Use of HIV Self-Test Kits to Increase Identification of HIV-Infected Individuals and Their Partners

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ABBREVIATIONS AND ACRONYMS

ARV: antiretrovirals
ART: antiretroviral therapy
CMC: clinical Management Committee
DSMB: data safety and monitoring board
CRF: case report form
EC: ethics committee
HDA: HIV diagnostic assistant
HSA: health surveillance assistant
IRB: Institutional Review Board
NHSRC: National Health Science Research Committee
OPD: outpatient department
PEPFAR: President's Emergency Plan for AIDS Relief
PID: Patient Identification Number
PIH: Partners in Hope
PITC: provider-initiated testing and counseling
SOC: standard of care
SOP: Standard Operating Procedure
STI: sexually transmitted infection
TA: Technical Assistance
USAID: United States Agency for International Development

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SCHEMA

Purpose: To evaluate the feasibility and cost-effectiveness of self-testing strategies within health facilities compared to standard of care in the following settings:
(1) group self-testing in outpatient departments (OPD) and sexually transmitted infection (STI) clinics compared to standard of care and optimized standard of care HIV testing and counseling; and
(2) self-testing for partners of HIV+ index clients compared to standard of care and optimized standard of care partner notification strategies.

Design: Unblinded cluster-randomized controlled trial

Study Population: Aim 1: Individuals 15 years of age and older not already known to be HIV-positive
Aim 2: HIV-positive individuals 15 years of age and older with at least one sexual partner with unknown HIV status

Sample Size: Aim 1: 15 clusters with a total of 15,000 participants (5,000 per arm, 1,000 per site)
Aim 2: 15 clusters with a total of 7,500 participants (2,500 per arm, 500 per site)

Intervention: Aim 1: To test the feasibility and cost-effectiveness of group HIV self-testing in outpatient department (OPD) and sexually transmitted infections (STI) clinics
- Arm 1: Standard of care for provider-initiated testing and counseling (PITC)
- Arm 2: Optimized standard of care for PITC
- Arm 3: Group HIV self-testing

Aim 2: To test the feasibility and cost-effectiveness of partner HIV self-testing
- Arm 1: Standard of care for partner testing
- Arm 2: Optimized standard of care for partner testing
- Arm 3: HIV self-testing

Study Duration: Approximately 18 months total

Aim 1: To test the feasibility and cost-effectiveness of group HIV self-testing for patients in waiting areas of outpatient department (OPD) and sexually transmitted infections (STI) clinics

Primary Objectives:
- To determine whether group self-testing in waiting areas of OPD and sexually transmitted STI clinics is superior in regard to number of individuals HIV tested compared to optimized standard of care (provider-initiated testing and counseling; PITC)
- To determine whether group self-testing in waiting areas of OPD and STI clinics is cost-effective compared to optimized standard of care using PITC

Secondary Objectives:
- To assess the acceptability of self-testing in waiting areas of OPD and STI clinics

- To determine whether group self-testing in waiting areas of OPD and STI clinics is superior in regard to number of HIV+ individuals identified (testing yield)
- To determine whether group self-testing in waiting areas of OPD and STI clinics is superior in regard to linkage rates for those who identify as HIV-positive compared to standard of care and optimized standard of care (PITC)

Aim 2: To evaluate the feasibility and cost-effectiveness of self-testing for partners

***Primary Objectives*:**

- To determine whether providing index clients with HIV self-test kits for partners results in a greater number of partners tested as compared to optimized standard of care for partner notification and testing (referral slip)
- To determine whether providing index partners with HIV self-test kits is cost-effective compared to optimized standard of care using referral slips

***Secondary Objectives*:**

- To assess the acceptability of giving self-test kits to index clients for partner testing
- To determine whether providing index partners with HIV self-test kits is superior to optimized standard of care in regard to identifying HIV+ partners (yield of testing)
- To determine whether providing index partners with HIV self-test kits is superior to optimized standard of care in regard to linkage rates among those who identify as HIV-positive
- To determine whether providing self-test kits to index clients and their partner is superior to optimized standard of care in regard to partner disclosure by the index client

1 INTRODUCTION

1. BACKGROUND

Despite increased access to HIV services, use of HIV testing in sub-Saharan Africa remains low. In Malawi, only 42% of the adult population received an HIV test in the last year.[1] Men are less likely to test than women (82% of women have ever tested in their lifetime compared to 70% of men).[1] In order to reach the UN 90-90-90 goals, innovative solutions must be approached to identify and test individuals living with HIV. Two initiatives promise to increase testing and yield: Provider Initiated Testing and Counseling and Partner Notification Services.

Provider initiated testing increases the ability to test people who are already attending health services and are either unwilling or unable to independently seek an HIV test.[2,3] The strategy is prioritized for high-risk clients (ANC, OPD, STI, and TB clients) and is an efficient and cost-effective way to identify new HIV cases among these groups.[4] However, PITC is rarely implemented in routine care.[5-8] Furthermore, men are still underrepresented in PITC efforts.[4,9]

Partner Notification Services, also known as Contact Tracing, have also been identified to augment HIV case finding.[10,11] The feasibility and effectiveness of Partner Notification Services in Sub-Saharan African countries has been demonstrated with much success.[12-16] Within study settings in Malawi and Cameroon, active partner notification was effective with high rates of partner testing, 51% and 66.8% respectively, and positivity rates between 50-64%.[13,14]

Partner notification services have the potential for high impact in new case identification as the rate of HIV cases among partners has been shown to be tenfold higher than the national prevalence.[10,13,14] Early case identification is also key in preventing late stage patient presentation with high morbidity and less efficacious treatment outcomes. The case finding effectiveness of Partner Notification Services can result in earlier diagnosis of individuals, earlier initiation of ART, and prevention of HIV transmission. However, men are being missed in Partner Notification Services, limiting the strategy's impact. The percent return rates of men during passive referral is half that seen by women partners.[14] Strategies to improve testing of men are needed.

Prior Research on Self-Testing

A recently introduced method of HIV self-test screening within Malawi has shown high testing uptake among men. A study piloting the use of HIV self-testing demonstrated high uptake in adolescent men (89.3% in men aged 16-19 years of age) with rates remaining as high as 60% among men up to age 39 (compared to only 42% of the general male population who have been tested in the previous year).[1,17] Self-test screening also promotes partner testing and can be used to facilitate status disclosure.[18,19]

Overall, feasibility and uptake of self-test screening has been successfully demonstrated within Malawi allowing self-test screening to serve as a new key tool in increasing access to testing.[17,18,20,21,22] HIV self-test screening has been shown to be accurate, safe, and cost/quality of life analysis has also demonstrated its usefulness.[17,18,20, 22-25] However, self-test kits have been primarily distributed in community settings outside the standard health care system. To date, self-test kits have not been distributed within health facilities nor studied for partner testing. Combining self-testing with existing health systems may improve the scalability of self-test kits at a national level.

This study compliments the existing STAR study conducted in Malawi and elsewhere. STAR focuses primarily on non facility-based distribution, such as communities and schools. We examine self-test integration for routine health services, addressing a gap in self-test knowledge.

2. RATIONALE

While self-testing and partner notification strategies have been studied separately, these strategies have never been examined jointly as a means to improve partner disclosure and testing. Furthermore, self-test kits have not been piloted within existing health systems, limiting the feasibility of self-test kits outside study settings.

We propose to study the role of self-testing in identifying HIV-positive individuals and to determine whether self-test kits can be given to index clients as a means to facilitate partner disclosure and partner testing.

3. HYPOTHESES

- Aim 1: Group self-testing will (1) increase the number of OPD and STI clients tested for HIV, (2) increase HIV testing yield, and (3) be cost-effective compared to the optimized standard of care
- Aim 2: Self-test kits given to index clients will (1) increase the number of index partners who test for HIV; (2) increase yield of partner testing, and (3) be cost-effective compared to the optimized standard of care for partner notification and testing, and will (4) increase partner disclosure by the index client

2. AIM 1: GROUP SELF-TESTING

2.1. OBJECTIVES

2.1.1. Primary Objectives:

- To determine whether group self-testing in waiting areas of outpatient departments (OPD) and sexually transmitted infection (STI) clinics is superior in regard to number tested compared to optimized standard of care (provider-initiated-testing-and-counseling; PITC)
- To determine whether group self-testing in waiting areas of OPD and STI clinics is cost-effective compared to optimized standard of care using PITC

2.1.2. Secondary Objectives:

- To assess the acceptability of self-testing in waiting areas of OPD and STI clinics
- To determine whether group self-testing in waiting areas of OPD and STI clinics is superior in regard to number of HIV+ individuals identified (testing yield)
- To determine whether group self-testing in waiting areas of OPD and STI clinics is superior in regard to linkage rates for those who identify as HIV-positive compared to standard of care and optimized standard of care (PITC)

2.2. STUDY POPULATION

This aim will be conducted among 15,000 individuals 15 years or older who seek OPD or STI services at participating health facilities. The aim will be conducted in 15 clusters (facilities) in Malawi.

Sites have been selected in collaboration with the Ministry of Health and represent medium to large health facilities in areas of high HIV prevalence. Sites represent a mixture of facility types (hospital versus health centre) and are balanced with regard to the number that have separate STI clinics (versus STI services offered within OPD clinics). Figure 1 outlines potential sites to be included in the study.

FIG 1. STUDY SITES BY FACILITY TYPE, REGION, AND STUDY ARM

Facility Name	Facility Type	Region	Study Arm
Likuni Mission Hospital	CHAM	Central	HIVST
Mponela Rural Hospital	Rural Hospital	Central	HIVST
Nsanje District Hospital	District Hospital	South	HIVST
Masenjere Health Centre	Health Centre	South	HIVST
Mgabu Rural Hospital	Health Centre	South	HIVST
St. Gabriel Mission Hospital	CHAM	Central	OSOC
Kasungu District Hospital	District Hospital	Central	OSOC
Kalulu Health Centre	Rural Hospital	South	OSOC
Sorgini Health Centre	Health Centre	South	OSOC
Kalemba Health Centre	Health Centre	South	OSOC
De Young	CHAM	Central	SOC
Chikwawa District Hospital	District Hospital	South	SOC
Mkumaniza Health Centre	Health Centre	South	SOC
Gaga Health Centre	Health Centre	South	SOC
Chankhungu Health Centre	Health Centre	Central	SOC

2.2.1. Inclusion Criteria

All of the following criteria must be met in order for an individual to be included in Aim 1:

- 15 years of age or older
- Being seen for OPD or STI services at the time of the study

We include children ages 15-18 years of age if they actively seek OPD or STI services and consent to participate in the study. Under Malawian law, children 15-18 are able to receive an HIV test without being accompanied by a parent or receiving parental consent.

2.2.2. Exclusion Criteria

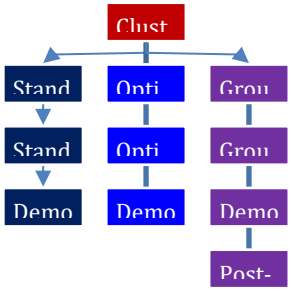
Individuals will be excluded from the study if any of the following exclusion criteria are present:

- Less than 15 years of age
- Not being seen for OPD or STI services at the time of the study
- Guardians attending clinics with OPD or STI clients

2.3. STUDY DESIGN

The study design for Aim 1 will be a cluster randomized trial comparing HIV testing rates and cost-effectiveness of group HIV self-testing compared to standard of care and optimized standard of care among OPD and STI clients (see Fig. 2). Clusters will be comprised of individual facilities in Malawi. Individuals waiting to receive OPD and STI health services who meet the inclusion criteria will be asked to participate in the study.

FIG 2. OVERVIEW OF STUDY DESIGN



2.3.1. Description of Randomization and Study Arms

Randomization will be conducted at the level of the cluster (1 cluster = 1 health facility). We will randomize 15 clusters evenly to one of three arms: (1) standard of care; (2) optimized standard of care (optimized with support for delivery of standard of care services including support for staff training, job aids, and quality of service delivery); or (3) group HIV self-testing. All patients enrolled at the site will follow the HIV testing assignment for the cluster in which they are randomized. We will use block randomization, blocking on variables that might predict outcomes, including facility type (hospital/health center), location (rural/urban), region (central or southern), and whether facilities have separate or combined STI and OPD clinics. This will help minimize residual confounding that can result in cluster randomized trials. We will then randomly allocate one cluster from each block to each of the three study arms. Clusters will be randomized to achieve a 1:1:1 allocation to each study arm.

Description of Study Arms

Microsoft Excel will be used to randomly assign clusters. Clusters will be assigned to one of three arms:

1. Standard of care arm: Facilities randomized to the standard of care arm will continue with standard of care without any intervention from the study team. Provider-initiated-testing-and-counseling (PITC) is standard of care for both OPD and STI clients. OPD or STI providers tell patients about HIV testing and refer them to the standard HIV testing services room at the health facility. HIV testing activities completed under standard of care will vary by facility based on adherence to national guidelines for PITC.

2. Optimized standard of care arm: Facilities randomized to the optimized standard of care arm will perform PITC for OPD and STI clients as per Ministry of Health National Guidelines. Facilities will be supported by the study team with initial trainings on the importance of HIV testing, the role of HIV testing as part of outpatient and STI care, and strategies used to discuss HIV testing with patients. The study team will also provide job aids to remind providers about the importance of referring patients for HIV testing and assist in the monitoring and evaluation of PITC implementation. When clients are referred for testing, they will use the standard HIV testing services room located in the same health facility. Testing will be available during all clinic hours and completed by trained HIV Diagnostic Assistants (HDA) who work at the facility (i.e., non-study staff).

3. Group self-testing arm: Facilities randomized to the group self-testing arm will have an HDA provide group education about HIV testing in the waiting areas of OPD and STI clinics. Education will include (1) information about the benefits of HIV testing and treatment, (2) a demonstration of how to use a self-test kit and who should use the kit for testing, and (3) and information about follow-up required for both HIV negative (re-testing at regular intervals) and positive results (referral for confirmatory testing and ART initiation and follow-up). Self-test kits will be distributed to eligible clients waiting for OPD or STI services and those who wish to use the kit will be free to do so. Group education and the distribution of self-test kits will take place every several hours to ensure that newly arriving OPD and STI clients are given the opportunity to participate in the study. Completed self-test kits will be anonymous and can be placed in a locked box in the waiting area or given to the standard OPD or STI service provider for interpretation of the result and further counseling. Trained HDAs will also be available in the OPD and STI waiting area in order to answer any questions that arise. Those with a positive self-test who disclose the result to the provider will be referred to undergo confirmatory testing by an HDA using the standard HIV testing services room located in the same health facility.

2.3.2. Recruitment and Enrollment Process

Standard of care arm

Facilities randomized to the standard of care arm will proceed with standard HIV testing within the facility. There will be no study “interventions” at the standard of care sites.

After completing the OPD or STI consultation, clients aged 15 years and older will be asked to participate in a brief 10 minute, anonymized exit survey to assess if they were offered testing, if they were tested, and why they chose to test or not. We will recruit all eligible OPD and STI clients for the survey – including clients who tested and those who did not. Survey participation is completely voluntary and can be refused at any point. Those who self-report as testing HIV positive during OPD or STI services will complete written consent and will provide identifiable information so the study can prospectively track linkage to care.

HIV testing registers, ART registers, OPD registers, and STI registers will be reviewed to measure (1) the number of individuals attending OPD and STI clinics over the study period (denominator), (2) the number of OPD and STI clients tested for HIV (numerator), (3) the proportion of those tested who are identified as HIV-positive (defined as a positive HIV test from two different types of tests – Determine and Uni-Gold), and (4) the proportion of those identified as HIV-positive who linked to ART services. All data will be anonymized from existing registers. Records from OPD and STI clients aged 15 years and older will be included in the study. Over the study period, we will be able to determine the proportion of all STI and OPD patients who receive an HIV test, the proportion of those tested who are HIV-positive, and the proportion of HIV-positive clients who link to ART services. We will also be able to determine differences by age sex, and service type. Because study data will be abstracted from existing clinic records in an anonymized format, no informed consent will be obtained.

Optimized standard of care arm

Facilities randomized to the optimized standard of care arm will provide standard PITC as recommended by the Ministry of Health. Facilities will be supported by the study team to implement standard PITC guidelines. HIV testing services will be available during all clinic hours and completed by trained HIV Diagnostic Assistants (HDA) who work at the site (non-study staff).

After completing the OPD or STI consultation, clients aged 15 years and older will be asked to participate in a brief 10 minute, anonymized exit survey to assess if they were offered testing, if they were tested, and why they chose to test or not. We will recruit all eligible OPD and STI clients for the survey – including clients who tested and those who did not. Survey participation is completely voluntary and can be refused at any point. Those who self-report as testing HIV positive during OPD or STI services will complete written consent and will provide identifiable information so the study can prospectively track linkage to care.

HIV testing registers, ART registers, OPD registers, and STI registers will be reviewed to triangulate the (1) number of individuals attending OPD and STI clinics over the study period (denominator), (2) number of OPD and STI clients tested for HIV (numerator), (3) proportion of those tested who are identified as HIV-positive (defined as a positive HIV test from two different types of tests – Determine and Uni-Gold), and (4) proportion of those identified as HIV-positive who linked to ART services. All data will be anonymized from existing registers. Records from OPD and STI clients aged 15 years and older will be included in the study. Over the study period, we will be able to determine the proportion of all STI and OPD patients who receive an HIV test, the proportion of those tested who are HIV-positive, and the proportion of HIV-positive clients who link to ART services. We will also be able to determine differences by age sex, and service type.

Group self-testing arm

OPD and STI clients in the waiting areas for these clinics will receive a health education talk from a trained HDA while waiting for their clinical consultation. Staff will review the oral consent script explaining that participation in HIV self-testing and study procedures is voluntary and that all data are anonymous. All OPD and STI clients aged 15 years and older will be offered a self-test kit. Those who would like to opt-out will be asked to take a kit and give the unopened kit to the study team during a brief exit survey.

Those who choose to participate in self-testing will be asked to keep the used kit in an opaque bag and give the anonymized self-test kit to the study team during the brief exit survey. The study team will NOT look at the test results, but will staple the opaque bag closed, link the unique identification number on the test bag to the exit survey, and drop the self-test kit into a secure lockbox. Those who do not want to directly give the self-test kit to the study team will be allowed to dispose their test kit in a lockbox located in the waiting area or a lockbox located in the provider consultation room.

After completing the OPD or STI consultation, clients aged 15 years and older will be asked to participate in a brief 15 minute, anonymized exit survey about their experience with self-testing why they chose to use the kit or not. We will recruit all eligible OPD and STI clients for the survey – including clients who used self-testing and those who opted-out of self-testing. Survey participation is completely voluntary and can be refused at any point. Those who self-report as testing HIV positive with a self-test kit will complete written consent and will provide identifiable information so the study can prospectively track linkage to care.

HIV testing registers, ART registers, OPD registers, and STI registers will be reviewed to triangulate the (1) number of individuals attending OPD and STI clinics over the study period (denominator), (2) number of OPD and STI clients tested for HIV (numerator), (3) proportion of those tested who are identified as HIV-positive (defined as a positive HIV test from two different types of tests – Determine and Uni-Gold), and (4) proportion of those identified as HIV-positive who linked to ART services. All data will be anonymized from existing registers. Records from OPD and STI clients aged 15 years and older will be included in the study. Over the study period, we will be able to determine the proportion of all STI and OPD patients who receive an HIV test, the proportion of those tested who are HIV-positive, and the proportion of HIV-positive clients who link to ART services. We will also be able to determine differences by age sex, and service type.

At the end of Aim 1 implementation, focus group discussions will be conducted with providers at participating OPD, STI, and HTC clinics to understand perceptions and acceptability of group self-testing at OPD and STI clinics. All core providers and supporting staff involved with the self-test intervention will be asked to participate (estimated 5 providers and 8 supporting staff at each site). Each site will complete two focus groups; one with providers and one with supporting staff (10 focus groups in total). Only providers over 18 years of age, actively involved in the self-test intervention, and willing and able to consent will participate. Focus groups will last approximately 45 minutes.

2.3.3. Informed Consent

For the group self-testing arm, oral informed consent will be obtained before any study-specific procedures are performed. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. Oral consent will be gained before being given an HIV self-test kit.

For all arms, oral consent will be obtained before completing a brief, anonymized exit survey about their experience with testing. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation.
For a subset of clients in the self-test arm, oral consent will also be obtained before completing an in-depth interview to gain more information about their experience with and acceptability of self-testing. During the brief exit survey, clients who self-report as (1) testing HIV positive that same day or (2) having not tested but wanting to test for HIV that same day will be taken through written informed consent and identifiable information will be collected to allow the study to track their uptake (linkage) and retention in ART. Identifiable information will NOT be collected for any other client group.

2.3.4. Participant Withdrawal or Termination from the Study

Individuals may withdraw from the study at any time. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Site investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs.

2.4. STUDY PROCEDURES

An overview of the study procedures is provided below. The same data collection processes will be used for ALL study arms.

2.4.1. Standard of Care Arm

2.4.2.1 Standard of Care

Facilities in the standard of care arm will provide routine HIV testing services. No intervention activities will be conducted. HIV testing will follow Ministry of Health National Guidelines using HDAs who will provide individual counseling and serial testing with Determine and Uni-Gold HIV test kits. Discordant results will result in re-testing using the MOH guidelines. Those with positive HIV tests will be counseled and referred to ART services following routine care.

2.4.1.2. Demographic Data Collection

Clients in the optimized standard of care arm who complete an OPD/STI consultation visit will meet briefly with a study staff member after their visit. The study staff member will collect anonymous demographic data including age, gender, highest level of education, and reason for visit to OPD/STI clinic. It will also capture if clients were offered testing, if they were tested, self-reported test result, and why they chose to test or not.

2.4.2.3 Additional Data Collection for those who: (1) test HIV positive that same day; (2) have not tested but want to test for HIV that same day, Participants who self-report as having (1) tested HIV positive that same day or **(2) not tested but want to test for HIV**

that same day will be asked to complete written consent for collection of identifiable information in order to track linkage and retention to ART.

2.4.2.4 *Registry Data for Triangulation and Linkage*
HIV testing, ART, OPD, and STI registers will be reviewed to measure the number of individuals seen in OPD and STI over the study period, the number tested from OPD and STI clinics, the proportion of those tested who are identified as HIV-positive, and the proportion of those identified as HIV-positive who link to ART services. All data will be anonymized from existing registers. Records from OPD and STI clients aged 15 years and older will be included in the study.

2.4.2. Optimized Standard of Care Arm

2.4.2.1 *Provider Initiated Testing and Counseling (PITC)*
Facilities randomized to the optimized standard of care arm will provide standard PITC as recommended by the Ministry of Health. Facilities will be supported by the study team with initial trainings on the importance of HIV testing, the role of HIV testing as part of outpatient and STI care, and strategies used to discuss HIV testing with patients. The study team will also provide job aids to remind providers about the importance of referring patients for HIV testing and assist in the monitoring and evaluation of PITC implementation. When clients are referred for testing, they will use the standard HIV testing services room located in the same health facility. Testing will be available during all clinic hours and completed by trained HIV Diagnostic Assistants (HDA) who work at the facility (i.e., non-study staff). HIV testing for OPD and STI clients will follow Ministry of Health National Guidelines using HDAs who will provide individual counseling and serial testing with Determine and Uni-Gold HIV test kits. Discordant results will result in re-testing using the MOH guidelines. Those with positive HIV tests will be counseled and referred to ART services following routine care.

2.4.2.2. *Demographic Data Collection*
Clients in the optimized standard of care arm who complete an OPD/STI consultation visit will meet briefly with a study staff member after their visit. The study staff member will collect anonymous demographic data including age, gender, highest level of education, and reason for visit to OPD/STI clinic. It will also capture if clients were offered testing, if they were tested, self-reported test result, and why they chose to test or not.

2.4.2.3 Additional Data Collection for those who: (1) test HIV positive that same day; (2) have not tested but want to test for HIV that same day, Participants who self-report as having (1) tested HIV positive that same day or (**2) not tested but want to test for HIV that same day** will be asked to complete written consent for collection of identifiable information in order to track linkage and retention to ART.

2.4.2.3. *Registry Data for Triangulation and Linkage*
HIV testing, ART, OPD, and STI registers will be reviewed to measure the number of individuals attending the clinics during the period of the study (denominator), the number HIV tested (numerator), the proportion of those tested who are identified as HIV-positive (yield), and the proportion of those identified as HIV positive who link to ART services. All data will be anonymized from existing registers. Records from OPD and STI clients aged 15 years and older will be included in the study. Over the period of the study, we will be able to determine the proportion of all STI and OPD patients who receive an HIV test, the proportion of those tested who are HIV-positive, and the proportion of HIV positive clients who linked to ART services.

2.4.3. Group Self-Testing Arm

A trained study member will meet with clients waiting in the OPD and STI waiting spaces and read the oral consent script explaining that participation in self-testing and study procedures is voluntary. The HDA will then provide group education in the OPD and STI waiting areas about (1) the benefits of HIV testing and treatment, (2) a demonstration of how to use a self-test kit and who should use the kit for testing, and (3) and group counseling about follow-up needed for both HIV negative (re-testing at regular intervals) and positive results (referral for confirmatory testing and ART initiation and follow-up). All individuals 15 years of age and older in the waiting area will be offered a self-test kit.

Clients who tested HIV negative within the past 3 months, previously tested HIV positive, are currently taking ART, are uncomfortable administering the self-test kit, or would like to receive an assisted HIV test either through standard HIV testing protocols or a provider observed HIV self-test kit will be advised to opt-out from the HIV self-test. Those who would like to opt-out for any reason will be asked to take a kit and give the unopened kit to the research team during a brief exit survey.

Those who would like to take the self-test will perform the test while waiting for their appointment. In order to avoid unintended disclosure to participants sitting in the waiting area, after the sample is obtained, individuals will be instructed to put the kit into the opaque testing bag while waiting for the test results in order to ensure privacy and minimize risk of adverse outcomes due to unintended disclosure (approximately 20 minutes). Participants will be allowed to perform the self-test while seated in the waiting area or may move to a more private location on the facility grounds. A private space (tent or other sectioned off area of the waiting area) will be available for individuals who wish to read their test before entering the provider consultation room. After completing the test, participants may do any of the following:

- Individuals who are willing to share the result with the provider will be asked to bring their kit to the provider for interpretation and counseling.
- Individuals will be asked to give the anonymized self-test kit to the study team during the brief exit survey. The study team will NOT look at the test results, but will staple the opaque bag closed, link the unique identification number on the test bag to the exit survey, and drop the self-test kit into a secure lockbox. Those who do not want to directly give the self-test kit to the study team will be allowed to dispose their test kit in a lockbox located in the waiting area or a lockbox located in the provider consultation room.

Trained research assistants and an HDA will be available in the waiting area to answer any questions.

2. Test Interpretation and Confirmatory Testing

Participants who test positive with the self-test method and disclose results to the provider will be referred to an HDA to have confirmation testing conducted with routine Ministry of Health testing guidelines. These individuals will receive standard of care counseling by facility HDAs and be referred for ART initiation if their confirmatory HIV test is positive.

2.4.3.4. Demographic Data Collection

Participants in the group self-test arm who complete an OPD/STI consultation visit will meet briefly with a study staff member after their visit. The study staff member will collect anonymous demographic data including age, gender, highest level of education, and reason for visit to

OPD/STI clinic. They will also ask whether or not participants performed the HIV self-test, what motivated them to use/not use the self-test, and self-reported test result (if willing to disclose). For those willing, the study staff member will also collect the self-test kit, staple the opaque bag closed (if used), link the unique identification number on the test bag to the exit survey, and drop the self-test kit into a secure lockbox. The study staff member will NOT look at test results.

2.4.3.4 Additional Data Collection for those who: (1) test HIV positive that same day; (2) have not tested but want to test for HIV that same day

Participants who self-report as having (1) tested HIV positive that same day or (2) not tested but want to test for HIV that same day will be asked to complete written consent for collection of identifiable information in order to track linkage other HIV services.

2.4.4. Post-Intervention Interview

A random subset of 60 OPD/STI clients (30 men and 30 women) in the group self-test arm will be asked to participate in an in-depth qualitative interview. These individuals will be selected from at least three different facilities in the group self-test arm and stratified by sex, use of self-testing (or not), and among those self-reporting a positive self-test result, HIV status. In the interview, participants will be asked about their experience with group self-testing, including concerns about privacy, problems performing or interpreting the test, and any perceived harms or benefits resulting from group self-testing.

2.4.4.1. *Registry Data for Triangulation and Linkage*

HIV testing, ART, OPD, and STI registers will be reviewed to measure the number of individuals attending the clinics during the period of the study (denominator), the number HIV tested using routine testing strategies (numerator), the proportion of those tested through routine test strategies who are identified as HIV-positive (yield), and the proportion of those identified as HIV positive who link to ART services. All data will be anonymized from existing registers. Records from OPD and STI clients aged 15 years and older will be included in the study. Over the period of the study, we will be able to determine the proportion of all STI and OPD patients who received a routine HIV test (Determine and Uni-Gold HIV test kits), the proportion of those tested who are HIV-positive, and the proportion of HIV positive clients who linked to ART services.

2.4.6.2. *Focus Group Discussions with Providers*

At the end of Aim 1 implementation, focus group discussions will be conducted with providers at participating OPD, STI, and HTC clinics to understand perceptions and acceptability of group self-testing at OPD and STI clinics. All core providers and supporting staff involved with the self-test intervention will be asked to participate (estimated 5 providers and 8 supporting staff at each site). Each site will complete two focus groups; one with providers and one with supporting staff (10 focus groups in total). Only providers over 18 years of age, actively involved in the self-test intervention, and willing and able to consent will participate. Focus groups will last approximately 45 minutes.

2.5. STATISTICAL METHODS

2.5.1. Outcome Measures

Power Calculations and Statistical Analysis for Primary Outcome Measures

We have 15 clusters available for randomization, and therefore, estimated our sample size assuming a fixed number of clusters (k) and an equal number of clusters per arm (k=5). We also assumed an equal number of participants per cluster (n=1,000) for a total sample size of 5,000 participant per arm (15,000 total). Assuming a type I error of 0.05, an intra-cluster correlation of 0.004, we would expect at least 95% power to detect study arm testing coverage of 5% in study arm 1, at least 10% in study arm 2, and 60% in study arm 3.

We will calculate descriptive statistics, including mean/median, variation (standard deviation, kurtosis), range, and frequency distributions for the demographic and clinical characteristics, overall and by study arm. The outcomes of interest include the proportion of participants tested and HIV-positivity among those tested. Differences in the prevalence of each of the outcomes of interest will be examined by study arm as well as by other factors of interest including demographic characteristics (e.g., age, gender), clinical characteristics (e.g., reason for clinic visit), and structural factors (e.g., geographic location). The differences will be evaluated using t-tests, Mann-Whitney U test (or other non-parametric tests), chi-square methods, and Fisher's exact test as appropriate. In order to assess factors associated with HIV testing/positivity, we will use hierarchical linear models in order to account for clustering of effects within each clinic. Separate models will be developed for each outcome of interest and covariates of interest include patient characteristics (e.g., age, gender) and other structural and contextual factors.

Qualitative Analysis for Secondary Outcome Measures

Our secondary outcomes measured will be feasibility and acceptability of group self-testing including privacy concerns, problems with performing or interpreting self-tests, and perceived harms or benefits resulting from self-testing. Qualitative methods (semi-structured in-depth interviews) will be conducted on a subset of individuals (n=40) from the group self-testing arm. Interviews will be translated and transcribed by trained personnel. Interviews will be analyzed in Atlas.ti v.6.2 using thematic analysis. Two investigators will code the first five interviews by themes and compare coding to reach a consensus. A codebook will be developed, and two coders will independently code all transcripts and compare codes to reach a consensus. For each theme, we will describe the range, central tendency, and context in which each theme emerges.

2.6. COST AND COST-EFFECTIVENESS METHODS

It is expected that group self-testing will be cost-effective compared to standard of care and optimized standard of care for HIV testing. For facilities, fewer HDA staff would be needed to achieve testing coverage, and it is possible that more positives will be identified. The study will estimate differences in overall costs for both standard of care arms and group self-testing. Costs of HIV testing will be estimated as the average cost per individual who completes an HIV test.

Using the average cost per patient tested we will estimate the cost for identifying each HIV-positive individual. We will compare average cost per HIV-positive individual identified among the three study arms with the primary comparison of optimized standard of care compared to group self-testing. To provide information for HIV program budgets, we will also estimate the annual cost of providing HIV testing at a site under the three strategies evaluated, independent of outcomes.

2.6.1. Costs to Provider (HIV Diagnostic Assistant)

Costs will be measured from the perspective of the HDA (the "provider" of HIV testing). We will use micro-costing methods to estimate the cost of HIV testing in each study arm.[25, 26, 27] We

will first create an inventory of all the resources used to achieve the observed study outcomes. Resources to be captured will include:

- HIV self-test kits
- Standard of care HIV testing supplies - Determine and Uni-Gold test kits
- Other services provided (e.g. counseling interactions)
- Fixed costs of patient care (building space, equipment, human resources)

For each study patient, the quantity (number of units) of resources used will be determined. Unit costs of resources, which are not human subjects data, will be obtained from external suppliers and the site's finance and procurement records and multiplied by the resource usage data to provide an average cost per study patient across centers in each study arm. Costs will be reported as means (standard deviations) and medians (IQRs) in U.S. dollars, using the exchange rate prevailing during the follow-up period.

2.6.2. Cost-Effectiveness

Using the average cost per patient as described above, we will then estimate the cost per outcome achieved in each arm. Two measures of effectiveness will be utilized for the cost-effectiveness analysis: the proportion of individuals tested for HIV and the cost per HIV-positive individual identified. We will calculate the difference in cost divided by the difference in effectiveness between study arms for both measures of effectiveness.

The price of the self-test (if self-testing were to become widely available in Malawi) is currently uncertain. As such, we will conduct a sensitivity analysis where all costs and outcomes remain constant, and the price of self-tests alone is varied. This analysis will then provide a plausible range of the cost-effectiveness of self-testing.

2.6.3. Accrual

Monitoring by the Protocol Team

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones and quality of study conduct.

The team will closely monitor participant accrual based on reports that will be generated at least monthly. The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants and actual accrual following activation. For any site that is delayed in completing the study activation process or that falls short of its accrual projections, the team will work with the research assistant assigned to the site to identify the barriers the site has encountered and the operational strategies and action plans to address these.

The Protocol Team will similarly review key indicators of the quality of study conduct (e.g. data quality, and data and specimen completeness) based on reports and take action with study sites as needed to ensure high quality study conduct.

Monitoring

Operational futility may be considered if the observed accrual patterns are exceedingly different than planned, and the protocol team has had a chance to address the shortcomings of accrual.

3. AIM 2: PARTNER SELF-TESTING

3.1. OBJECTIVES

3.1.1. Primary Objectives:

- To determine whether providing index clients with HIV self-test kits for partners results in a greater number of partners tested as compared to optimized standard of care for partner notification and testing (referral slip)
- To determine whether providing index partners with HIV self-test kits is cost-effective compared to optimized standard of care using referral slips

3.1.2. Secondary Objectives:

- To assess the acceptability of giving self-test kits to index clients for partner testing
- To determine whether providing index partners with HIV self-test kits is superior to optimized standard of care in regard to identifying HIV+ partners (yield of testing)
- To determine whether providing index partners with HIV self-test kits is superior to optimized standard of care in regard to linkage rates among those who identify as HIV-positive
- To determine whether providing self-test kits to index clients and their partner is superior to optimized standard of care in regard to partner disclosure by the index client

3.2. STUDY POPULATION

This study will be conducted among approximately 1,800 individuals 15 years or older who have at least one sexual partner with unknown HIV status. The study population may include participants from Aim 1 who test HIV-positive under any of the three study arms.

The study will be conducted in the same 15 clusters used in Aim 1. The cluster randomization will be retained for Aim 2 such that sites identified as intervention sites for Aim 1 will remain intervention sites for Aim 2 (likewise for standard of care and optimized standard of care sites).

3.2.1. Inclusion Criteria

All of the criteria listed below must be met in order for an individual to be included in this study.

- At least 15 years of age or older
- Willing and able to provide informed consent for participation in this study
- HIV-positive
- Have at least one sex partner in the catchment area with an unknown HIV status at the time of study enrollment (defined as never testing for HIV or testing HIV negative more than 6 months ago)
- No history of intimate partner violence in the past 12 months
- No fear of intimate partner violence as a consequence of participating in the study
- Not enrolled in the INTERVAL study (no co-enrollment)

3.2.2. Exclusion Criteria

Individuals will be excluded from the study if any of the following are identified during screening or any other time during the study:

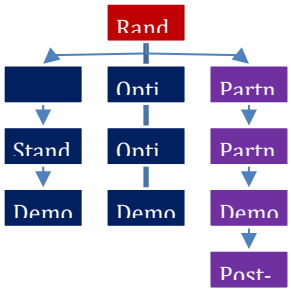
- HIV-negative
- Younger than 15 years of age

- No sex partners with unknown HIV status in the catchment area at the time of study enrollment
- Experienced intimate partner violence during the past 12 months
- Fear of intimate partner violence as a consequence of participating in the study
- Enrolled in the INTERVAL study
- Unwilling or unable to provide informed consent

3.3. STUDY DESIGN

The study will utilize the cluster randomization of Aim 1 and compare use of HIV self-test kits for index clients to provide to partners compared with index partner testing using standard of care and optimized standard of care partner notification strategies (Fig. 3).

FIG 3: OVERVIEW OF STUDY DESIGN



3.3.1. Description of Randomization and Study Arms

Randomization from Aim 1 will be accomplished such that facilities randomized to the self-test intervention in Aim 1 will be self-test intervention sites for Aim 2 and sites randomized to standard of care and optimized standard of care for Aim 1 will continue as standard of care and optimized standard of care sites for Aim 2.

Description of Study Arms

1. Standard of care arm: Facilities randomized to the standard of care arm will use MOH approved referral mechanisms, without any intervention from the study team. Standard of care quality will vary by facility and may include some level of partner referral services for index partners such as referral slips. Referral slips may be given at HIV testing or ART clinics. Sites will be asked to counsel clients to have their partners bring referral slips back to the clinic to document the number of partners presenting for HIV testing. A random subset of HIV-positive clients in the standard of care arm will complete an anonymous survey to answer questions about whether they used referral slips and whether they know if partners came to a health facility for testing.

2. Optimized standard of care arm: Facilities randomized to optimized standard of care will be supported by the study team to systematically perform referral services following Ministry of Health Guidelines. Providers will receive an initial refresher training on partner testing followed by regular mentoring visits. Job aids will also be used to remind providers about the importance of partner testing. Standard of care procedures involve counseling HIV-positive individuals about the importance of partner testing and providing 'referral slips' to the index client to distribute to every sexual partner within the prior 12 months. Referral slips will be used to encourage partners to come to the facility for HIV testing. Sites will be asked to counsel clients to have their partners bring referral slips back to the clinic to document the number of partners presenting for HIV testing. A random subset of participants in the optimized standard of care arm will complete an anonymous survey to answer questions about whether they used referral slips and whether they know if partners came to a health facility for testing.

3. Partner self-testing arm: Facilities randomized to partner self-testing will have study staff give self-test kits to index clients to distribute to every sexual partner with unknown status who lives in the facility catchment area within the prior 12 months (up to three sexual partners). They will also be given self-test kits for themselves so they can participate in couples testing if they choose. All index clients will be counseled on the importance of partner notification and testing and receive a demonstration on how to perform the self-test, so they can show partners. Self-test kits will contain information on how to use the test and a referral card. The referral card will contain information on where to present for confirmatory testing and where partners can receive ART, including a map to the facility. Index clients will be counseled to tell their partner to drop the completed test in a lockbox at the local health facility. A study phone number will also be provided in order to facilitate community-based collection of kits if participants are unwilling or unable to attend the facility. Written instructions, picture instructions, and maps will also be provided to the index client to give to the index partner. Index clients will also be counseled to encourage partners to present to the facility for routine HDA testing if they are unable or uncomfortable completing the self-test.

3.3.2. Recruitment, Screening, and Enrollment Process

Standard of care arm

There will be no study "interventions" at the sites. A random subset of individuals will be recruited to complete a survey at the time they complete ART visits. Individuals will be screened to confirm they meet inclusion criteria, including having at least one partner of unknown status living within the facility catchment area at the time of their last clinical visit. After oral informed consent has been obtained, enrolled participants will complete a brief anonymous survey.

Optimized standard of care arm

Recruitment, screening, and enrollment will be the same as described above for standard of care sites.

Partner self-testing arm

Individuals will be recruited and initially screened by providers (HDAs and/or ART providers) who will identify HIV-positive clients 15 years of age and older with at least one partner who has unknown HIV status. Screening will be performed in a private space where no other clients or staff can hear the exchange of information. Eligible index clients will be referred to study staff for further screening (see 2.2.1 and 2.2.2 for inclusion/exclusion) and those who provide written informed consent will be enrolled.

1. Informed Consent

Written informed consent will be obtained before any study-specific procedures are performed. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. For standard of care and optimized standard of care arms (arms 1 and 2), informed consent will include a broad, general description of study objectives. Specific descriptions about the primary outcome of interest (index partner testing) will not be discussed in detail as the discussion may influence client behavior regarding partner testing, skewing findings. For the intervention arm (arm 3, self testing), the process will emphasize the randomized nature of the study and the differences that participants may experience as part of the study relative to current local standards of care.

2. Participant Withdrawal or Termination from the Study

Individuals may withdraw from the study at any time. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Site investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs

4. STUDY PROCEDURES

4.1. Standard of Care Arm

3.4.1.1 Provision of Services

Facilities in the standard of care arm will provide routine services. No intervention activities will be conducted. Standard of care procedures involve counseling HIV-positive individuals about the importance of partner testing and providing 'referral slips' to the index client to distribute to sex partners. Partner testing will follow Ministry of Health National Guidelines using serial testing with Determine and Uni-Gold. Those that test positive will be counseled and referred to ART services following routine care.

3.4.1.2 Baseline Visit for Index Client

A random sample of individuals will be screened and consented as they exit their ART visit. This will include ART clients who report having a sexual partner with an unknown HIV status. After written informed consent has been obtained, study staff will collect basic socio-demographics (including age, gender, marital status, and number of partners), HIV characteristics (date of HIV diagnosis, whether on ART and date started), and the number of eligible sexual partners who qualify for index testing referral slips. Individuals will also be asked whether they were offered a referral slip on the day of the survey.

Follow-up Visit of Index Clients

All index clients will be seen by study staff when they come for their next ART follow-up visit. A brief survey will be performed to collect information about whether the client disclosed their HIV status to their sex partner(s), whether they gave referral slips to their partner(s), and knowledge about whether partners completed a test, knowledge of their partner's test result, and knowledge about their partner's linkage to care. We will also survey the index client to determine whether any gender-based violence or fear of gender-based violence resulted from use of the self-tests. Index clients who do not return for their ART follow-up visit (more than two weeks late) will be traced through standard site protocols and surveyed either in the community or at the facility, if they return to care.

HIV testing registers will also be reviewed to measure the number of individuals tested through partner referrals and the proportion of partner referral tests who were identified as HIV-positive. All registry data will be anonymized. Records from partner notification clients aged 15 years and older will be included in the study. For those who are HIV-positive, the HTC and ART registers will be reviewed to determine if the patient started ART and presented for their four-week follow-up visit.

4.2. Optimized Standard of Care Arm

4.2.1. Partner Notification and Referral

The study team will provide trainings, job aids, and regular mentorship to promote optimized standard of care in regards to partner notification and referral strategies for HIV-positive clients with partners who have an unknown HIV status. Under optimized standard of care, providers will ask clients at every ART visit whether they have current or recent (within 12 months) sex partners with unknown HIV status or tested negative for HIV more than 6 months ago. Clients will be counseled on the importance of partner notification and testing and given a partner notification slip to assist in partner notification and testing referral. Individuals will be counseled to ask their partners to return the referral slips when they come for testing. Partners who present at the facility for HIV testing will be tested in private rooms by trained HDAs following Ministry of Health guidelines. HDAs will ask all clients presenting for testing whether they were referred by a partner and this will be indicated in a column in the HIV testing register. Serial HIV testing will be performed with Determine and Uni-Gold as per standard of care. Those that test positive will be counseled and referred to ART services. ART initiation will follow standard clinic protocols under the universal treatment (Test and Treat policy).

3.4.2.2 Baseline Visit for Index Client

A random sample of individuals will be screened and consented as they exit their ART visit. This will include ART clients who report having a sexual partner with an unknown HIV status. After written informed consent has been obtained, study staff will collect basic socio-demographics (including age, gender, marital status, and number of partners), HIV characteristics (date of HIV diagnosis, whether on ART and date started), and the number of eligible sexual partners who qualify for index testing referral slips. Individuals who consent will also be asked whether they were offered a referral slip on the day of the survey.

Follow-up Visit of Index Clients

All index clients will be seen by study staff when they come for their next ART follow-up visit. A brief survey will be performed to collect information about whether the client disclosed their HIV status to their sex partner(s), whether they gave referral slips to their partner(s), and knowledge about whether partners completed a test, knowledge of their partner's test result, and knowledge about their partner's linkage to care. We will also survey the index client to determine whether any gender-based violence or fear of gender-based violence resulted from use of the self-tests. Index clients who do not return for their ART follow-up visit (more than two weeks late) will be traced through standard site protocols and surveyed either in the community or at the facility, if they return to care.

HIV testing registers will also be reviewed to measure the number of individuals tested through partner referrals and the proportion of partner referral tests who were identified as HIV-positive. All registry data will be anonymized. Records from partner notification clients aged 15 years and older will be included in the study. For those who are HIV-positive, the ART register will be reviewed to determine if the patient started ART and presented for their four-week follow-up visit.

At the time of follow-up, a random sample of 40 index clients (20 men and 20 women) will be selected and asked to participate in semi-structured, in-depth interviews to explore the feasibility and acceptability of providing referral slips to partners, including challenges with disclosure and questions around harm or perceived risk of harm due to distributing the referral slip.

4.3. Partner Self-Testing Arm

3.4.4.1 Baseline Visit for Index Client

A random sample of individuals will be screened and consented as they exit their ART visit. This will include ART clients who report having a sexual partner with an unknown HIV status. After written informed consent has been obtained, study staff will collect basic socio-demographics (including age, gender, marital status, and number of partners), HIV characteristics (date of HIV diagnosis, whether on ART and date started), and the number of eligible sexual partners they plan to give self-test kits.

The study staff will counsel the index client on how to administer an HIV self-test and will provide one self-test kit for each sexual partner within the last 12 months with unknown status (or HIV-negative more than 6 months ago) who lives within the catchment area of the facility and for whom the index client is willing to provide the test kit (up to three sexual partners). Index clients will also be given self-test kits for themselves if they wish to use them to complete couples counseling. All HIV self-test kits will be labeled with a unique ID linked to the index client participant. The ID will also be used to link index client survey responses with returned self-test kits.

The number of partners and the number of kits provided will be documented by study staff. Each self-test kit will be in a package that also contains a referral card. The referral card can be used for (1) those who test HIV-positive and need to present for confirmatory testing and link to care, (2) those who do not want to use the self-test kit and would rather test with an HDA, or (3) clients who experience difficulty or discomfort with the self-test kit and choose to test at a facility. The referral card will include information about the fa-

cility, including a map. The card will also contain a notation that if it is returned to another facility, the facility should contact the study team so that the card can be collected and recorded as "returned". Study staff will periodically visit nearby testing sites to determine if any referral cards have been returned to those sites.

3.4.4.2 Partner Self-Testing

Index clients will provide their partners with the following instructions verbally. The following instructions will also be provided on the referral form in picture form and in the local language:

1. Complete HIV self-test
2. If the self-test is positive, bring the self-test kit and referral card to the clinic for confirmatory testing and linkage to care.
3. If the self-test is positive and the client does not wish to present for further care, the self-test kit should be disposed of in the lockbox at the HSA house.
4. If the test is negative, the client will be instructed to dispose the self-test kit in a lockbox at the HSA house in the local community or may bring the kit to the lockbox at OPD/STI.

Any individual who has difficulty with the self-test kit or needs help with interpretation can come to the facility with the kit and the referral card and be seen by an HDA for assistance and/or standard of care HIV testing.

3.4.4.3 Follow-up of Partner Self-Testing

The number of index partners tested will be determined based on the number of self-test kits returned to village and health facility lockboxes and triangulated with self-reports from a follow-up survey with the index client. Additionally, partners with a positive self-test kit who present to the facility for confirmatory testing and linkage to care, and/or partners who did not use the self-test kit but present to the facility for HIV testing will be accounted for through the returned referral cards. Like self-test kits, referral cards will be identified with a unique code, allowing the partner to be linked to the index client.

For those who are HIV-positive and present to the clinic for care, the ART register will be reviewed four weeks later to determine if the patient starts ART and presents for their four-week follow-up visit. All data from registers will be anonymized for use by the study team. In addition, index clients will provide self-reports about partner linkage to ART during a follow-up survey.

3.4.4.4 Follow-up Visit of Index Clients

All index clients will be seen by study staff when they come for their next ART follow-up visit. A brief survey will be performed to collect information about whether the client disclosed their HIV status to their sex partner(s), whether they gave self-test kits to their partner(s), and knowledge about whether partners completed the test, knowledge of their partner's test result, and knowledge about their partner's linkage to care. We will also survey the index client to determine whether they were able to successfully show their partner(s) how to use the kit and whether any gender-based violence or fear of gender-based violence resulted from use of the self-tests. Index clients who do not return for their ART follow-up visit (more than two weeks late) will be traced through standard site protocols and surveyed either in the community or at the facility, if they return to care.

A random sample of 40 index clients (20 men and 20 women) and 40 index partners (20 men and 20 women) will be selected and asked to participate in semi-structured, in-depth interviews to explore the feasibility and acceptability of providing self-test kits to partners, including challenges with disclosure and questions around harm or perceived risk of harm due to distributing the kits.

2.4.4.5 *Follow-up Visits with Index Partners*

Index partners will be recruited for in-depth interviews through index clients (n=40). During follow-up visits with index clients, a random subset of clients will be given a study invitation card to be given to their sexual partner who was given a self-test kit. The study invitation card will describe the in-depth interview they are being recruited for and provide a study-specific phone number the index partner can call in order to participate in the study. In addition, index clients will be asked if the study team could call the randomly selected partner to discuss the study. Index clients will be told the purpose of the call. If index clients give permission to contact the index partner, up to 2 phone numbers will be collected. Index partners will be called up to 3 times over a 2-week period for recruitment into the study. If the index partner cannot be reached after the third try, the partner will be listed as "unreachable" and excluded from the study.

For index partners contacted by the study staff, oral consent for screening and eligibility screening will take place via phone. Those who agree and are deemed eligible for the study will decide on a time and place for completing full oral consent to participate in the study and completing one in-depth interview. Interested respondents will choose the location of their choice, either at the facility or in their local community. Interviews will last approximately 60 minutes. Interviews will provide additional information about the feasibility and acceptability of providing self-test kits to partners, including challenges with completing the test, questions around harm or perceived risk of harm, and challenges linking to care at health facilities.

5. STATISTICAL METHODS

5.1. Outcome Measures

3.5.1.1 Sample Size and Statistical Analysis for Primary Outcome Measures

We will have 15 clusters (facilities) available for randomization, and therefore, estimated our sample size assuming a fixed number of clusters (k) and an equal number of clusters per arm. We also assumed an equal number of participants per cluster. The below calculations were determined using a minimum sample size. Assuming a type I error of 0.05, an intracluster correlation of 0.004 and sample sizes of 600 HIV-positive patients per arm, we have 89% power to detect a difference in testing coverage of 20% in study arm 2 (optimized standard of care) and 40% in study arm 3 (self-testing). Because we are uncertain about the proportion of partners who will test under each arm, we have considered a range of possibilities, with the majority of scenarios providing at least 87% power to detect a difference between the two arms of interest (optimized standard of care and self-testing) (Figure 4).

We will calculate descriptive statistics, including mean/median, variation (standard deviation, kurtosis), range, and frequency distributions for the demographic and clinical characteristics, overall and by study arm. The outcomes of interest include the proportion of partners tested and HIV-positivity of partners. Differences in the prevalence of each of the outcomes of interest will be examined by study arm as well as by other factors of interest including demographic characteristics (e.g., age, gender), clinical characteristics (e.g., reason for clinic visit), and structural factors (e.g., geographic location). The differences will be evaluated using t-tests, Mann-Whitney U test (or other non-parametric tests), chi-square methods, and Fisher's exact test as appropriate. In order to assess factors associated with partner's HIV testing/positivity, we will use hierarchical linear models in order to account for clustering of effects within each clinic. Separate models will be developed for each outcome of interest and covariates of interest include patient characteristics (e.g., age, gender) and other structural and contextual factors.

Qualitative Analysis for Secondary Outcome Measures

Our secondary outcomes measured will be feasibility and acceptability of partner self-testing, privacy concerns, problems with performing or interpreting self-tests, and perceived harms or benefits resulting from self-testing. Qualitative methods (semi-structured in-depth interviews) will be conducted on a subset of index clients (n=30) from the partner self-testing arm and 30 from the optimized standard of care arm (n=30). Qualitative methods will be the same as those outlined in Aim 1.

6. COST AND COST-EFFECTIVENESS METHODS

It is expected that partner self-testing will be cost-effective compared to optimized standard of care. For facilities, fewer HDA visits by patients should save the time of HDA staff. Partner self-testing may also lead to an increase in HIV-positive individuals identified because clients may be more comfortable doing the test in a private place. The study will estimate differences in overall costs for both optimized standard of care and partner self-testing. The average cost per successful outcome (index partner completes an HIV test) will be calculated.

Using the average cost per patient as described above, we will then estimate the cost for each newly identified HIV-positive partner. We will compare average cost per HIV-positive individual identified between study arms. To provide information for HIV program budgets, we will also estimate the annual cost of providing HIV testing under the two main strategies being evaluated (optimized standard of care and self-testing), independent of outcomes.

6.1. Costs to Provider

Costs will be measured from the provider perspective. We will use micro-costing methods to estimate the cost of HIV testing in all three study arms.[25, 26, 27] We will first create an inventory of all the resources used to achieve the observed study outcomes. Resources to be captured will include:

- HIV self-test kits
- Standard of care HIV testing supplies
- Other services provided (e.g. counseling interactions)
- Fixed costs of patient care (building space, equipment, human resources)

For each study patient, the quantity (number of units) of resources used will be determined. Unit costs of resources, which are not human subjects data, will be obtained from external suppliers and the site's finance and procurement records and multiplied by the resource usage data to provide an average cost per study patient across centers in each study arm. Costs will be reported as means (standard deviations) and medians (IQRs) in USD, using the exchange rate prevailing during the follow up period.

6.2. Cost-Effectiveness

Using the average cost per patient as described above, we will then estimate the cost per outcome achieved in each arm. The main measure of effectiveness for the cost-effectiveness analysis will be both the primary study outcome of proportion of partners tested as well as yield (newly identified HIV-positive partners of index cases). We will calculate the difference in cost divided by the difference in effectiveness among study arms for both effectiveness measures.

The price of the self-test itself is currently uncertain because it is not widely available in Malawi. As such, we will conduct a sensitivity analysis where all costs and outcomes remain constant, and the price of self-tests alone is varied. This analysis will then provide a plausible range of the cost-effectiveness of partner self-testing.

6.3. Sample Size and Accrual

Monitoring by the Protocol Team

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones and quality of study conduct.

The team will closely monitor participant accrual based on reports that will be generated at least monthly. For any site that falls short of its accrual projections, the team will communicate with the site research assistants and leadership to identify the barriers the site has encountered and the operational strategies and action plans to address these.

The Protocol Team will similarly review key indicators of the quality of study conduct (e.g. data quality and data completeness) based on reports and take action with study sites as needed to ensure high quality study conduct.

4. DATA HANDLING AND RECORD KEEPING

4.1. DATA MANAGEMENT RESPONSIBILITIES

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including CRFs and supporting source data. Depending on capacity and infrastructure of sites/regions, data will either be collected by hand and entered into a database or collected electronically with data uploaded to a database.

All data must be transferred to the central database within timeframes specified in the forms' instructions; queries must also be resolved in a timely manner.

5. SITE MONITORING

Site monitors will visit study sites to inspect study facilities and review participant study records including consent forms and CRFs, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. Site investigators will make study facilities and documents available for inspection by the monitors.

6. SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study.

7. HUMAN SUBJECTS PROTECTIONS

7.1. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE REVIEW AND APPROVAL INCLUDING INFORMED CONSENT

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and ICFs; subsequent to initial review and approval, IRBs/ECs must review the study at least annually.

All IRB/EC policies and procedures must be followed, and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the EQUIP Protocol Team.

Informed consent will be obtained before any study-specific procedures are performed. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will emphasize the randomized nature of the study and the differences that participants may experience as part of the study relative to current local standards of care.

7.2. POTENTIAL BENEFITS

There may be no direct benefit to participants who take part in this study, though participants who are randomly assigned to the self-testing study arms may benefit from the convenience and privacy of completing an HIV test at a location and time of their choosing. Information learned in this study may be of benefit to participants and others in the future, particularly information that may lead to optimized testing guidelines.

7.3. POTENTIAL RISKS AND DISCOMFORTS

Most study procedures are routine clinical care associated with minimal to no risk in participants. Participation in the group self-testing arm in Aim 1 may feel some psychological stress or discomfort from testing and receiving HIV test results in a public setting. Participation in surveys and qualitative interviews may also cause some psychological stress or discomfort. Participants may decline to participate in the self-testing or decline to answer any questions that make them uncomfortable. Participants in Aim 2 will be screened for risk of intimate partner violence, and those with any risk will be excluded.

7.4. REIMBURSEMENT/COMPENSATION

Participants who complete qualitative interviews will be reimbursed/compensated for their time and any transport costs. Participants in the self-testing arm of AIM 2 (partner self-testing) will also be reimbursed/compensated for their time. Index partners participating in a in-depth interview will be reimbursed for transport costs associated with the interview if they choose to conduct the interview at the health facility. The amount of reimbursement will be deemed appropriate by the Malawi NHSRC.

7.5. PRIVACY AND CONFIDENTIALITY

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only.

Study sites are encouraged to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password-protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information will be stored in a separate, locked location in an area with limited access.

7.6. MANAGEMENT OF NEW INFORMATION PERTINENT TO STUDY PARTICIPATION

Study staff will provide participants with any new information learned over the course of the study that may affect their willingness to participate.

8. ADMINISTRATIVE PROCEDURES

8.1. REGULATORY OVERSIGHT

This study is sponsored by USAID/PEPFAR and implemented through Partner in Hope (PIH)-EQUIP. PIH-EQUIP staff will perform monitoring visits. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable regulatory requirements.

Site-specific ICFs will be reviewed and approved by the EQUIP key personnel, and sites will receive an Initial Registration Notification from EQUIP that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the EQUIP Protocol Team. EQUIP key personnel will review the submitted protocol registration packet to ensure that all the required documents have been received.

8.2. STUDY IMPLEMENTATION

Study implementation at each site will also be guided site-specific standard operating procedures (SOPs). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

8.3. PROTOCOL DEVIATION REPORTING

All protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported to the Protocol Team as soon as possible.

9. PUBLICATIONS

All presentations and publications of data collected in this study are governed by EQUIP and USAID/PEPFAR policies.

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