The Outreach and Prevention at ALcohol Venues in East Africa Study

Statistical Analysis Plan for OPAL-East Africa – Aim 1: Evaluating Two Mobilization Strategies on Uptake of Biomedical HIV Prevention

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Table of Contents

1. Study Overview

The overall objective of OPAL is to improve uptake and use of biomedical HIV prevention among persons at risk of HIV acquisition in Kenya and Uganda. In the first phase of OPAL ("Aim 1"), we are conducting a cluster randomized trial (CRT) to evaluate to the **effectiveness of a multi-disease mobilization strategy (intervention) versus a HIV-focused mobilization strategy (control) on uptake of biomedical HIV prevention** among adults (aged≥18 years) at alcohol-serving venues (NCT05862857). In the second phase of OPAL ("Aim 2"), we are conducting an individually randomized trial to evaluate the effectiveness of a brief alcohol counseling intervention on use of biomedical HIV prevention among adults recruited from alcohol-serving venues who are starting prevention and have unhealthy alcohol use (NCT06036238).

Details of the trial design and procedures can be found in the corresponding Study Protocol. This Statistical Analysis Plan only covers the quantitative outcomes in Aim 1. Analysis plans for qualitative and cost-effectiveness outcomes in Aim 1 and all outcomes in Aim 2 are provided elsewhere.

For the Aim 1 CRT, we first mapped all alcohol-serving venues in the 8 study communities (with ~10,000 residents/community) in rural Western Kenya and in rural Southwestern Uganda. The venues were then grouped into clusters based on

geographic proximity. Within each community, we created matched pairs of clusters based on the number of rooms for sex work and average number of patrons. Within each matched pair, we randomized the clusters 1:1 to the intervention or control. From July 2023 through December 2024, study staff visited the participating venues to distribute recruitment cards for multi-disease screening (including HIV, hypertension, diabetes, malaria, tuberculosis, pregnancy and sexually transmitted infections [intervention]) or HIV-only screening (control) at the nearby health clinic. In both arms, persons who present the recruitment card at the clinic received 5 USD for travel reimbursement.

The primary objective is to compare the effectiveness of multi-disease versus HIV-focused mobilization on uptake of biomedical HIV prevention within 4 weeks. Secondary endpoints include uptake within 8 weeks, uptake within 12 weeks, HIV testing uptake, yield of adults with untreated HIV, yield of adults with heavy alcohol use, and initiation of antiretroviral treatment (ART) among participants with untreated HIV.

2. Study Flow & Description of Participants

We will provide a CONSORT diagram to describe the study flow: recruitment and randomization of clusters of alcohol-serving venues, distribution of recruitment cards to persons aged 18+ years who are working or patronizing alcohol-serving venues, and their linkage to clinic for health screening.

Overall and stratified by trial arm, we will summarize the following characteristics of persons who received a recruitment card: country, age, sex, and patron/worker status. Overall and stratified by trial, we will also describe participants who screened for HIV. Our summaries will include characteristics at the individual-level (e.g., age, sex, alcohol use) as well as venue-level (e.g., condoms availability and onsite rooms for sex work).

3. Evaluation of the Primary Endpoint

The **primary endpoint** is initiation of biomedical HIV prevention – including oral pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), and the dapivirine vaginal ring – by 4 weeks of HIV screening. The target population is all adults with HIV risk who receive a mobilization card at alcohol-serving venues. Our analyses will account for differences between members of this target population who did versus did not screen for HIV risk at the clinic. To do so, we will use Two-Stage targeted minimum

loss-based estimation (TMLE).[1] Two-Stage TMLE is a CRT approach that reduces bias due to missing data, while improving efficiency through adjustment for baseline covariates. Two-Stage TMLE has been used as the primary analysis of several CRTs for HIV prevention/treatment.[2–4]

In the first stage, we take each cluster in turn to identify and estimate an endpoint accounting for missing data. Specifically, we aim to quantify the probability of initiating PrEP/PEP among *all* with HIV risk – including those who did not test for HIV at the clinic: $Y^{c*} = \mathbb{P}(start = 1 \mid risk^* = 1)$. Here, the superscript *c* is used to emphasize this is a cluster-level variable, and the star is used to emphasize that we are missing data on HIV risk in the entire target population. As we have done previously,[1,5–8] we re-express this parameter as the following ratio:

$$Y^{c*} = \frac{\mathbb{P}(start = 1, risk^* = 1)}{\mathbb{P}(risk^* = 1)}$$

We can then identify and estimate the numerator and denominator in turn. Here, the numerator simplifies to the probability of initiating prevention, because only persons with HIV risk are eligible to start PrEP/PEP: $\mathbb{P}(start = 1)$. For the denominator, we will adjust for differences between persons who participated in HIV screening versus did not. In our primary analyses, our adjustment set W will include age group (18-24 years vs. 25+ years), sex, and patron/worker status. In secondary analyses, we may expand our adjustment set to include venue-level variables. In sensitivity analyses, we will not adjust ($W = \emptyset$). Under the following assumptions, we can identify $\mathbb{P}(risk^* = 1)$ from the observed data distribution in each cluster:

(1) risk prevalence among persons screened is representative of risk prevalence among persons missed within all values of the adjustment variables;
(2) there is a positive probability of participating in HIV screening within all possible values of the adjustment variables.

Then the statistical estimand for denominator is $\mathbb{E}(\mathbb{P}(risk = 1|screen = 1, W)]$.

Altogether, our statistical estimand for Stage 1 is

$$Y^c = \frac{\mathbb{P}(start = 1)}{\mathbb{E}(\mathbb{P}(risk = 1|screen = 1, W)].}$$

For estimation of the numerator, we will use the empirical proportion initiating PrEP/PEP in each cluster. For estimation of the denominator in each cluster, we will use TMLE with Super Learner to combine estimates from logistic regression, stepwise regression, and the mean. Taking the ratio provides an endpoint estimate $\hat{Y}_j^c$ for each cluster $j = \{1, \dots, J\}$.

In Stage 2, we will use these endpoint estimates to evaluate effectiveness. To do so, we implement a cluster-level TMLE to compare endpoints between randomized arms, adaptively selecting the adjustment variables to optimize precision, while tightly preserving Type-I error control.[1,9,10] Specifically, we will use cross-validation (i.e., sample-splitting) to select from the following baseline covariates the combination that maximizes empirical efficiency: country, indicator that the cluster has at least one venue where condoms are available, indicator that the cluster has at least one venue with onsite rooms for sex work, or nothing (unadjusted). Secondary analyses will be unadjusted (i.e., the contrast in the average endpoints by randomized arm).

The primary effect measure will be on the absolute scale (i.e. risk difference). In secondary analyses, we will examine the effectiveness on the relative scale. The primary analysis will weight individuals equally;[11] specifically, we will weight by the number of cards distributed. Secondary analyses will weight clusters equally. We will test the **null hypothesis** that there was no difference in PrEP/PEP uptake with multi-disease vs. HIV-focused mobilization strategy 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 cluster-level influence curve, and statistical inference will follow from the Central Limit Theorem.[12]

All analyses will exclude clusters where fewer than 18 cards are distributed. We will repeat all analyses within the pre-specified subgroups of country, age group, and sex.

4. Evaluation of Secondary Endpoints

We will use analogous approach to evaluate the impact on the secondary endpoints.

4.1 Uptake of biomedical HIV prevention by 8 weeks and by 12 weeks
We will repeat the primary endpoint analyses on the secondary endpoints of prevention uptake by 8 and by 12 weeks.

4.2 Uptake of HIV testing
We will use analogous methods to evaluate HIV testing uptake: the proportion of HIV-unknown adults who accept clinic-based HIV testing. Here, the target population is all adults who are not previously diagnosed with HIV and receive a mobilization card at

alcohol-serving venues. Using Two-Stage TMLE, our analyses will account for differences between members of this target population who did versus did not test for HIV the clinic. Our Stage 1 estimand is

$$Y^c = \frac{\mathbb{P}(test = 1)}{\mathbb{E}(\mathbb{P}(unknown\ status = 1 | test = 1, W)]}$$

with the adjustment variables W defined as in the primary endpoint analyses. We will use the same approach for estimation and inference in Stage 2 as the primary endpoint analyses.

4.3 Yield of adults with untreated HIV

We will again use our Two-Stage approach to evaluate the yield of adults with untreated HIV: the proportion of persons accepting HIV screening who are newly diagnosed HIV or previously diagnosed but not on ART. In Stage 1, we will estimate the proportion of persons who screened for HIV with untreated HIV with the empirical mean in each cluster. In Stage 2, we will compare these endpoints and evaluate effectiveness as in the primary endpoint analyses.

4.4 Yield of adults with heavy alcohol use

We will again use our Two-Stage approach to evaluate the yield of adults with heavy alcohol use: the proportion of persons screened for alcohol use with AUDIT-C levels indicating heavy use. In Stage 1, we will estimate the proportion of persons who screened for alcohol use with an AUDIT-C score ≥4 for men and ≥3 for women. In Stage 2, we will compare these endpoints and evaluate effectiveness as in the primary endpoint analyses.

4.5 ART initiation among adults with untreated HIV

We will again use our Two-Stage approach to evaluate the ART initiation among adults with untreated HIV. In Stage 1, we will estimate the proportion of untreated persons who start or restart ART within 1 week of their linkage visit. In Stage 2, we will compare these endpoints and evaluate effectiveness as in the primary endpoint analyses.

Appendix: Power Calculations

We refer to the Study Protocol for the sample size and power calculations were based on standard formulas for cluster randomized trials with a binary outcome.[13]

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