STUDY PROTOCOL

PROJECT TITLE: Traditional healers as a treatment partners for PLHIV in Rural Mozambique.

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Principal Investigators	Dr. Carolyn M. Audet, PhD, Institute for Global Health Vanderbilt University, USA
Funding Agency	NIMH K01 Award (Dr. Carolyn M. Audet, PI)
Location	Namacurra District, Zambézia Province - Mozambique
Expected Start Date	May 1, 2015
Expected End Date	48 months from approval to finish
Type of Study	A pre-post pilot evaluation.
Main objective	The primary objective of this study is to learn about how traditional healers can aid patients in becoming adherent to their HIV medications.
Clinical Trials Registration	NCT03076359
Key words	Antiretroviral therapy (ART) HIV care Traditional healers Adherence Psychosocial support Community Health Worker

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Acronyms

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
APSS	Psychosocial Support (*Apoio PsicoSocial para a Saúde)*
CAPS	Center for AIDS Prevention Studies
CDC	U.S. Centers for Disease Control and Prevention
DPS	Provincial Directorate of Health
EPTS	Electronic patient tracking system
FGH	Friends in Global Health
GoM	Government of Mozambique
HCW	Health care worker
HIV	Human Immuno-deficiency Virus
MOH	Ministry of Health
PLHIV	People Living with HIV
PMTCT	Prevention of Mother to Child Transmission
PP	Positive Prevention
PwP	Prevention with Positives
STI	Sexually transmitted Infections
TA	Technical Assistance
TWG	Technical Working Group
UCSF	University of California, San Francisco
VU	Vanderbilt University
WHO	World Health Organization

Introduction and Justification

HIV in Mozambique

Zambézia province in north-central Mozambique is among the world's poorest and most medically underserved regions. Its adult HIV prevalence was 12.6% in 2009 (most recent survey).[1] Vanderbilt University (VU), through its non-governmental organization (NGO), Friends in Global Health (FGH), supports 68 rural HIV service sites in 10 Zambézia districts with CDC PEPFAR funding. FGH clinical sites are providing ART to ~18,000 persons.

HIV stigma is so severe in rural Mozambique that preliminary research has found that persons living with HIV (PLHIV) are trying and failing to manage their care in secret, without disclosure to family members.[2-4] This results in very high levels of patient attrition.[5-9] Only 48% of these adults are retained in care one year after initiation of antiretroviral therapy (ART).[9] Too few health care workers (HCW) practice in rural sub-Saharan Africa (SSA).[10-12] In Zambézia, only 2000 nurses, medical technicians, and physicians care for a population of 4.6 million. In lieu of crowded and substandard allopathic treatment, many PLHIV seek traditional medicine.[5,13-25] Over 25,000 healers are currently registered with the Mozambican Ministry of Health (MISAU) in the province. While once viewed as the enemy to encouraging health service uptake,[17] recent clinic-healer engagement in Zambézia (including training, increased dialogue, and healer referral systems to identify severely ill patients) has yielded increased referrals to HIV, tuberculosis (TB), and malaria testing services.[26] Patients report concerns with disclosure/stigma,[17] gender based violence,[27] lack of food and or transportation,[17] perceptions of poor health care,[5] and a preference for use of traditional medicine[13,27] in their decision to abandon care. In effort to stem high levels of loss to follow up, MISAU policy mandates the use of "treatment partners" to support adherence for PLHIV on ART. Many patients are hesitant to recruit someone in their "circle of trust" (e.g., family or friend) for fear of disclosure. Hence, they forego care.

Traditional Healers and the HIV Epidemic

It has been demonstrated that healer consultations can delay or interrupt HIV treatment engagement[28] which can lead to poorer health outcomes and potentially higher rates of transmission.[29] For persons living with HIV (PLHIV), the long-term effects of delayed, interrupted or discontinued ART are severe, both due to rapid disease progression and the risk of transmission to sexual partners.[30-34] People with a CD4+ cell count <200/µL are especially infectious, and are themselves at enormous risk of opportunistic infections and malignancies, most preventable with earlier ART.[35,36] Median CD4+ cell counts in the PEPFAR-supported program in Mozambique are only 140 cells/µL for persons at the time of initiating cART, reflecting late arrival, treatment refusal, and the historical use of clinical services only for acute needs.[37-39] With 2009 adult HIV prevalence of 12.6% in Zambézia (20-28% in our ANC centers)[40] successful engagement in ART-based care is vital to reducing morbidity, mortality, and transmission rates in this high-prevalence region.

Medical Pluralism in sub-Saharan Africa (SSA)

Medical pluralism (the use of multiple health systems) is common among PLHIV in SSA.[21,28,41-43] Throughout SSA, healers act as a patient's first (and often preferred) line of treatment.[14,18,44-58] This preference and behavior has been demonstrated in Mozambique.[13,28] Healers can specialize in different forms of treatment, e.g., herbal, spiritual, religious[13,14,38,51,53,59,60] and address ailments from spiritual sources, e.g., spirits, sorcery, and social transgressions. Healers themselves do not necessary believe themselves to be competing with allopathic clinics: they believe they treat the spiritual component of the disease while the clinician treats the biological agent.[26] Healers live locally, spend on average two hours with each patient, and are perceived as an alternative to allopathic services.[5,26,28,61]

Integrating Traditional Healers in ART Adherence

Incorporating healers as ART adherence counselors can help reduce the crisis of treatment. Healers are often accused of encouraging patients to abandon HIV care,[16,20] but they can also serve as strong advocates for patient health.[62,63] When healers were engaged as TB adherence counselors in South Africa, their patients were as successful as those supported by non-healer counselors.[62] Although there are no Mozambican data on patient willingness to partner with a healer, the South African TB findings are promising with 84% of participants having accepted a healer as a treatment partner.[62] Given the strong association between TB and HIV in SSA,[64] similar acceptability is expected among the patients in this study. The only published, analogous work in Mozambique is from myself and Felisbela Gaspar of MISAU.[26] Our implementation of referral forms to track patients from healer to clinician allows patients to use referral forms to both "jump the queue" and avoid paying the one meticais fee ($0.03 USD) for a walk-in doctor's visit.[26] Patients seek assistance from healers post-diagnosis. In a recent survey of 230 healers in Namacurra (our proposed study site), 54% reported providing ART adherence support to PLHIV and 51% reported treating ART side effects in the past month (C. Audet unpublished data). Despite interest in providing support, they lack ART knowledge and counseling training to provide useful assistance.[47,65-68]

An innovative solution would be to engage trained healers as treatment partners to support medication and appointment adherence for PLHIV. Healers are well positioned to address reported patient concerns, including: (1) keeping a patients HIV status a secret while providing support; (2) assisting with partner disclosure and initiating community/clinical systems of assistance if gender base violence is threatened/occurs; and (3) advocating for patients during clinical visits to ensure quality care is provided. Other programs in SSA have shown that incorporating healers into an allopathic health system as adherence supporters for TB treatment is feasible, but healer use in HIV treatment is not well-documented.[62,69-72] This novel intervention would provide patients newly initiated on ART a choice to nominate a specially trained healer as a treatment partner, and assess acceptability, feasibility, and patient outcomes using an interrupted time series quasi-experimental design. Community-based treatment partners can improve pharmacy adherence and LTFU, while decreasing stigma and isolation.[73-77]

Engaging healers to conduct counseling sessions in a community setting to improve ART adherence necessitates technical clinical and psychosocial training. The ART Adherence Support Worker Training program (from FHI 360)[10,78] will be adapted (using ADAPT-ITT)[79] and used to train healers to be quality treatment partners and advocates. The training will ensure healers have the knowledge and skills to effectively: (1) Educate PLHIV about ART and HIV care; (2) Assess serious ART side effects or HIV co-infections; (3) Counsel patients about safer strategies for partner disclosure (with assistance if needed); (4) Accompany the patient for each clinical appointment; and (5) Advocate for quality health care delivery when assisting each patient. The FGH training team will conduct training of the healers. All patients initiating ART will be screened for interest in having a healer treatment partner. Control and intervention patients will be followed for one year, allowing us to compare outcomes at 12-months to study the effectiveness of healers as adherence partners.

1. Objectives

The overall goal of this project is to adapt and assess the impact of a traditional healer training program/intervention on the adherence, retention, and viral load of patients newly initiated on ART.

Obj. 1 To implement the training program with traditional healers, and evaluate the intervention effect on adherence to treatment.

If proven effective, this intervention can provide built-in sustainability by establishing partnerships and a strong local presence, leveraging resources from PEPFAR-funded work in Mozambique to strengthen local capacity and improve the sustainability of the program. A greater integration between healers and clinicians could be achieved with this novel design.

2. Design and Study Questions

This is a mixed methods study, including qualitative interviews, focus groups, surveys, and the collection of clinical data. The pilot intervention at the end of the study will be a pre/post design. Process indicators around patient and healer perception of intervention fidelity and strategies for improvement will also be measured. This study design was chosen for three reasons: (1) with a few notable exceptions (a handful of healers well-known for treating particular ailments) healers tend to treat patients who live in the same communities in which they live. Thus randomizing at the level of the individual patient would result in patients inadvertently seeking care/support from trained healers (i.e., cross-contamination); (2) randomizing healers to an intervention or control arm within the same community would result in logistic, ethical, and political problems; and (3) a definitive cluster-randomized controlled trial is beyond the financial scope of a K award.

3. Study Population

a. Population

Patients: The population of interest is adults, ages 18 and over, who are newly initiating ART.

Traditional Healers: The population of interest will be recruited from the cohort of 140 trained traditional healers living in Namacurra.

b. Inclusion Criteria

Patients: Individuals will be eligible to participate in the study if they are 18 years of age or older, are known to be HIV-infected, and are newly enrolled in ART and treatment services in Namacurra.

Traditional Healers: Healers will be eligible to participate if they live within 10 km of the health facility, received previous training from FGH, are 18 years of age or older, and see at least one patient per month.

c. Exclusion Criteria

Patients: Individuals will not be eligible to participate if they are currently pregnant, HIV-uninfected, and/or not yet enrolled in HIV care, or if they cannot give consent due to mental limitations or intoxication.

d. Calculation of Sample Size

Objective 3: All power calculations use 5% type I error (2-sided). Prior data indicate 56% of patients remain in care at 1 year following ART initiation.[9] If the intervention improves retention to 75%, then 97 patients will need to be enrolled to SOC and 97 to intervention (N=194) to be able to reject the null hypothesis that retention is equal with 80% power. Given high rates of patient mortality and low rates of completion of viral load measurement, enrollment will continue until 170 patients who agree to work with a healer are accrued in each group.

e. Sampling

Participants: HIV infected patients will be enrolled for 3 months during the pre- and post-intervention periods (~100 new patients enroll in care and treatment each month, allowing for sufficient time to recruit).

Traditional Healers: The recruitment of healers will be on a first-come, first-served basis as identified by AMETRAMO and our FGH liaison.

4. Methodology

a. Measurement of Results

Improving adherence to ART

Routinely collected demographic, community-based social support, and HIV care and treatment data will be used in the analysis. Select demographic, clinic, and laboratory data from these forms are entered routinely into OpenMRS (an electronic medical record "EMR" system) at FGH-supported sites.

b. Study procedures

All prospective participants in both the intervention and control group will be asked whether they would be willing to work with a healer as an adherence partner. Only those patients in the post-intervention phase will be linked with a trained healer. A list of trained healers will be provided to patients and they will be asked to choose the healer they prefer. Healers will be expected to partner at least 1 but no more than 6 patients to ensure sufficient support time. The study nurse will contact the chosen traditional healer, setting up a meeting session for the patient-healer dyad at their next clinical visit. During this subsequent visit, the healer and patient will jointly confer with the patients' provider to ensure competency of treatment regimen and timing of subsequent clinical visits. Healers will accompany patients to all clinical visits (with the exception of pharmacy refills) for 12 months and will visit the patient (at a mutually agreeable location) weekly to provide necessary counseling, assess side effects, talk about adherence, assist with partner disclosure (if acceptable) and assess signs of gender based violence, particularly as associated with HIV infection. FGH-support staff (physician, psychologist, and counselors) is based in Namacurra district and can provide psychosocial or technical support if necessary. All healers will accompany patients to regularly scheduled medical appointments and will be provided training about local herbs, methods/materials for preparing and distributing topical remedies (for safe, sustainable income), and uniforms to identify them as members of the clinical team. Participants will continue to receive SOC HIV care and treatment services that include: (1) monthly clinical services; (2) free cotrimoxazole, ART and medications for any opportunistic infections; and (3) peer navigator support at the health facility. HIV viral load (VL) measurement will be assessed using

dried blood spots in the Automated Abbott m2000 Real-Time HIV-1 Assay© at treatment initiation and at one year.[82] Of patients enrolled in the intervention phase, 20 will be selected randomly for in-depth qualitative interviews about their experience working with healers at the completion of the study. Participants will be followed for ≥12 months.

5. Locations of study

The study will be conducted in Namacurra, Zambézia, Mozambique.[83] The research team has worked with this community/clinic for the past six years.

6. Data Management and Analysis

Data Management and Security

Quantitative Data: Data will be stored in a restricted access folder that sits on the FGH server. In addition, data will be password-protected to limit access to staff involved in the study and to ensure confidentiality. Data will be encrypted, backed up on FGH servers, and uploaded to the Vanderbilt servers as needed for PI access. FGH servers have daily backups scheduled; therefore, all data will be backed up on a day-to-day basis.

Data from the surveys will be coded and transferred into an MS Excel file or Red Cap database by field staff trained in data entry. The original surveys will be locked in a file cabinet in the FGH office in Quelimane for 5 years. Only the PI and Lazaro Calvo at the FGH Quelimane office will have access to the coded data. The data files will be password-protected to ensure confidentiality. All routine monitoring data will be documented by health facility staff into patient clinical records. Data are extracted from patient clinical records into electronic patient tracking systems already established and functioning as part of routine monitoring by FGH data entry specialists. The staff has specific training on data confidentiality; all FGH staff sign confidentiality agreements as they come into contact with patient clinical files.

With the initiation of expanded HIV care in Mozambique, medical records were implemented using standardized national forms and an HIV service card, known as the “Green Card", which the patient keeps in order to be identified as part of the service. As the HIV care program has grown, FGH and other PEPFAR partner organizations within the province have implemented electronic databases using either ACCESS® or OpenMRS, depending on the district, to collect patient information facilitating the maintenance of these records for the Ministry of Health’s program. At the end of each patient encounter, data entry personnel based at the health facility enter information collected on the paper forms into the electronic database. This database does not have the capacity to collect information from the various different services and connect them to a specific patient. As a result, only information from the HIV care is currently collected in the electronic database.

The OpenMRS databases are password protected and can only be accessed by FGH monitoring and evaluation staff. Data quality assurance for the Open MRS is ensured through semi-annual audits as well as automatic data validation steps. All data are reviewed by FGH regional data supervisors at the district level and by data analysis officers based in the FGH provincial offices in Quelimane. Corrective measures are taken as necessary as a result of data quality audits and regular reviews of data.

For this project, data will be extracted into a restricted dataset by FGH employees from the existing OpenMRS databases and sent to VU Biostatistician Wu Gong for analysis (Table 1:c) . All routine programmatic data are owned by the MOH. All routine programmatic data are part of the clinical record and as such will not be destroyed.

Data Analysis

Objective 3 (Clinical Data): Our primary outcome is patient retention, defined as proportion of time on medication. Specifically, every patient is given 30, 60, or 90 days to pick up their medication as indicated in the medical charts. If a patient picks up medication after the indicated date they will be considered "non-adherent" for each day after their specific pick-up date; this will be assessed over the course of the one-year follow-up. For all analyses, patients who die or are lost to follow-up will be assumed to not be on medication/retained. Patients who are known to transfer to other clinics not participating in this study will be censored at the time of transfer. For our primary retention outcome, proportion of time on medication, we will fit a linear model. Covariates include age, gender, marital status, and education.

7. Ethical Considerations

The sites that participate in this proposal meet the requirements for the conduct of research using funds from the US Government. The protocol and consent forms will be reviewed and approved by the Vanderbilt University IRB (FWA00005756, IRB00000475-7, IRB00002125) and the Ministry of Health in Mozambique (FWA00003139 IRB# IRB00002657). The proposed project is Non-Exempt Human Subjects Research.

a. Recruitment and Consent

Recruitment and Consent of HIV+ Patients: Patients recently diagnosed with HIV in Namacurra will be asked a whether they would be willing to consent to having a traditional healer assist them throughout the first year of their treatment. Patients who answer positively will then be asked if they would be interested in enrolling in a study that wants to look at the impact of this type of assistance on treatment outcomes. If the patient is interested, they will be provided a one-on-one consultation with the study coordinator, at which point they will be asked to give informed consent through our consent form. This consent will include their willingness for us to access medical records and participate in interviews about the intervention (to assess successes and failures).

Participant confidentiality

All participants who are consented in the study will be assigned a study ID number. Only study members will have the codebook that links the identifiers. Identifying information associated with these ID codes, such as names, will be kept in a data file separate from the survey data and clinic records. All data will be managed in a way that meets Vanderbilt IRB and Mozambique Bioethics standards for the protection of human subjects and to ensure confidentiality and the protection of sensitive health information.

A participant's study information will not be released without the written permission of the participant. All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in locked rooms, i.e., access is limited to study staff. All study data collection, process, and administrative forms and other reports will be identified by a coded number to

maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator or informed consent forms, will be stored separately from study records identified by a code number. All databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

8. Limitations

A limitation to this study is the lack of randomization in the study design. Inherent in a pre-post study design with no control arm is the inability to control for the time effect (changes due to other factors that are not related to the study)

9. Dissemination Plan

Results from this study will be collected into a report, and will be shared with MISAU and the DPS. The results will also be disseminated to government officials and physicians working in these communities. If results are deemed by the authors to be potentially of interest to a wider scientific audience, we would plan on sharing these data in manuscript form, after obtaining appropriate clearances.

10. Timeline

Activities	Year 1				Year 2				Year 3				Year 4			
Evaluate the intervention effect on three key outcome indicators – adherence, retention, and viral load.																
Enroll patients and follow up pre-intervention			■	■	■	■										
Enroll patients and follow up post-intervention								■	■	■	■					
Conduct In-depth Interviews with participants											■					
Data analysis												■	■	■	■	
Manuscript preparation					■				■	■			■	■	■	■

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CONSENT form: Patients living with HIV

This informed consent document applies to adults 18 years or older

Age: _____

We would like to talk with you about a new study we are starting here in Namacurra. This paper describes your rights and is meant to answer your questions. We will read this form to you. Please feel free to ask any questions you may have about this. You will be given a chance to ask questions, and your questions will be answered. Also, you will be given a copy of this consent form.

You can choose if you want to participate in this study or not. If you say yes, you can also later choose to say no and stop participating at any time you want to. You do not have to complete the study. You can answer any of the questions or refuse to answer questions that you do not wish to answer.

Purpose of the study:

This study is being conducted by collaborators from Vanderbilt University and Friends in Global Health. We are thinking about trying a new way for the health system to collaborate with traditional healers. Right now, healers are referral agents: but we believe they can play a more important role as adherence coaches for people living with HIV. We want to include you in this study because we believe you can help us create this system. We would like to see if a traditional healer can help you stay adherent to medication and act as an advocate for you in the health system.

Procedures to be followed and approximate duration of the study:

This study will begin today and last for the next year. We will give you a list of trained traditional healers and you will have the opportunity to choose the one you wish to work with. Once you have made your choice, our study coordinator will arrange a meeting with you, your health provider and your healer in the next week. Your healer will meet with you (at your home or in a place of your choosing) weekly for the first 4 weeks you are on treatment, and subsequently once a month to see how you are doing. Your healer will also accompany you to the clinic on each of your appointment days. We will access your medical records to see what medications you are taking, medical indicators of your health (CD4 cell count and viral load), and the dates you pick up your medications. We may also select you to participate in an interview about your experience working with your traditional healer at the end of the study. Your responses will be tape recorded so we can listen to the interview again later. After the interview, the study staff will write out your responses word for word and delete the recording. At the end of the study, the tape recording from the Interview will be destroyed. The transcript of your interview will be securely stored in a locked box at the FGH office in Quelimane. You do not need to answer all the questions in the interview if you do not want to. If a question makes you feel uncomfortable or you do not know the answer, it is ok to tell the Interviewer that you do not want to answer the question. You can also stop the Interview at any time without any penalty.

Expected costs:

None.

Possible Discomforts and Risks:

The idea of partnering traditional healers and clinicians to improve the health of patients is new and untested. While we will train traditional healers to be a part of the health system, we may find that some healers and clinicians may have trouble communicating at the beginning. If you experience any discomfort or problems with the healer or clinician we want you to contact us as soon as possible so we can resolve it. We know that talking about your personal experiences with health care workers, traditional healers and HIV can be uncomfortable. Although we will try to have a comfortable and relaxed discussion, we understand that some of the questions we ask might make you feel uncomfortable. We will attempt to limit embarrassment as much as possible, and try to have an open and honest discussion. We also want you to feel free to speak about how you feel about your care providers and the health services you have received. To protect you, your name will not be asked for or written down at any point during the interview. No one on the staff will tell anyone else that you were interviewed.

What happens if you choose to withdraw from study participation?:

Nothing. You are free to stop your participation at any point without problem. You simply need to say that you would like to withdraw from the study. You can tell this to me at any time.

Possible Benefits:

The information you give us may help us to offer better services for people living with HIV who access services at this clinic. This could benefit Mozambican society through improved health programs for people living with HIV.

Contact Information:

If you should have any questions about this research study or possible injury, please feel free to contact the study coordinator Lazaro Calvo at the Friends in Global Health Mozambique office at 258 24217100.

For additional information about giving consent or your rights as a participant in this study, please feel free to contact the Vanderbilt University Institutional Review Board Office at +1-615-322-2918.

Confidentiality:

All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. The information obtained during this study will be stored in a secure online database that is password protected and supported by Vanderbilt University.

Privacy Information:

Your information may be shared with Vanderbilt or the government, such as the Vanderbilt University Institutional Review Board, Federal Government Office for Human Research Protections, Mozambican Ministry of Health, if you or someone else is in danger or if we are required to do so by law. Vanderbilt may give or sell your data without identifiers for other research projects not listed in this form. There are no plans to pay you for the use or transfer of this de-identified information.

Right to Refuse or Withdraw:

Being in this Interview is voluntary. You have the right to refuse to discuss any questions. You can leave the interview at any time.

STATEMENT BY PERSON AGREEING TO PARTICIPATE IN THIS STUDY

Do you have any questions?

Moderator: Answer the participant's questions about the interview before proceeding to the next question.

You have read and/or had read to you the explanation of this study, you have been given a copy of this form, a chance to ask questions, and you know that you can refuse to participate. I am going to ask for your consent to do this interview. By saying yes, you agree to do the interview. By saying no, you decline to do the interview. Do you agree to take part in the interview?

I agree to take part in the interview.

_____ _____

Date Signature, mark, or fingerprint of patient/volunteer

I have explained to the participant the study purpose and procedures and we have discussed all the risks that are involved. I have answered questions to the best of my ability that the participant had.

Consent obtained by (signature of moderator):

_____ _____

Date Signature

_____

Printed Name and Title

Revised January 2015