analogous subgroup and sensitivity analyses.
4.3. Secondary Endpoint Analysis: Effect on HIV Incidence
A key secondary endpoint is incident HIV infection. For each participant, we will calculate person-time-at-risk (PT) as the difference between enrollment into the extension and

Last negative HIV test for persons who did not acquire HIV
Imputed HIV infection date, defined as the midpoint between last negative and first positive test, for persons who did acquire HIV.

We will then compare the HIV incidence rate, defined as the sum of incident infections divided by the sum of PT, between randomized arms with the unadjusted effect estimator. Due to the anticipated rarity of the outcome, we will not apply TMLE for additional precision gains.
Our approach to inference will be implemented analogously to the primary endpoint.
As before, the primary comparison will be on the absolute scale (i.e., the difference in the incidence rates between arms) with secondary comparisons on the relative scale. Again, standard error estimation will be based on the estimated influence curve, accounting for clustering and inference based on the Central Limit Theorem. We will test the null hypothesis of no difference in HIV incidence rates with a two-sided test at the 5% significance level. In sensitivity analyses, we will, instead, use the non-parametric bootstrap for standard error estimation and exact tests for inference.
We will repeat these analyses within groups defined by sex and age group. However, we will not conduct hypothesis testing for these groups.
5. ADDITIONAL DESCRIPTIVE ANALYSES
We will summarize participant follow-up, overall and by arm. Follow-up in the CAB-LA extension study starts at enrollment and ends at the earliest of HIV diagnosis, death, withdrawal, or December 31, 2023. Follow-up time is censored during periods without data on use of biomedical HIV prevention.

Overall and by arm, we will report the number and proportion of participants who withdrew, died, or had other adverse events. We may also report on outcomes among women who become pregnant after initiating CAB-LA. We will summarize data on biomedical HIV prevention product use by arm. These summaries will exclude participants without any follow-up data on biomedical prevention use. We will use heatmaps to depict participantlevel use of prevention products over months of follow-up in the extension. We will also provide descriptive statistics about product use over time, including the month prior to the extension study, at baseline in the extension study, and ever use during the extension study. When calculating these descriptive statistics, missing values at baseline product use will be imputed from the first follow-up month.

6. SENSITIVITY ANALYSES

In this extension study, participants will maintain their original randomization arm. As a result, there is a legitimate concern that arms will be imbalanced at the start of the extension study. We will address this concern by conducting the following sensitivity analyses for the effect on biomedical HIV prevention coverage (primary endpoint) and atrisk coverage (secondary endpoint). These analyses will incorporate data from all persons who participated in the 3 Dynamic Choice HIV Prevention trials – regardless if they continued in the extension and/or had their endpoint ascertained in the extension.

This sensitivity analysis is informed by the Causal Roadmap[16] and aims address possible bias due to selection and missing data. Specifically, we can frame the analysis as asking, "What is the effect of the SEARCH Dynamic Choice HIV Prevention intervention (including the option of CAB-LA) if all participants had continued in the extension and had their endpoint ascertained?" While the treatment arm is randomized, we need to make the following missing data assumption: within values of adjustment variables, participants with their endpoint measured in the extension (and, thus, continued in the extension) are representative of participants who do not. Here, our adjustment set includes variables measured at recruitment into the initial trials (hereafter "baseline"): age, sex, country, recruitment site, alcohol use, and mobility. Importantly, our adjustment set also includes trial arm as well as post-intervention variables measured prior to the extension start: biomedical HIV prevention coverage, at-risk coverage, follow-up time, and follow-up time with self-reported risk of HIV acquisition. We additionally need that there is a positive probability of endpoint ascertainment within all possible values of these adjustment variables.

Under these assumptions, our statistical estimand is given by the Longitudinal G-computation formula:[17]

$$\mathbb{E}\{\mathbb{E}[\mathbb{E}(Y|\Delta = 1, L1, A = 1, L0)|A = 1, L0]\} - \mathbb{E}\{\mathbb{E}[\mathbb{E}(Y|\Delta = 1, L1, A = 0, L0)|A = 0, L0]\}$$

where Y is the endpoint, Δ is an indicator of having that endpoint measured and, thus, continuing in the extension, $L1$ are the time-varying covariates, A is an indicator of being randomized to the intervention arm, and $L0$ are the baseline covariates.

For estimation and inference, we will use longitudinal TMLE as implemented in the ltmle package.[4,14,18] In the main analysis, we will employ Super Learner, which is an ensemble machine learning method, to flexibly adjust and to improve efficiency.[19] Within Super Learner, we will combine predictions from main terms logistic regression (GLM), generalized additive models (GAM), multivariate adaptive splines (MARS), and the mean. The main analysis will also bound the estimated propensity scores (for measurement) from below at 1%. We will use the same approach for statistical inference and multiple testing as the primary analysis.

We will further examine the sensitivity to our assumptions and analytic choices by implementing TMLE as follows:
TMLE with Super Learner (as described above) but bounding the estimated propensity scores from below at 2%
TMLE with main terms logistic regressions (instead of Super Learner)
TMLE with Super Learner but only adjusting for baseline variables
TMLE with main terms logistic regressions and only adjusting for baseline variables

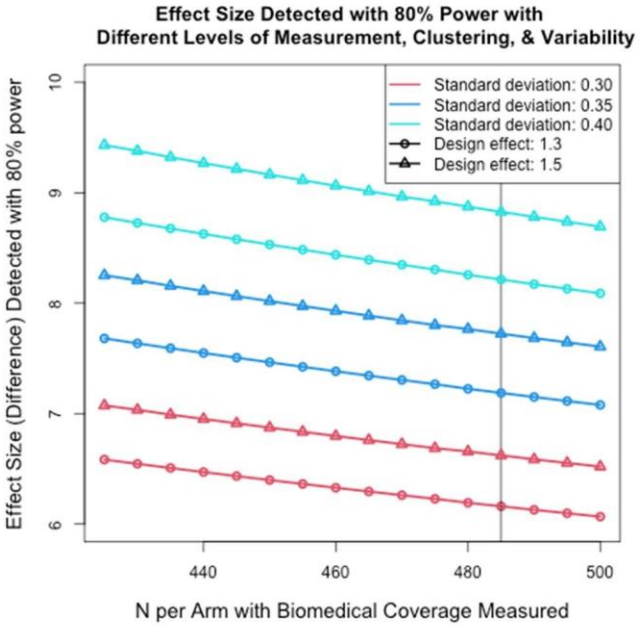
We will implement these analyses for biomedical HIV prevention coverage (primary endpoint) and at-risk coverage, overall and within the predefined subgroups.

7. POWER CALCULATIONS

We assume 70% of participants in the 3 Dynamic Choice HIV Prevention trials enroll in the extension. Of those, we assume 90% have measures of biomedical HIV prevention coverage (the primary endpoint). Then using standard formulas for continuous outcomes with clustering,[20,21] we anticipate at least 80% power to detect at least a 7.5% absolute increase in prevention coverage with 485 participants/arm, an outcome standard deviation of 0.35, and a design effect of 1.3. As shown in Figure 2, these calculations are fairly robust to alternative assumptions, including lower outcome measurement

and higher design effects. We further expect these calculations to be conservative given the precision gains due to covariate adjustment with TMLE in the primary analysis.

Figure 2: Minimal effect size (difference) detected with 80% power with a two-sample t-test (via power.t.test in R) after deflating the sample size by the design effect



8. HISTORY OF CHANGES

Version 1.0: This version includes updated power calculations (as compared to the Study Protocol v7.0) to reflect enrollment into the extension and that the primary analysis pools over and adjusts for (versus stratifies on) recruitment setting.

Version 1.1 (current version): This version includes additional details about the pre-specified sensitivity analyses (Section 5.0).

9. REFERENCES

Kabami J, Koss CA, Sunday H, et al. Randomized trial of dynamic choice HIV prevention at antenatal and postnatal care clinics in rural Uganda and Kenya. JAIDS. 2023;In Press.

Koss CA, Ayieko J, Kabami J, et al. Dynamic choice HIV prevention intervention at outpatient departments in rural Kenya and Uganda: a randomized trial. AIDS. Published online October 20, 2023. doi:10.1097/QAD.0000000000003763

Kakande ER, Ayieko J, Sunday H, et al. A community-based dynamic choice model for HIV prevention improves PrEP and PEP coverage in rural Uganda and Kenya: a cluster randomized trial. J Int AIDS Soc. 2023;26(12):e26195. doi:10.1002/jia2.26195

van der Laan M, Rose S. Targeted Learning: Causal Inference for Observational and Experimental Data. Springer; 2011.

Moore KL, van der Laan MJ. Covariate Adjustment in Randomized Trials with Binary Outcomes: Targeted Maximum Likelihood Estimation. Statistics in Medicine. 2009;28(1):39-64. doi:10.1002/sim.3445

Rosenblum M, Laan MJ van der. Simple, Efficient Estimators of Treatment Effects in Randomized Trials Using Generalized Linear Models to Leverage Baseline Variables. The International Journal of Biostatistics. 2010;6(1):Article 13. doi:10.2202/1557-4679.1138

Colantuoni E, Rosenblum M. Leveraging Prognostic Baseline Variables to Gain Precision in Randomized Trials. Stat Med. 2015;34(18):2602-2617.

Balzer L, van der Laan MJ, Petersen M, SEARCH Collaboration. Adaptive Pre-specification in Randomized Trials With and Without Pair-Matching. Statistics in Medicine. 2016;35(10):4528-4545.

Havlir DV, Balzer LB, Charlebois ED, et al. HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa. New England Journal of Medicine. 2019;381(3):219-229.

Balzer LB, van der Laan M, Ayieko J, et al. Two-Stage TMLE to Reduce Bias and Improve Efficiency in Cluster Randomized Trials. Biostatistics. 2021;kxab043.

Benkeser D, Díaz I, Luedtke A, Segal J, Scharfstein D, Rosenblum M. Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes. Biometrics. 2021;77(4):1467-1481. doi:10.1111/biom.13377
Balzer LB, Cai E, Garraza LG, Amaranath P. Adaptive Selection of the Optimal Strategy to Improve Precision and Power in Randomized Trials. Biometrics. 2023;In Press.
Benitez A, Petersen ML, van der Laan MJ, et al. Defining and estimating effects in cluster randomized trials: A methods comparison. Stat Med. 2023;42(19):3443-3466. doi:10.1002/sim.9813
Petersen ML, Schwab J, Gruber S, Blaser N, Schomaker M, Laan MJ van der. Targeted Maximum Likelihood Estimation for Dynamic and Static Longitudinal Marginal Structural Working Models. Journal of Causal Inference. 2014;2(2). doi:10.1515/jci-2013-0007
Schnitzer ME, Laan MJ van der, Moodie EE, Platt RW. Effect of breastfeeding on gastrointestinal infection in infants: a targeted maximum likelihood approach for clustered longitudinal data. Annals of Applied Statistics. 2014;8(2):703-725.
Petersen ML, Laan MJ van der. Causal Models and Learning from Data: Integrating Causal Modeling and Statistical Estimation. Epidemiology. 2014;25(3):418-426.
Robins JM. A new approach to causal inference in mortality studies with sustained exposure periods–application to control of the healthy worker survivor effect. Mathematical Modelling. 1986;7:1393-1512. doi:10.1016/0270-0255(86)90088-6
Lendle SD, Schwab J, Petersen ML, van der Laan MJ. ltmle: An R Package Implementing Targeted Minimum Loss-based Estimation for Longitudinal Data. Journal of Statistical Software. 2017;81(1):1-21.
van der Laan MJ, Polley EC, Hubbard AE. Super learner. Stat Appl Genet Mol Biol. 2007;6:Article25. doi:10.2202/1544-6115.1309
Hayes RJ, Moulton LH. Cluster Randomised Trials. Chapman & Hall/CRC; 2009.
Eldridge SM, Ashby D, Kerry S. Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method. International Journal of Epidemiology. 2006;35(5):1292-1300. doi:10.1093/ije/dyl129