Expanding HIV testing among Ugandan Adults who Utilize Traditional Healers: a cluster randomized controlled trial

Version Date 1 August 2018

WCMC IRB number: 18030119105
MUST Ethical application number: 16/01-17
Clinicaltrials.gov NCT #03718871

Study sponsor: National Institute of Mental Health/US National Institutes of Health (K23MH111409)

Principal Investigator:
Radhika Sundararajan, MD PhD
Assistant Professor
Weill Cornell Department of Emergency Medicine and Center for Global Health
525 East 68th Street
New York NY 10068

Co-Investigators:
Juliet Mwanga-Amumpaire, MD
Director, Epicentre Research Centre and
Associate Professor of Pediatrics
Mbarara University of Science and Technology
Mbarara, Uganda

Daniel Fitzgerald MD
Director, Weill Cornell Center for Global Health
402 East 67th Street
New York NY 10068

Table of Contents

ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
DSMB	Date Safety and Monitoring Board
HIV	Human immunodeficiency virus
IRB	Institutional Review Board
ISS	Immune suppression syndrome
MUST	Mbarara University of Science and Technology
NIH	National Institutes of Health
NIMR	National Institute of Medical Research
PI	Principal Investigator
POC	Point of care
PrEP	Pre-exposure prophylaxis
TH	Traditional healer
WCMC	Weill Cornell Medical College
WHO	World Health Organization

1. PROTOCOL SUMMARY

Study Summary: HIV antiretroviral therapy has the potential to dramatically decrease HIV transmission worldwide[1]; yet, a barrier to ending the AIDS epidemic in low-resource settings is the fact that healthcare is largely provided by traditional or spiritual healers rather than biomedical providers[2-4], and there are no strategies in place to identify HIV-infected patients among Traditional Healer patients and link them to HIV care. In order to reach the UNAIDS 90-90-90 benchmarks HIV services must reach marginalized populations in endemic regions[5], such as in southwestern Uganda. Uganda is one of seven sub-Saharan African countries accounting for 90% of all new HIV infections in this region[6]. HIV prevalence is 7.3%, with ~1.5 million people living with HIV/AIDS and 99,000 new infections in 2014[7]. However, only 50% of sexually active Ugandans have *ever* tested for HIV[8,9]. Like much of sub-Saharan Africa, the majority of Ugandans utilize traditional and faith-based healers[10,11]. Healers are more accessible than biomedical providers in resource-poor settings. Use is driven by preference as well as accessibility: healers are considered uniquely qualified to treat afflictions believed incurable by biomedicine[12]. They are respected community leaders who shape clients' utilization of HIV services[4]. Those who utilize traditional healers may present to biomedical facilities late in their illness, or not at all[13].

Study Aim and Overall Study Design: Develop a *POC HIV testing intervention at TH locations using* a cluster randomized study design. This study will be conducted among TH clients at 10 TH practice locations, to be compared with a control group receiving usual TH care. This pilot will offer HIV testing at TH practice sites to 250 TH clients. Primary outcome for this study will be *rates of HIV testing among TH clients*. Secondary outcomes will include i) *number of new HIV diagnoses* among TH clients, ii) *socio-demographic factors that predict HIV testing*, and iii) *percentage of patients with +HIV POC test who successfully link to HIV care in 3 months*.

This novel approach will have significant public health impact by expanding HIV testing and linkage to care, thereby reducing morbidity, mortality, and HIV transmission in a highly endemic region. This approach could be scaled for delivery in other HIV-endemic, medically pluralistic communities. Pilot results will be integrated with data from ongoing research in southwestern Uganda to propose a large-scale, cluster-randomized trial of this community-based HIV testing program in Eastern Africa.

Study Duration: 12 months (July 2019 – June 2020)

Primary Endpoint: Rate of HIV testing among TH clients at 3 months

Secondary Endpoints: i) number of new HIV diagnoses among TH clients at 3 months post enrollment; ii) percentage of patients with +HIV POC test who successfully link to HIV care at 3 months post enrollment and iii) variables that predict HIV testing.

2. BACKGROUND AND RATIONALE

HIV antiretroviral therapy (ART) has the potential to dramatically decrease HIV transmission worldwide[1,2]. UNAIDS has set the goal that 90% of HIV-infected people should be tested and know their status, so they can access life-saving ART[14,15]. In order to reach the UNAIDS benchmarks, HIV testing must reach marginalized populations in endemic regions[16]. Decentralized[5], community-based[4,5] approaches have been promoted as the key to expanding access to HIV care within low-resource settings. However, successful implementation of community-based services requires an understanding of the social and cultural context that influence community engagement with HIV services. Specifically, many HIV endemic regions are also *medically pluralistic* communities, where multiple explanatory frameworks for health and disease co-exist. In these areas, HIV testing and ART clinical care do not occur in isolation; traditional healers are commonly utilized instead of or concurrently with biomedical services[8,9]. Therefore, the success of decentralized, community-based HIV services must be founded upon a thorough understanding of medical pluralism, and engagement with traditional healers as stakeholders in community health.

Uganda is one of seven sub-Saharan African countries accounting for 90% of all new HIV infections in this region[17]. HIV prevalence is 7.3%, with ~1.5 million people living with HIV/AIDS and 99,000 new infections in 2014[6]. However, only 50% of sexually active Ugandans have *ever* tested for HIV[7]. These data indicate poor progress towards the UNAIDS 90-90-90 targets for ending the HIV epidemic[8,9]. *Our study will characterize factors that shape HIV testing behavior among communities with poor biomedical engagement and pilot an intervention to expand access to HIV testing.* Patients prefer to visit traditional healers to treat "African" diseases, believed incurable by biomedicine[16]. Healers in sub-Saharan Africa serve as herbalists, counselors, social workers, spiritual guides, and legal advisors[12]. Pregnant women may prefer healers as home birth attendants over biomedical facility deliveries[10,12,13,18-21]. Healers are authorities on health concerns, and considered more credible sources of health information than healthcare workers or biomedical clinicians[18,20,21]. As higher rates of HIV testing[3,11,13] and improved engagement with HIV care[22] are correlated with regular contact with a health provider, healers are potential partners for HIV-infected clients throughout the care continuum[23-25]. Our study *will investigate feasibility of involving TH in HIV testing and pilot an intervention to expand HIV testing within communities that use traditional medicine.*

An AIDS-free generation cannot be achieved until HIV care is expanded to communities where the burden of disease continues undetected[26-28]. Healers have access to patients and potential influence to promote HIV testing and engagement with ART services. The proposed research holds promise for dramatically expanding HIV testing and early engagement with HIV services to a large population who otherwise may not access biomedical care.

3. STUDY DESIGN

3.1 Design: Previously conducted qualitative work and observational data will inform implementation of a pilot study, offering HIV testing at traditional healer locations in southwestern Uganda. No compensation will be provided for healers in the intervention or control arms of the intervention. We will follow Ugandan National protocols[29] to administer voluntary HIV counseling and testing at healer practices in Mbarara District. Clustering for this trial will occur at the level of healer practices. For the intervention arm, we will recruit 250 clients from ten healer practice locations. For the control arm, we will observe 250 healer clients at ten healer locations undergoing "enhanced standard of care", where healers will participate in a pre-trial educational session describing community HIV resources available for clients, and how to access them. Enrollment will take place from twenty traditional healer practices, over a period of four months. The follow up period will be three months. Primary outcome for this intervention *will be rates of HIV testing among TH clients* (**Figure**).

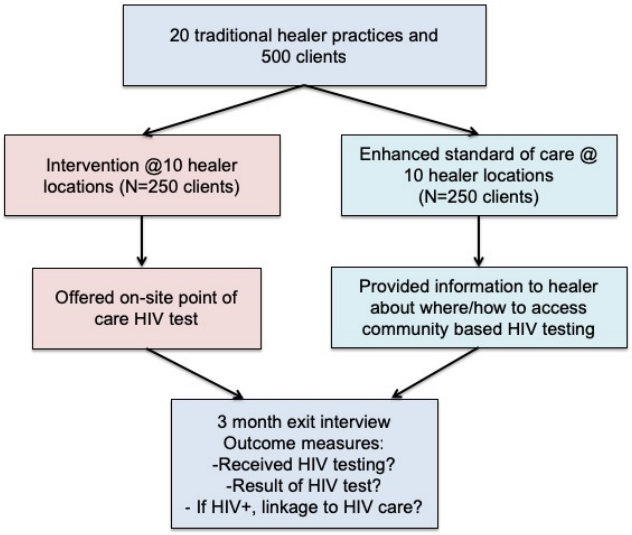

Figure. Approach for HIV testing pilot

3.2 Overall Approach: We will select twenty traditional healer practices to participate in this study from among the ~170 known practices in this District, and group them by specialty (herbalist, birth attendant, spiritualist, bone setter). Within each specialty group, we will randomly select half to participate in the intervention arm (N=10); the remaining half will participate in the control arm (N=10). Healers in both study arms will keep a log of participants indicating whether HIV testing was delivered (intervention) or if the participant was referred to HIV testing (control). Many healers have little formal education and describe themselves as "illiterate"; study logbooks will be created accordingly. Research assistants will create stickers with de-identified study identification numbers for each participant. The healer will place the participant ID sticker in the log book (thereby avoiding the need to be able to write numbers); logs will show pictures for receiving point-of-care HIV testing, or not testing (in the intervention arm), or referral to the District HIV clinic for HIV testing, or not referring (for the control group). Healers will circle the corresponding picture for each participant based on the outcome of the session. Research assistants will be on site, or reachable via mobile phone, to answer any questions the healers have about record keeping or study procedures.

4. RECRUITMENT AND ENROLLMENT

4.1 Inclusion and Exclusion Criteria: Inclusion criteria for healer clients are 1) 18 year of age or older; 2) able to provide informed consent, 3) not known to be HIV infected; 4) willing to be contacted for monthly follow up for 3 months; and 5) willing to complete an exit survey after 3 months. For the intervention (HIV testing) arm, participants must agree to receive their POC HIV test results. Exclusion criteria include being under the age of 18, incapable of giving informed consent, previously being diagnosed with HIV, being unwilling to receive HIV test results, and

unwilling to participate in the testing intervention. Participating healers are eligible to participate if they meet the UNAIDS definition of traditional healer[8], and are willing to participate in study procedures. We will select from among healers with patient volume greater than 7 patients per week in order to ensure that participant recruitment progresses in a timely manner for this pilot study.

4.2 Informed Consent: We will obtain written informed consent from both traditional healers (N=20) and their clients (N=500) participating in this study. Participating clients must consent to providing three telephone contact numbers (self, friend, and family member), home address, and permission for the research team access to medical records from the District HIV clinic. In addition, they must consent to a home visit, if they are not reachable for follow up via phone. Healers must consent to keeping a logbook of which patients received HIV testing (intervention arm) or referred to HIV testing (control arm).

4.3 Subject Enrollment: One research assistant will be assigned to each arm of the study and will base themselves at healer practices to consecutively enroll 25 clients from each healer until we reach as sample size of N=500 (four-month enrollment period). The research assistant will assign a unique study ID number to each participant, collect demographic information, and locator information for the participant and two back up contacts. This information will be used for monthly follow-up assessments, and to deliver the exit interview.

4.4 Sample size: N=250 adults will be enrolled in each arm. Community-based HIV-testing in sub-Saharan Africa has excellent uptake (~97%)[30]; based on these data, we expect 90% uptake of HIV testing in our intervention arm. Assuming HIV prevalence is equivalent to that in our cross-sectional study (9%), we will identify ≥20 newly diagnosed HIV-infected patients among our sample of TH clients ([250 x .90] x 0.09 = 20.25). This aim is exploratory in nature. Sample size will be calculated based on data from an observational census of traditional healers in the study area and will be included in a forthcoming amendment.

5. STUDY PROCEDURES

5.1 Intervention arm: Healers assigned to the intervention arm (N=10) will attend a half-day training session prior to trial initiation, led by District HIV clinic staff. This training session will demonstrate proper use and disposal of the point-of-care HIV testing kit and provide training regarding patient pre- and post-test counseling. Healers will be instructed to discuss the benefits of linking to HIV care, including importance of initiating treatment for HIV infection, reducing possible transmission to others, and health benefits of starting ART early, as part of post-test counseling. In addition, this training session will discuss resources available at the ISS clinic, including mental health counselors, family and partner support groups, counselors trained to discuss serostatus disclosure strategies, and reproductive health counselors. Supplies for point-of-care HIV testing and biohazard-compliant disposal will be provided to healers at the start of the trial. HIV 1/2 antibody point of care test (Oraquick©) will be administered to participants who agree to test. This test is non-invasive, conducted using oral fluids (rather than whole blood), and is FDA-approved for adult use, with results in 20 minutes. Test results are clearly marked with lines, rather than letters or numbers; this test is validated for use by non-medical personnel, with 99.9% specificity and 91.6% sensitivity. Clients with positive tests will be referred to the HIV clinic for Western Blot confirmation, and linkage to care. Following the healer visit, participants will be contacted once per month, for a period of 3 months, to assess for POC test results, and linkage to care for those who test HIV+.

5.2 Control arm: Control arm healers (N=10) will participate in a half-day session prior to trial initiation, led by District HIV clinic staff. This educational session will discuss WHO and Ministry of Health guidelines for HIV testing, who should receive HIV testing and how often, and where to receive it. Participating patients of healers will then receive "enhanced standard of care" as part of the control arm of the trial. Following the visit, study staff will contact the client once per month, for 3 months, to assess for HIV testing since enrollment in the study.

5.3 Follow up: We will contact participants using their mobile phone numbers. If unable to reach after multiple attempts, study staff will call the backup contact to inquire about the participant's (taking care not to mention HIV). If this inquiry is not informative, study staff will visit the participant's home, wearing unmarked clothes and not speaking about HIV with anyone except privately with the participant. In 2014, a Pew Research Center survey indicated that 65% of Ugandans owned a mobile phone (http://www.pewglobal.org/2015/04/15/cell-phones-in-africa-communication-lifeline/); therefore, we anticipate that a majority of participants will have a mobile contact number. If unable to reach the participant at their mobile phone number after multiple attempts, the backup contact will be called. If no mobile number is available for the participant, we will ask for a mobile number for a backup contact to use for communication. Study staff will call the backup contact to attempt to speak with the participant (taking care not to mention HIV). All calls will be made from study cell phones, not linked to any hospital or clinic, such that caller ID or callbacks to the outgoing number will not indicate correlation with HIV research. This process will be followed for participants in both the intervention and control groups. If these inquiries via phone are not informative, a single member of the study staff will visit the participant's home at the address provided, via personal vehicle, wearing unmarked clothes. This staff member will ask to speak with the participant, and will not discuss the study, or the topic of HIV with anyone, except privately with the participant. If home visits are necessary to establish follow-up, we will send a gender-matched staff member (i.e., female staff member for female participant), to minimize suspicion from family or partners who may not be aware of client's participation in the study. This staff member will describe him/herself as a friend from Mbarara, who is inquiring about the whereabouts of the participant.

6. STATISTICAL CONSIDERATIONS

6.1 Outcomes: The primary outcome for this Aim is *rate of HIV testing among TH clients*. Secondary outcomes will include i) *new HIV diagnoses* among TH clients, ii) *patients with +HIV test who successfully link to HIV care in 3 months*[30], and iii) variables that predict HIV testing. The results of this Aim are central to demonstrating feasibility for a subsequent R01 proposal.

6.2 Analysis plan: Descriptive statistics will characterize participants and summarize the data. A multi-level logistic regression model – with individual clients in level 1 nested within healers in level 2 – will be used to calculate the odds ratio for primary outcomes within three months in the intervention compared with the control arms. Adjusted analyses will be conducted as secondary or sensitivity analyses using multivariable, multi-level analyses for both binary and continuous variables. All analyses will be performed in R software.

6.3 Intervention evaluation: 3 months following enrollment, all participants will be contacted for an exit survey to understand experiences of participation in the study, undergoing HIV testing, or deciding not to test. In-depth interviews will be conducted with participating healers at the close of the intervention to obtain feedback on delivering POC testing at their practice locations and assess how the study may have impacted their beliefs and practices.

7. DATA COLLECTION AND MONITORING

7.1 Training and Considerations: All study staff will receive extensive human subjects/research ethics training, including the need for complete confidentiality and to approach questions with sensitivity and in a supportive manner and to provide appropriate referrals when needed. All interviews, surveys and HIV tests will be conducted in private. Study staff will be trained not to press participants to answer questions or engage in intervention activities that seem to be distressing to them, and sessions are terminated if the participant is too distressed, too fatigued, or too frustrated by the effort. Qualitative interviews will be terminated if the participant is too distressed, too fatigued, or too frustrated by the effort. In the event that significant depression symptoms or suicidality are noted, the staff will be instructed to follow procedures in the safety protocol, which include immediately contacting Dr. Mwanga-Amumpaire to arrange referral to appropriate service agencies at Mbarara Regional Referral Hospital or within the community, and reporting incidents or concerns to Dr. Mwanga-Amumpaire or the US-based PI, Dr. Sundararajan.

7.2 Privacy and Confidentiality: We will safeguard against loss of confidentiality in a number of ways. To minimize risk during the consent process, all recruitment and consent for participation will be done in a private tent, with closed panels. Individuals will be recruited separately and undergo informed consent separately (regardless of whether they arrived at the healer location with a friend or family member). This will reduce risk of loss of confidentiality as well as risk of coercion from others. All interviews, surveys, and POC HIV testing will take place in private locations. Pretest and post-test counseling will similarly take place in private tents, therefore minimizing risk of loss of confidentiality during relaying of HIV testing results. During the follow up period, study stuff will not identify the project as one related to HIV; study staff will contact the participant via mobile phone. They will be instructed not to discuss anything related to the study except with the participant. They may visit the participant's home if unable to contact via phone numbers provided. For this, they will wear unmarked clothes and not speak about HIV or the study with anyone, except in private with the participant.

Loss of confidentiality will also be minimized through de-identification of study data. Only the participant's study ID number will appear in the paper or computer-generated files. The key to participants' code number will be encrypted in a computer file, which will be kept in locked offices at MUST. Only Dr. Sundararajan (PI), Dr. Mwanga-Amumpaire, and the research assistants will be able to unencrypt these computer files. In addition, all study staff will be asked to sign a confidentiality pledge. In signing this pledge, the researcher agrees not to divulge the identity of any study participant outside of the study team, nor discuss the particularities of any participant's story with anyone outside the study team.

Study participants may feel reticent to share information about sexual orientation, and this may be a limitation of our study approach. However, the vast majority of HIV transmission in sub-Saharan Africa occurs through heterosexual intercourse[31], and therefore we do not anticipate that unwillingness to disclose homosexual orientation will negatively impact our data collection or results. Participants will be reminded during questionnaire administration that answers regarding sexual orientation will be kept between study participant and research team, and that numerous mechanisms are being undertaken to safeguard their identity, including de-identification of study data.

For potential participants for the testing intervention arm who presents with sexual partners, we will carry out private, individual recruitment and consent, and request if we could include the partner in the HIV testing process. If permission is granted by the participant, then we will 1)

assess if the partner meets criteria for inclusion as a participant; 2) if s/he meets inclusion criteria, the participant will undergo informed consent; and 3) we will conduct the remainder of the study procedures with both members of the couple present, and participating. If the partner does not meet criteria for inclusion, then the partner will be present for his/her partner's study procedures. If permission is refused, we will continue with pre-test counseling, testing, relaying of POC HIV test results, and post-test counseling in private. We will specifically train our research assistants to conduct post-test counseling that discusses issues specific to serodiscordant couples, including reducing risk of HIV transmission, reproductive issues and efficacy of PrEP. In addition, we will encourage the participant to disclose to his/her partner, and refer them to the HIV clinic, which has counselors who specifically assist clients with serostatus disclosure strategies and has resources for serodiscordant couples. By following a strict strategy of individual, private consent, our study procedures seek to reduce coercive influences from partners or family members who may be present with the participant.

MUST has completed numerous research studies on human subjects and maintained full confidentiality of participant records over the preceding decade. MUST has close collaborative relationships with the local HIV clinic, with no-cost resources for testing, treatment and counseling; participants will be referred to these resources as necessary over the course of this research. Due to the nature of this research, we will ensure that study staff undergo training on good clinical practices for human subjects research, with extensive piloting of informed consent and study practices, until staff are comfortable and knowledgeable. Specifically, we will train them to identify situations where coercion may be occurring as to avoid placing undue risk on the potential participant. Refresher courses on relevant topics will be carried out as needed, at least once every 6 months.

7.3 Data Safety and Monitoring: No stopping rules have been defined for this project, given the minimal risks to participants. The research procedures are minimally invasive and present low risks to the study participants. Subjects are volunteers and may drop out of the study at any time, without any recourse. They are informed of such during the consent process.

This study is a pilot intervention, so a DSMB is not required. The PI, Dr. Sundararajan, and local Co-Investigators will review study progress during bi-monthly conference calls. MUST and WCMC IRBs will receive reports annually. Additionally, if necessary, we may utilize the services of the Weill Cornell Medical Center's Data Safety and Monitoring Board (DSMB), which has been designed to ensure the safety and welfare of participants and the validity and confidentiality of data. The board's responsibilities include reviewing protocols, informed consent documents, and plans for data safety and monitoring, evaluating the progress of intervention trials, participant risk versus benefit, periodic assessments of data quality and timeliness, and other factors that can affect the safety of study participants. The board makes recommendations to the PI and NIH (e.g., the observed beneficial or adverse effects of the study, interim analysis of efficacy). The WCMC DSMB meets monthly. The DSMB will receive all adverse event reports and will review stopping rules and interim analyses, where applicable. Data analysis will be conducted every 3 months and discussed with the research team. Annual reports will be submitted to the WCMC IRB, MUST IRB and NIMH.

7.4 Adverse Event Reporting: The Principal Investigator, Dr. Sundararajan, and the Weill Cornell Medical Center IRB will be directly responsible for monitoring the security of the data and safety of participants. Project staff will report emotionally distressed participants to Dr. Sundararajan and Dr. Mwanga-Amumpaire. Dr. Mwanga-Amumpaire will be responsible for evaluating and referring the participant to an appropriate agency at MUST or in the community. Drs. Sundararajan and Mwanga-Amumpaire will be responsible for immediately reporting any

breaches of protocol, breakdowns in the consent process, violations of confidentiality of the data, complaints by participants or any serious problems or adverse events. An incident report will be filed with Dr. Sundararajan. Incident reports, serious problems or adverse events will be reported to the WC IRB by Dr. Sundararajan. The IRB will report to NIH and DHHS if warranted. Requests for the use of these data by persons outside of the project will be decided upon by the PI, Dr. Sundararajan and a committee comprised of coinvestigators. The IRB will be informed and any concerns will be addressed before data are released.

As participation in this study involves minimal commitment, we do not anticipate any negative impact from study closure or from the subject voluntarily leaving the study. Study subjects will not be terminated for any specific reason. All potentially adverse events or serious problems will be reported by Dr. Mwanga-Amumpaire within 48 hours on a standard form and this information will be immediately shared with Dr. Sundararajan for reporting to the Weill Cornell IRB with a copy to the Office of Human Subjects. Study staff will also be debriefed on a weekly basis to address issues that have come up throughout the course of data collection. All project staff will receive verbal and written instructions pertaining to the rules governing the maintenance of confidentiality upon completion of the study or if they leave the study before its completion.

7.5 Quality Assurance: The PIs will oversee data quality control and assurance. They will review all informed consent documents and study eligibility checklist forms. Dr. Sundararajan and Dr. Mwanga-Amumpairewill review data files for internal validity and completeness and send queries to the data management team in Mbarara each week. The team will respond to queries within one week. During the trial, all informed consent and data collection documents will be verified by the study research coordinator.

7.6 Expected Outcomes: The goal of the proposed research is to expand access and engagement with HIV testing in Mbarara by delivering point of care tests at traditional healer locations. This study also has important benefits to healthcare delivery in Uganda as it focuses specifically on early diagnosis of HIV, the leading cause of hospital admissions in this country. The primary and secondary outcomes of the proposed intervention seek to improve health in these regions such that morbidity and mortality are decreased as a result of linkage to outpatient care. The proposed study has the potential to improve rates of HIV testing throughout Uganda, reduce HIV transmission and improve linkage to care. People from other African countries who utilize the services of traditional healers may benefit in the future from the knowledge gained in this study. The results of this study may be expanded to improve access to HIV testing among adults in Uganda and other similar settings. Outcomes will be used to better understand factors influencing engagement with HIV services in endemic areas, where traditional medicine is commonly used. We also hope that the Community Advisory Board formation will facilitate positive, ongoing relationships between healers, biomedical providers, and patients.

8. HUMAN SUBJECTS

8.1 Problems Anticipated:

8.1.2 Psychological risks: For Aim 1, some participants may find it distressing to discuss past HIV testing behaviors, their healthcare seeking trajectory, or experiences with biomedical providers. All study staff will be trained not press participants to answer questions or discuss information that seem to be distressing to them, and to terminate sessions if the participant is overly distressed, fatigued, or frustrated by the effort. In the event that clinically significant depressive symptoms, suicidality, or other psychiatric conditions are noted, the staff will be

instructed to report any incidents or concerns to Dr. Mwanga-Amumpaire, who will assess the participant, offer needed support or arrange for appropriate referral to a counselor or community service provider. In addition, the PI, and all team members have completed Human Subjects Training and Certification Program or equivalent certification at their institution. Dr. Sundararajan has had experience conducting social science research among international, marginalized populations and received previous training in the ethical issues that may arise, and procedures utilized to handle protection against risks. Dr. Mwanga-Amumpaire has years of experience conducting confidential and interviews regarding sensitive topics among socially marginalized and key populations. All study staff will receive extensive human subjects/research ethics training, including the need for complete confidentiality and to approach questions with sensitivity and in a supportive manner and to provide appropriate referrals when needed. Qualitative interviews will be terminated if the participant is too distressed, too fatigued, or too frustrated by the effort. In the event that significant depression symptoms or suicidality are noted, the staff will be instructed to follow procedures in the safety protocol, which include immediately contacting Dr. Mwanga-Amumpaire to arrange referral to appropriate service agencies at MUST or within the community, and reporting incidents or concerns to the US-based PI, Dr. Sundararajan.

It is possible that participants may be identified by others as receiving HIV testing, including healthcare personnel, or sexual partners, or become the subject of HIV-related stigma through participating in this study. In addition, any time a person receives a new diagnosis of being HIV-infected there is a possibility that they will be exposed to stigma from family, partners and other members in their community; external stigma in these cases may involve rejection, estrangement, loss of employment or harassment[32]. Internal stigma may also develop, resulting in shame, depression, and psychological isolation. For women, being HIV-infected may be associated with higher risk of experiencing intimate partner violence. We will work with healers and HIV clinic staff to educate the community to lessen stigma against HIV. Healers will provide post-test counseling for all participants, which will include resources to support their psychosocial health, and provide resources for partners and family members.

8.1.3 HIV test related discomfort: The Oraquick testing process is non-invasive and produces results based on oral fluid samples. We do not anticipate any physical discomfort as a result of the tests administered in the intervention.

8.1.4 Possibility of false HIV test results: Given the high specificity and sensitivity of the rapid tests (99.9% specificity and 91.6% sensitivity), false positives and negatives are unlikely. Participants with positive rapid HIV tests will be referred to the Mbarara Referral Hospital HIV clinic for confirmatory testing, and where they will have CD4 testing and subsequent clinical evaluation. They will be provided specific instructions on how to get there and what to do when they arrive. Healers in the intervention arm will undergo training prior to trial implementation to ensure they are delivering the point of care tests correctly. We note that these point of care tests have been validated for use among laypersons, with extremely high sensitivity/specificity. Research assistants will work with intervention arm healers every few days to ensure testing procedures are followed. Patients with positive HIV testing will be directed to the Mbarara Referral Hospital HIV clinic for confirmatory testing. Patients with negative HIV tests will be counseled to follow up in 3-6 months for re-testing, as is standard protocol according to Ugandan HIV testing guidelines.

8.1.5 Loss of confidentiality: Though this study will include both HIV-infected and non-infected adults, it is possible that participants may be identified by others, including healthcare personnel, as being HIV infected by participating in this study. We will safeguard against this by

conducting interviews, recruitment, and point-of-care testing in private locations. All subject data will be de-identified using a study identification number consisting of a unique code unrelated to any patient identifying information, as per Good Clinical Practice guidelines. Any identifiers linked to the participant will be secured and only available to study staff, to ensure subject confidentiality. Study data will be stored in a locked room at MUST, and on a password protected, encrypted computer. Access to study data will be limited to study staff only. No personally identifiable information will be available during data coding, organization, analysis, or publication. NIMR computers and servers are protected by firewall protection and are only accessible with a password. Study staff will be trained in Good Clinical Practice regarding maintaining confidentiality. We will provide intensive counseling and education to all participants on the importance of confidentiality. In keeping with Ugandan Ministry of Health policy, MUST and Mbarara Regional Referral Hospital does not divulge individual HIV or other results to any third party.

For monthly follow up in Aim 3, study staff will contact the participant via mobile phone. They will be instructed not to discuss anything related to the study except with the participant. They may visit the participant's home if unable to contact via phone numbers provided. For this, they will wear unmarked clothes and not speak about HIV or the study with anyone, except in private with the participant. Participants will be asked to report any breeches in confidentiality, and these will be reported to the IRBs.

8.2 Reasonableness of risks: The research procedures are minimally invasive and present low risks to the study participants. The possible risks include the possibility that participants will become emotionally distressed during the interview process and the potential loss of confidentiality. We have described procedures for dealing with emotional distress or threats to harm self/others, and for minimizing the risk of loss of confidentiality, if it should arise. Given the minimal risks and the safeguards that will be put in place, we believe that the importance of the knowledge to be gained outweighs the potential risks to the subjects involved.

8.3 Obtaining Informed Consent: Written and verbal informed consent will be completed for each participant. During informed consent, the research assistant and potential participant will find a suitable, private location. All potential participants will be told that information gathered in the study is confidential, voluntary, and they are free to take breaks or terminate their participation at any time. A written copy of the informed consent form will be presented in Runyankole or English, depending on the preference of the potential participant. This form will be reviewed orally, and potential participants given opportunity to ask questions. The research assistant will pause after each section and check for understanding by asking the potential participant to describe critical points in his/her own words. If the potential participant agrees to participate, written consent will be documented via signatures from both the research assistant and participant. For those unable to write, they will be allowed to place a thumbprint or "X", with a witness co-signing to ensure proper methods of informed consent have been followed. Each research aim of the study will have its own consent form. Please see those documents attached to this application. No additional consent is necessary. Traditional Healers are considered to have special roles in their communities, as trusted authorities on health, culture and relationships[33] and should be considered key stakeholders for any community-based interventions. As such, their participation and support of this project is highly regarded within specific cultural context. However, this support does not tacitly provide community consent. We will require individual, informed consent for all participants.

The research assistant will review the consent for orally and pause after each section in the consent form to check for understanding by asking the potential participant to describe critical

points in his/her own words. The research staff who will be responsible for obtaining informed consent will assess whether the potential participant has understood the study and consent form by asking key questions (e.g., “How much time will this take you?”; “What are the possible benefits for you?”). Because it is possible that some participants may be cognitively impaired, or they may not initially understand this second consent process, we will test all potential participants for their comprehension of critical in the consent form. Errors will be corrected, and these potential participants will then be asked if they need further clarification. If, after further attempts to clarify any misunderstandings, we determine that they may not fully comprehend the critical aspects of the study, they will not be enrolled.

The vast majority of participants will be non-English speaking, as the primary language in this region is Runyankole. A written copy of the informed consent form will be presented in Runyankole or English, depending on the preference of the potential participant. This form will be reviewed orally, and potential participants given opportunity to ask questions. In addition, we anticipate a significant proportion of potential participants will have low literacy. For those unable to write, they will be allowed to place a thumbprint or “X”, with a witness co-signing to ensure proper methods of informed consent have been followed.

Informed consent documents will be retained in locked filing cabinets and storerooms, accessible only to senior investigators or designated study staff. All study logs are identified by study ID numbers, and names are removed. All computerized databases will only contain study ID numbers. The lists linking study numbers to names are kept separately in a password protected computer, accessible only to PI, Co-Investigator, and Project Manager. Clinicians and counselors have received training on the need to maintain full confidentiality of client data.

9. DISSEMINATION AND PUBLICATION

All collaborators will participate in data analysis and research dissemination. Preliminary results will be presented twice per year to the Community Advisory Board, and to the local academic community through conferences at MUST. Abstracts will be submitted to both international and domestic conferences, and we expect that our results will generate two peer reviewed publications (“HIV testing and traditional healing in northeastern Tanzania: results from a qualitative study”, and “Delivering HIV testing in eastern Africa at traditional healer practices: results from a pilot intervention”). Data from this pilot will serve as the foundation for an R01 submission to the National Institute of Mental Health, for September 2020 (“A cluster-randomized trial of HIV testing at traditional healer practices in eastern Africa”).

REFERENCES

1. Mills EJ, Bakanda C, Birungi J, et al. Life Expectancy of Persons Receiving Combination Antiretrovial Therapy in Low-Income Countries: A Cohort Analysis from Uganda. Annals of Internal Medicine 2011;155:209–16.

2. Bodeker G, Kabatesi D, King R, Homsy J. A regional task force on traditional medicine and AIDS. The Lancet 2000;355(9211):1284.

3. Homsy J, King R, Balaba D, Kabatesi D. Traditional health practitioners are key to scaling up comprehensive care for HIV/AIDS in sub-Saharan Africa. AIDS 2004;18(12):1723–5.

4. King R, Balaba D, Kaboru B, Kabatesi D, Pharris A, Homsy J. The Role of Traditional Healers in Comprehensive HIV/AIDS AIDS AIDS AIDS Prevention and Care in Africa: Untapped Opportunities. In: Marlink R, Tietelman SJ, editors. From The Ground Up. 2009. p. 301–32.

5. Camlin CS, Seeley J, Viljoen L, et al. Strengthening universal HIV “test-and-treat” approaches with social science research. AIDS 2016;30(6):969–70.

6. Joint United Nations Program on HIV/AIDS (UNAIDS). PREVENTION GAP REPORT. 2016.

7. UNAIDS. The HIV and AIDS Uganda Country Progress Report [Internet]. httpwww.aidsuganda.org. 2015 [cited 2015 Sep 21];Available from: http://www.unaids.org/sites/default/files/country/documents/UGA_narrative_report_2015.pdf

8. D CALP, Knowlton AR. Micro-social structural approaches to HIV prevention: a social ecological perspective. AIDS Care 2006;17(sup1):1–82.

9. Ministry of Health II. Uganda Aids Indicator Survey 2011 [Internet]. 2012 [cited 2015 Dec 30];:1–252. Available from: https://www.usaid.gov/sites/default/files/documents/1860/Uganda_AIDS_Indicator_Survey_2011.pdf

10. World Health Organization. WHO Traditional Medicine Strategy 2014 - 2023 [Internet]. httpapps.who.intmedicinedocspdfsese.pdf. 2013 [cited 2015 Dec 30];:1–74. Available from: http://apps.who.int/medicinedocs/pdf/s2297e/s2297e.pdf

11. King R, Homsy J. Involving traditional healers in AIDS education and counselling in sub-Saharan Africa: a review. AIDS 1997;11 Suppl A:S217–25.

12. Green EC. Sexually transmitted disease, ethnomedicine and health policy in Africa. Social Science & Medicine 1992;35(2):121–30.

13. Bodeker G, Carter G, Burford G, Dvorak-Little M. HIV/AIDS: Traditional Systems of Health Care in the Management of a Global Epidemic. The Journal of Alternative and Complementary Medicine 2006;12(6):563–76.

14. Andersen R, Newman JF. Societal and Individual Determinants of Medical Care Utilization in the United States. The Milbank Memorial Fund Quarterly Health and Society 1973;51(1):95.

15. Gelberg L, Andersen RM, Leake BD. The behavioral model for vulnerable populations: Application to medical care use and outcomes for homeless people. Health Services Research 2005;34(6):1273–302.

16. Joint United Nations Program on HIV/AIDS (UNAIDS). 90-90-90: An ambitious treatment target to help end the AIDS epidemic [Internet]. httpwww.unaids.orgsitesdefaultfilesmediaasset--en.pdf. 2014 [cited 2015 Dec 30];:1–40. Available from: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf

17. Ellman T. Demedicalizing AIDS prevention and treatment in Africa. N Engl J Med 2015;372(4):303–5.

18. Ndyomugyenyi R, Neema S, Magnussen P. The use of formal and informal services for antenatal care and malaria treatment in rural Uganda. Health Policy Plan 1998;13(1):94–102.

19. Morris K. Treating HIV in South Africa–a tale of two systems. The Lancet 2001;357(9263):1190.

20. Bulterys M, Fowler MG, Shaffer N, et al. Role of traditional birth attendants in preventing perinatal transmission of HIV. BMJ 2002;324(7331):222–4.

21. Kyomuhendo GB. Low use of rural maternity services in Uganda: impact of women's status, traditional beliefs and limited resources. Reproductive Health Matters 2003;11(21):16–26.

22. Ojikutu B, Nnaji C, Sithole-Berk J, Bogart LM, Gona P. Barriers to HIV Testing in Black Immigrants to the U.S. J Health Care Poor Underserved 2014;25(3):1052–66.

23. Cabral HJ, Tobias C, Rajabiun S, et al. Outreach program contacts: do they increase the likelihood of engagement and retention in HIV primary care for hard-to-reach patients? AIDS Patient Care STDS 2007;21 Suppl 1(s1):S59–67.

24. Tobias C, Cunningham WE, Cunningham CO, Pounds MB. Making the connection: the importance of engagement and retention in HIV medical care. AIDS Patient Care STDS 2007;21 Suppl 1(s1):S3–8.

25. Nyamathi A, Hanson AY, Salem BE, et al. Impact of a rural village women (Asha) intervention on adherence to antiretroviral therapy in southern India. Nurs Res 2012;61(5):353–62.

26. O'Laughlin KN, Wyatt MA, Kaaya S, Bangsberg DR, Ware NC. How treatment partners help: social analysis of an African adherence support intervention. AIDS Behav [Internet] 2012;16(5):1308–15. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3354325&tool=pmcentrez&rendertype=abstract

27. Audet CM, Hamilton E, Hughart L, Salato J. Engagement of Traditional Healers and Birth Attendants as a Controversial Proposal to Extend the HIV Health Workforce. Curr HIV/AIDS Rep 2015;12(2):238–45.

28. Moshabela M, Zuma T, Orne-Gliemann J, et al. “It is better to die”: experiences of traditional health practitioners within the HIV treatment as prevention trial communities in rural South Africa (ANRS 12249 TasP trial). AIDS Care 2016;28 Suppl 3(sup3):24–32.

29. Abdool Karim SS. Overcoming Impediments to Global Implementation of Early Antiretroviral Therapy. N Engl J Med 2015;373(9):875–6.

30. Audet CM, Blevins M, Moon TD, et al. HIV/AIDS-related attitudes and practices among traditional healers in Zambézia Province, Mozambique. J Altern Complement Med 2012;18(12):1133–41.

31. Ugandan Ministry of Health. Uganda National Policy Guidelines for HIV Counselling and Testing. httpwww.who.inthivpubguidelinesugandaart.pdf. 2007;:1–41.

32. King R. Collaboration with traditional healers in HIV/AIDS prevention and care in sub-Saharan Africa. httpdata.unaids.orgpublicationsirc-pubjc-tradhealen.pdf. 2000;:1–57.

33. Sharma M, Ying R, Tarr G, Barnabas R. Systematic review and meta-analysis of community and facility-based HIV testing to address linkage to care gaps in sub-Saharan Africa. Nature 2015;528(7580):S77–S85.

Summary of Changes to Protocol

September 4, 2019:
As planned in section 4.4 of the protocol, an observational census of traditional healers was conducted in the study area in 2018.

Changes to the inclusion criteria for traditional healers were submitted as follows:
We predetermined an 8-kilometer one-way travel distance to the ISS HIV clinic as the geographic boundary within which to include traditional healers as recruitment locations for this trial. This distance was established as a walking distance to one or more HIV testing resource are centralized. Twenty-five traditional healers were identified within this area. Traditional healers will be considered eligible for participation as cluster sites if they are 1) were aged 18 years or older; 2) have a practice located within eight kilometers of the ISS clinic; 3) were identified in the 2018 population-level census of traditional healers in Mbarara District; and 4) delivered care to at least 7 patients per week. The final criterion excludes healers with average patient volumes in the lowest quartile in order to ensure that participant recruitment progresses in a timely manner for this pilot study.

Changes to the sample size were submitted as follows:
We assumed a baseline testing rate of 39% among our population based on Ministry of Health population-level data[8]. We predicted that the HIV testing rate would increase by 35% to 74% in the intervention arm. Using intracluster correlation coefficient estimate = 0.2, we calculated that we would need to include a minimum of 16 clusters total, with an average of 30 participants recruited per cluster (total sample size of 480 participants), to detect this difference, with 80% power and alpha = 0.05. We plan to recruit 20 healers as clusters in our study to maximize analytical power. Target enrollment number for clients will be 250 per study arm, divided equally among cluster sites in each study arm.

Secondary outcome of “variables that predict HIV testing” was also removed