HIV Self-Testing AfRica (STAR) Malawi: A cluster randomised trial of community-based distribution of HIV self-testing kits to improve testing rates and promote ART initiation in rural, Malawi

Statistical analysis plan

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1. INTRODUCTION

In Malawi, adult HIV prevalence remains high, with pronounced social and economic inequity in HIV testing and linkage to HIV services. Self-testing for HIV (HIVST) is becoming an established option for providing highly accurate results when used by lay individuals. However, more research is needed to establish the potential role of HIVST in rural Africa, where coverage of HIV testing services is especially low. This project aims to investigate the feasibility, affordability, and health and social impact of introducing HIVST to rural communities through existing community-based distribution agents (CBDA).

The HIV STAR Malawi General Population study includes a cluster-randomized trial investigating the effects of introducing HIVST through CBDAs in 4 districts in Malawi's Southern region. This research protocol is nested within the UNITAID/Population Services International (PSI) HIV Self-Testing Africa (STAR) project. PSI is leading the implementation of this project, with the evaluation conducted by the Malawi-Liverpool-Wellcome Trust (MLW) and the London School of Hygiene and Tropical Medicine (LSHTM).

This document outlines the plan for primary analysis of the STAR Malawi cluster randomized trial for the publication of primary results. Only the randomization of clinics to the HIVST intervention is discussed below; the planned second randomization of CBDAs to home-based ART initiation was not implemented due to delays in study initiation.

2. TRIAL DESIGN

2.1 Research objectives

The primary objectives of this trial are to: estimate the impact of introducing HIVST through CBDAs on i) coverage of recent testing (within the last 12 months) and lifetime testing among residents ages 16 years and older and ii) cumulative incidence of ART initiation per 100,000 population in primary care clinics.

2.2 Trial arms, randomization, and blinding

This study will be conducted in rural settings in Malawi's Southern region. The study was originally designed with two randomization stages, but only one was completed. We refer to outcomes for the first randomization only.

Stage 1 randomization. The first randomization was conducted at the clinic (cluster) level, because the intervention is administered at this level. Primary care clinics offering ART services (22 total) and their catchment areas were randomized to either HIVST or standard of care (SOC) arms.

- **Arm A (11 clinics). HIVST**. All CBDAs working within the catchment area of clinics in the HIVST arm were trained by PSI to provide HIVST (OraQuick HIV Self-Test). Some CBDAs had been working with PSI before the study to distribute reproductive health products, while others were hired and trained for the study. CBDAs provide i) brief pre-test information; ii) a self-referral form with all kits to facilitate linkage into HIV care and prevention services; iii) generic or results-based post-test advice, depending on disclosure of results to CBDAs.
- **Arm B (11 clinics). SOC.** In the SOC arm, no kits will be provided to CBDAs working with PSI, and no additional CBDAs were trained to distribute reproductive health products.

Allocation was completed using restricted randomization, with allocation options restricted to ensure balance by geography; proportion of positive tests in each clinic; total number of tests

conducted in each clinic; and catchment population. To ensure that intervention and control clinics were distributed geographically across the study area, we applied the following restrictions.

(1) **Blantyre district**: 8 clinics were located in Blantyre. Of these, at least 3 and no more than 5 were assigned to the intervention. 4 clinics (Madziabango Health Centre, Mpemba Health Centre, Pensulo Health Centre, and Soche Maternity) were located south of Blantyre. Of these, at least 1 and no more than 3 were assigned to the intervention. 4 clinics (Chikowa Health Centre, Dziwe Health Centre, Lirangwe Health Centre, and Makata Heath Centre) were located north of Blantyre. Of these, at least 1 and no more than 3 were assigned to the intervention.
(2) **Machinga district**: 7 clinics were located in Machinga. Of these, at least 3 and no more than 4 were assigned to the intervention.
(3) **Mwanza district**: 3 clinics were located in Mwanza. Of these, at least 1 and no more than 2 were allocated to the intervention.
(4) **Neno district**: 4 clinics were located in Neno. Of these, at least 1 and no more than 3 were allocated to the intervention.

The following additional criteria were used to ensure balance across arms by clinic characteristics:

- **Number of testers:** We calculated the total number of testers in clinics in each arm and removed randomization options having the largest difference between the two arms (10% greatest positive difference between intervention and control and 10% greatest negative difference between intervention and control).
- **Proportion positive tests:** We calculated the average proportion of HIV tests that were positive across each arm and removed randomization options having arms with the greatest difference (10% greatest positive difference between intervention and control and 10% greatest negative difference between intervention and control).
- **Clinic catchment population:** We calculated the total catchment population in each arm and removed randomization options having the largest difference between the two arms (10% greatest positive difference between intervention and control and 10% greatest negative difference between intervention and control).

An analyst based at LSHTM (MN) generated a list of 1,000 randomization options falling within the restriction parameters described above. The final randomization scheme was selected at a public ceremony on 21 March 2016.

Blinding. Because of the nature of the intervention, implementers cannot be blinded to the allocation of the clinic. However, analyses will be conducted on data with arm identification removed, and the analyst will be un-blinded only after results have been finalized.

2.3 Duration of intervention and timing of baseline and endline surveys

The HIVST intervention will be evaluated after at least 12 months of implementation. The interventions will be implemented across all areas in September 2016.

The baseline household survey was conducted between May-August 2016, and the household endline survey is expected to begin in September 2017 and end in December 2017-January 2018. Clusters will be surveyed in the same order for the baseline and endline surveys.

2.2 Study population and informed consent

Selection of clinics and evaluation areas. The population included in the impact evaluation are all residents ages 16 and older living in selected evaluation villages and areas located in 4 districts.

22 clinics were selected from rural areas within these districts for inclusion in the study. We identified clinics in areas where PSI had existing CBDAs of reproductive health services and that offered ART initiation. 23 clinics met these criteria, and the clinic with the lowest HIV prevalence was removed.

While HIVST distribution will occur across the entire catchment area of randomly selected clinics, evaluation data collection, including both household survey data collection and clinic data extraction, will be conducted only within selected areas. Evaluation villages represent villages selected for inclusion in the household survey. Evaluation areas represent the area of residence for clients whose data will be captured at the clinic.

Two villages in each cluster served as evaluation villages, with one village randomly receiving the baseline survey and the other receiving the endline survey. Eligibility requirement for the evaluation villages include:

- Location within the catchment area of an eligible ART clinic, with the clinic acting as the most dominant source of ARTs for the village.
- Presence of at least one active PSI CBDA.
- Population of at least 250 residents (ages 16 years and older) per village.
- Road access for most/all of the year.
- Sufficient distance and separation from administrative boundaries and other intended evaluation villages to minimise 1) 'contamination' between HIVST and control villages, and 2) missed linkage to events from seeking HIV care at a remote clinic not included in the evaluation.
- Villages delineated by natural boundaries (e.g., rivers, roads, forests, etc.) will be preferentially selected.

Selection of respondents for baseline and endline surveys. Within evaluation villages, all households were enumerated and a variable fraction were selected to ensure that at least 250 residents (16 years and older) within households were surveyed. Within selected households, all eligible household members were interviewed with the basic questionnaire, and 20% of surveyed individuals received an extended questionnaire. All residents (ages 16 years and older) living in households within the intervention area are eligible to receive HIVST from CBDAs.

Participants provided verbal consent to participate in the baseline and endline surveys. Written informed consent (for residents ages 18 years and older) or assent with parental consent (for residents ages 16-17 years) was required to participate in the extended household survey and midline survey. Children ages 15 years and younger and those unable or unwilling to provide informed consent were excluded from the extended household survey.

3. OUTCOME EVALUATION AND DATA DESCRIPTION

3.1. PRIMARY OUTCOME AND SAMPLE SIZE CALCULATION

The primary outcome is the proportion of residents (16 years and older) who tested for HIV within the 12 months prior to the endline survey, which will begin at least 12 months after initiation of the HIVST intervention.

Outcome data (numerators and denominators) will be collected during the endline survey.

The survey sample size was estimated to ensure sufficient power to identify a difference in the primary outcome between those receiving the HIVST intervention and those receiving the SOC, and accounted for clustering by incorporating the cluster coefficient of variation (*k*) using methods outlined in Hayes and Moulton (2009). The average cluster size was estimated to be 250-500 residents (16 years and older), which is the average size of a rural village based on from previous experience in Malawi. We estimated that the cluster coefficient of variation (*k*) was 0.25. Using 2010 DHS data, the proportion of individuals testing in the last 12 months is estimated to be 25% to 40% and ever tested at 42% to 60% in the SOC arm. Using these assumptions, we have 80% power to detect a 30% relative difference in recent HIV testing and a 45% relative difference in lifetime HIV testing in the HIVST arm with α=0.05.

3.2. SECONDARY OUTCOME

There are two secondary outcomes for the HIVST intervention. First, we will compare between arms the proportion of residents (16 years and older) who tested for HIV in their lifetime. Outcome data (numerators and denominators) will be collected during the endline survey.

We will also compare between arms cumulative incidence of ART initiation per 100,000 population for residents (16 years and older) during the intervention period, with ART clinic records used for this assessment. Data to measure ART initiation will be extracted from clinic records at three-month intervals for clients initiating ART from evaluation areas. The denominator will be the population (16 years and older) of evaluation areas, with data collected from village heads. We will cross-reference the population from village heads and baseline survey enumeration and ensure that differences between the two data sources are similar in the HIVST and SOC arm.

3.3. ADDITIONAL ITEMS IN BASELINE AND ENDLINE SURVEY

In addition to the primary and pre-specified testing outcomes, the following data were collected from all respondents in the baseline and endline survey.

- **Questions on HIV testing and self-testing**, including partner testing and acceptability of HIVST.
- **Socioeconomic status and educational attainment** at household and individual level. Socioeconomic status was ascertained at the household level using an assets index and the household food insecurity assessment scale (HFIAS). All individuals were asked about salaried employment status and educational attainment.
- **Sexual behaviour**
- **Circumcision status and intention to access VMMC** (men only)

The extended survey was given to a 20% sub-sample of respondents, chosen at random using a random number generated in the electronic data capture tool. The extended survey included all elements from the baseline survey, as well as:

- **Detailed questions on previous three HIV tests,** including mode of testing, harms or regrets experienced after testing
- **Household decision-making** questions from Malawi Demographic and Health Survey 2010 (National Statistical Office (NSO) and ICF Macro, 2011, Bossuyt et al., 2015)
- **Conformity of masculine norms inventory** (Mahalik et al., 2003)
- **HIV care** (HIV-positive respondents only)
- **Stigma,** including anticipated stigma and knowledge of treatment effectiveness

- **Intimate Partner Violence** questions adapted from a measure used in the WHO Multi-Country Study on Women's Health and Domestic Violence (women only) (Garcia-Moreno et al., 2006)
- **Discrete choice experiments and costs of HIV testing**

4. STATISTICAL METHODS

All analyses will be completed in Stata version 14, on an intention-to-treat basis, and will use methods appropriate for cluster randomized trials with a small number of clusters. Reporting will conform to the 2010 Consort statement (Campbell et al., 2012).

4.1. RECRUITMENT AND REPRESENTATIVENESS OF SAMPLE

The trial flow chart will show the process of recruitment of study participants.

4.2. BASELINE AND ENDLINE SURVEY RESPONSE RATES

Baseline and endline survey response rates at the household and individual level will be calculated by cluster for the total population, as well as separately for women and men and adolescents ages 16-17 years and adults 18 years and older.

4.3. BASELINE COMPARABILITY OF ARMS (STAGE 1 RANDOMIZATION - HIVST INTERVENTION)

Following baseline data collection, we will summarize baseline data by arm by the following characteristics:

- Age
- Sex
- Marital status
- Educational attainment and socioeconomic status measured using assets variables.
- HIV status, previous HIV testing and self-reported ART use

Baseline analyses will be completed before the endline data collection period begins. The study team will identify substantial differences between arms in terms of the above factors (excluding HIV status and self-reported ART use) and adjust for endline measures of these baseline differences in the outcome analysis (see below). This assessment will not be completed using statistical tests, and p-values will not be shown, as any difference will be due to chance if the randomisation was correctly performed.

4.4. UNADJUSTED ANALYSIS

This analysis will give each cluster equal weight. The overall risk for each cluster will be calculated, and a log transformation will be applied to the summary value for each cluster if necessary. For binary outcomes where there are clusters with no events, one event will be added to all clusters so that the log transformation can be conducted. The mean of these log risks will be used to obtain the geometric mean (GM).

The risk difference, 95% CI and p-value will be estimated using a t-test of the risk by arm, based on 20 degrees of freedom. The risk ratio, 95% CIand p-value will similarly be estimated using a t-test of the log risk.

4.5. ADJUSTED ANALYSIS

Factors for adjustment will be determined as stated above. If there are substantial baseline differences in recent testing across arms, we will adjust for baseline differences using cluster-level

summaries of baseline values. To adjust for other imbalances across arms, we will use endline measurements of these factors for adjustment, and will assume that there will be no substantial changes in these in the months between the baseline and endline surveys. The adjusted analysis will be the primary analysis.

The following covariates will be assessed as potential adjustors:

- Age
- Sex
- Marital status
- Educational attainment
- Assets index (in tertiles)

Logistic regression will be used to adjust for confounding bias at the individual level, adopting a two-stage approach as outlined in Hayes and Moulton (2009). In the adjusted analysis, the regression model will include terms for the individual-level adjustment factors, but not study arm. The fitted model will be used to obtain the difference and ratio of observed and expected events for each cluster. The ratio will be log-transformed as appropriate. A t-test will be used to estimate the risk difference and risk ratio and their respective 95% CIs and p-values. If adjustment for cluster level factors is considered necessary, this will be conducted at the second stage using linear regression, with appropriate adjustment for the degrees of freedom.

Because restricted randomization was used to allocate clinics, we will also report p-value and 95% confidence interval from a permutation test incorporating the restriction parameters described above (Li et al., 2016).

4.6. METHODS FOR ADDRESSING MISSING DATA

Missing data will be examined for each variable and for each cluster or participant. A systematic assessment of missingness will be conducted to ascertain the reason and possible mechanism for missing data by identifying the quantity of missing data and patterns within the data. Missingness will be particularly examined by cluster and between study arms to assess for systematic biases. Sensitivity analysis for the primary outcome of recent HIV testing will be carried out – comparing complete case analysis results with those where missing outcome status are re-classified as yes and no. Multiple imputation will be considered in the analysis as appropriate.

4.7. PLANNED SUBGROUP ANALYSES

In addition to the main analyses, we will conduct analyses to assess differences in the effect of the HIVST intervention on the primary outcome by sex and age (adolescents ages 16-19 years versus adults ages 20 years and older). We will also estimate the differential impact of the HIVST intervention by socioeconomic status using the assets index.

For the HIVST intervention, analyses of effect modification will be conducted using the method for testing for interaction in community randomized trials developed by Cheung el al. (2008). This method estimates the difference between intervention and control outcomes within each subgroup, then tests the hypothesis that the subgroups have the same intervention effect using a two-sample t-test.

5. PROCESS EVALUATION

Together with the main trial analysis, we will provide quantitative process data summarizing the strength and reach of the intervention, as well as a summary of harms reported in the household survey tabulated by respondent gender and allocation.

A full process evaluation, including both quantitative and qualitative data analysis, will be published separately.

6. OTHER ANALYSES

6.1. ECONOMIC ANALYSES

Economic analyses, including discrete choice analysis and cost-effectiveness analyses, are described separately.

6.2. MIDLINE ANALYSIS

A midline round of surveys and analysis will be conducted 4-6 months after the intervention begins to assess implementation. Midline data collection will occur within intervention clusters only, and will include a subset of questions asked at baseline about the following items.

- Sociodemographic data on age, sex, educational attainment, literacy
- Any HIV testing: location and mode of most recent test,
- Experiences with HIVST: familiarity with HIVST, where kit was obtained, care obtained after self-testing, harms or regrets experienced after self-testing

We propose a sample size of 550 individuals across 11 clusters (50/cluster) to detect a prevalence of 55% recent testing (as reported in the baseline survey) with 15% precision and ρ=0.03 (calculated using baseline data).

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