

Partners-based HIV Treatment for Sero-concordant Couples attending Antenatal Care

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STUDY PROTOCOL

PROJECT TITLE: *Partners-based HIV Treatment for Sero-concordant Couples attending Antenatal Care*

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Key words	Elimination of Mother to Child Transmission Male-engagement HIV care Antenatal care Community Health Worker

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Acronyms

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
APSS	Psychosocial Support (<i>Apoio Psicossocial para a Saúde</i>)
HoPS	Homens para Saúde “Men for Health”
RCT	Randomized controlled trial
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
EMTCT	Elimination of Mother to Child Transmission
ANC	Antenatal Clinic
EID	Early infant diagnosis
SOC	Standard of care
VUMC	Vanderbilt University Medical Center
WHO	World Health Organization

1. Principal Investigator

The principal investigator (PI) for this evaluation will be Carolyn Marie Audet at Vanderbilt University Medical Center. The PI will be responsible for all aspects of evaluation coordination, including design, implementation, and analysis.

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2. Funding

This project will be funded by a National Institute for Mental Health R01 award (PI. Audet).

3. Collaborators

Various project staff from the Ministry of Health (MOH) and FGH/Vanderbilt University Medical Center (VUMC) will be involved in this activity. From the MOH, this includes an assigned member of the Operational Investigation Committee of Zambézia (NIOZ). From FGH, this includes Sara van Rompaey, M.D., M.P.H.; Lazaro Calvo, Ph.D; and Fernanda Alvim, M.P.H. From VUMC this includes Carolyn Audet, Ph.D, Erin Graves, N.P., MPH; and Heather Jordan, M.P.H.

Table 1. Other participants in the study.

Name	Organization	Role	Role in the Evaluation
Focal person TBD	MOH	Operational Investigation Committee of Zambézia (NIOZ)	Technical oversight
Sara Van Rompaey	FGH	Quality Improvement Advisor	Co-Investigator
Caroline DeSchacht	FGH	Director of Evaluations	Technical oversight; support of HoPS+ Study manager

Lazaro Calvo	FGH	Impact Assessment & Program Evaluation Director	Technical oversight for surveys and ethics trainings
Fernanda Alvim	FGH	Director, Monitoring and Evaluation	Data Quality Monitoring
Focal person TBD	FGH	HoPS+ Study Manager	Coordination and supervision of study
Erin Graves	VUMC	Program Manager	Technical and administrative oversight
Carolyn Audet	VUMC	Principal Investigator	Technical oversight and mentoring
Heather Jordan	VUMC	Program Manager	Finance and technical support

4. Introduction and Justification

Poor PMTCT Treatment Retention among Women in Mozambique

Mozambique has one of the world's highest HIV/AIDS burdens, and is the home of one of the world's poorest and most medically underserved regions, Zambézia province, located in north-central Mozambique (Fig.1). Adult HIV prevalence in 2009 was 12.6%, but among pregnant women was substantially higher (estimated 20%-28%).[1] According to the 2011 Demographic and Health Survey, 74% of pregnant women in Zambézia attended at least one prenatal visit.[2] In our 2014 unpublished Presidents Emergency Plan for AIDS Relief (PEPFAR) program data, 81% of pregnant woman who came to the antenatal clinic (ANC) were tested for HIV, but only 80% of them initiated antiretroviral therapy (ART). Half of HIV+ pregnant women abandoned care within six months of ART enrollment. Fewer than 40% returned with their infants for Early Infant Diagnosis (EID) services. Among returnees, only 70% of infants received a PCR test to determine HIV status and only 30% of HIV-infected infants were enrolled on ART (unpublished data, FGH-Zambézia). Thus, only 2% of women received all steps of the cascade necessary for PMTCT, probably the lowest program coverage rate in all of sub-Saharan Africa.

In Mozambique, all HIV-infected pregnant women are now eligible for life-long antiretroviral therapy (ART), regardless of CD4+ cell count (Option B+).[3-5] However, retention in care among women enrolled through Option B+ programs remains sub-optimal in sub-Saharan Africa (SSA) [6-8] primarily due to the need for male partner approval to access health services.[9] Poor medication adherence in Option B+ programs increases risk of mother-to-child transmission and ART resistance.[10, 11] In 2012, there were 94,000 HIV-positive pregnant women in Mozambique.[12] PEPFAR implementer, Friends in Global Health data indicated 8.0% of all pregnant women were HIV-positive; 60% had HIV-infected partners in 2014.[9] Eighty percent of HIV-infected pregnant women and <10% of HIV-infected partners identified during antenatal care (ANC) enrolled on ART. Retention was abysmal: 50% of women and 88%

of men abandoned care within six months (FGH M&E data). At one year, 8% of exposed infants in Mozambique were HIV infected vs. only 1.8% in neighboring South Africa.[13, 14]

Role of Male Partners in Retention and Adherence to HIV Health Services

Women have identified a lack of support from husbands or male partners as a principal barrier to engagement in ANC and HIV testing services.[15-17] Qualitative[16, 18-20] and clinical data[21] across SSA reveal that women are reluctant to accept HIV testing and treatment if their partners are unsupportive, highlighting the importance of partner engagement and programmatic adjustment to prevailing social gender norms. Our HoPS evaluation revealed that a male partner is the most influential family member affecting a woman's health decisions in rural Mozambique.[22] Yet long-standing community norms inhibit men from engaging in the prenatal care of wives or partners.[23] Mozambique is not unique: socially acceptable engagement of male partners in HIV counseling during ANC has also resulted in increased acceptability of testing and treatment uptake across SSA.[24-32]

Integrating Male Partners to Improve Treatment Adherence

By engaging the HIV-infected male partner, we can address multiple patient-reported barriers to retention in care in rural Mozambique, notably partner support, transportation and security while traveling to and from the health facility, and disbelief or denial of the HIV diagnosis by family members.[33, 34] In addition, the couple becomes a de-facto adherence groups.[35-38] Including partners in medical treatment improves patient retention by creating an accountability and support triad: a patient's commitment to treatment is enhanced when both the partner and provider offer support.[22] In addition, partners exist in one's lived environment. Through the provision of partner-based ART services, adherence to treatment becomes entwined with lived experiences rather than messages only delivered when at clinic. Thus, to achieve elimination of mother-to-child transmission (EMTCT) and improve the health of HIV-infected couples, innovative strategies to engage HIV-infected male partners in ANC are essential.[18, 19, 26, 27, 39, 40].[41-44]

Our proposed research builds on a 4-year pilot intervention that developed a community-based strategy to engage male partners in the ANC services of their wives in rural Mozambique. **Homens para Saúde (HoPS) – (“Men for Health”)**, deployed respected men as community health workers and Traditional Birth Attendants (TBAs) to provide community-based counseling and accompany couples to ANC/HIV testing, and led to substantially improved service uptake within two years. In our new project, **“HoPS+”, we will implement a novel partner-based ART enrollment immediately when both partners receive simultaneous HIV diagnoses in ANC.** Our intervention will create an integrated structure to provide couple-based ART within comprehensive HIV care and treatment services. Anchored on professional and peer couples counseling, this intervention will ensure that partners are engaged and retained in care throughout pregnancy and the post-partum period.

5. Objectives

The overall goal of this project is to develop and assess the impact of a partner-based ART delivery intervention among HIV-positive expectant couples.

Our specific objectives are as follows:

Objective 1: To implement, monitor, and evaluate the impact of couple-based services on retention in care, viral suppression, and early infant diagnosis (EID) among HIV+ pregnant women and their HIV+ male partners through a cluster RCT. Implementation process variables will be collected (number of expert-couple counseling sessions, adherence to content, and evaluation of participant and peer experiences).

Objective 2: To investigate the impact of the HoPS+ intervention on hypothesized mechanisms of change.

We will determine the intervention's impact on hypothesized mechanisms of change, including (1) partner social support;[45] (2) HIV stigma;[46] (3) relationship empathy [47](4) HIV knowledge;[48] and (5) patient trust in provider[49] through quantitative surveys with patients at baseline and 6 months.

Objective 3: To use validated simulation models to evaluate cost-effectiveness of the HoPS+ intervention.

This study is important because it targets the health and well-being of the mother-infant-male partner triad,[50] the essential family group that has eluded effective engagement strategies in HIV care. It builds on our research team's extensive experience in: (1) HIV care and treatment; (2) male partner engagement; (3) and cost-effectiveness analysis. Our results will improve outcomes by effectively engaging couples in HIV care and treatment during pregnancy and beyond. Without effective innovation in culturally appropriate adherence support to all stages of the care continuum, EMTCT efforts will fail in rural Africa.

6. Design and Study Questions

We propose to conduct a matched-pair cluster Randomized Controlled Trial to evaluate the effects of our intervention. To our knowledge, this is the first ANC-based couples study that will assess definitive treatment outcomes within a randomized controlled trial (RCT), and analyze the cost-effectiveness of the intervention. Twenty-four primary and secondary level health care facilities in Zambézia Province will be matched and then randomized to the control (standard-of-care [SOC]) or intervention (HoPS+) arms (12 sites per arm). We opted for a study design in which the unit of randomization is the EMTCT clinic (not the individual) because it would be extremely difficult to implement the intervention to only a subset of clients within each facility. We will match clinics on ART uptake rates, retention in care among patients on treatment, patient volume, HIV prevalence in ANC, and level of facility (secondary or primary)[51] using reweighted Mahalanobis distances[52] and then randomize clinics in each matched pair to intervention and SOC arms – 12 clinics per arm, 24 total. Intervention and control sites will be >100 km of each other to prevent contamination.

There are four specific study questions:

Question 1: Is our intervention idea (partners-based ART services for expectant and post-partum couples) acceptable to expectant couples?

Question 2: Does our intervention positively impact partner support for ART medication adherence and retention in care? Does it increase empathy among partners enrolled? Does it increase knowledge about HIV? Does it reduce HIV stigma among couples enrolled into the intervention?

Question 3: Does our intervention improve the proportion of exposed infants who are tested for HIV (early infant diagnosis)? Does it decrease the number of infants who are HIV-positive at 12 months?

Question 4: Is the intervention cost-effective? Would the Ministry of Health be willing to scale it up based on our costing data?

7. Study Population

a. Population:

Couples consisting of two adults 18 years or older (one HIV-infected pregnant woman and her HIV-infected male partner) presenting for ANC services together at one of 24 clinical sites in Zambézia province.

b. Inclusion Criteria:

Couples, one HIV+ pregnant woman and her infected male partner, will be eligible to participate if the woman's due date is >2 weeks from enrollment. Both persons must also be 18 years or older, able to give consent, willing to consent to an infant record search, and must agree to enroll in ART together.

c. Exclusion Criteria:

Couples will not be eligible to participate in the study if the woman is not pregnant, if both persons are not HIV+, if either person is younger than 18 years, if one member of the couple is unwilling to enroll in ART or consent to the infant record search, or if one member of the couple is unable to give consent due to mental limitations.

d. Calculations of Sample Size:

Objectives 1 & 3: With 24 clusters and 45 couples per cluster, we have over 80% power to detect a 30% increase in the proportion of pregnant women who initiate ART from 55% to 71.5% with $\alpha = 0.05$. Our power calculations count adults and babies who dropout during the EMTCT cascade (e.g. do not initiate ART) as failures for downstream aims (e.g. retention on ART or viral suppression). For example, SOC ART retention was calculated as the proportion of women who initiated ART multiplied by the proportion of women retained in care ($0.55 \times 0.56 = 0.31$). In our sample size calculation, we power for a 20% increase in adult ART retention (above and beyond the 30% increase in adult ART initiation, for an improvement in retention from 31% to 48%), 90% vs. 80% viral suppression among women or men, 20% increase in EID testing, and 40% reduction in infant HIV positivity. Women, men and infants will be evaluated as separate study populations.

Objective 2: Aim 2 analyses will utilize a subset of the 1,080 enrolled couples (2,160 individuals) who are alive and can be contacted to provide data by 6 months after enrollment, regardless of whether or not they are retained in care. Because the psycho-social data collected by 6 months may be influenced by whether or not participants were retained through 6 months, our analyses will initially only consider retention outcomes after 6 months to maintain the temporal order needed to infer any mediation effects.

e. Sampling

Participants: HIV infected couples will be enrolled for 6 months at each study site. Patients will be enrolled on a first come, first enrolled basis until 40 couples have been enrolled.

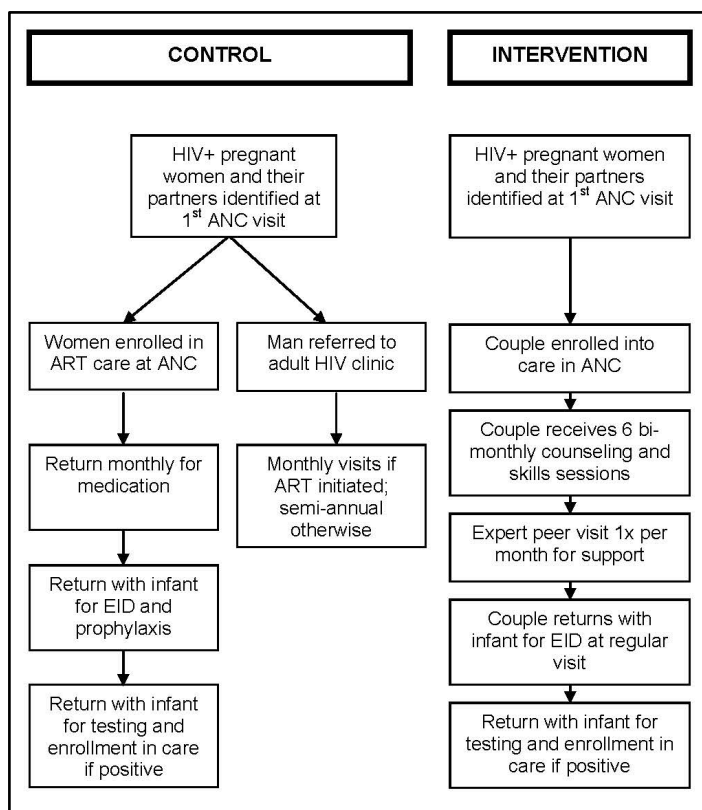
f. Patient participant retention and withdrawal:

As per standard clinic procedure, couples on the control arm will receive separate clinical services at the ANC building and the adult HIV clinic, respectively. Peer educators will track all clients who miss appointments at control and intervention sites. The Home Based Care workers will document clients as terminating care if they: (1) discontinued services due to death; (2) transferred their care to another clinic that is not in the study; (3) are lost to follow-up (defined as being >90 days late for a clinic appointment plus 3 failed attempts at tracking the client); or (4) discontinue for any other reason, including patient choice. Clients will not receive any remuneration for participating in the study, per Mozambican National Medical Ethics Committee, but interview participants will be provided a small snack. Clients will be allowed to discontinue participation and may decide that their medical data cannot be used in the analysis at any time during the study.

8. Methods

a. Study Procedures

Couples in the intervention and SOC arms will be consented into the study immediately after testing positive for HIV through couples counseling at an ANC appointment. Enrollment will be completed by a study assistant based at the site. A similar enrollment protocol in Zambézia has yielded study enrollment >95% immediately after an HIV test is completed; so we anticipate few recruitment problems. Patient management and monitoring forms will be completed for all HIV-infected couples enrolled in the study. Select demographic, clinical and laboratory data from these forms will be routinely entered into the OpenMRS electronic medical record system (EMR) at FGH-supported sites. OpenMRS data are managed by the FGH data manager who identifies discrepancies, works with sites to resolve them, and updates the database accordingly.[53]



Standard-of-care services (SOC) (Objectives 1 & 2):

The 12 clinics randomized to the **control arm** will continue to provide SOC EMTCT services that include: standard HoPS male engagement (male invitation to ANC services and couples HIV testing), opt-out rapid HIV testing of all pregnant women attending ANC, HIV-specific counseling and support for all women

who test positive, provision of cotrimoxazole prophylaxis, and universal

Figure 1: Procedures in Standard of Care vs. Intervention

ART, as per option B+ guidelines (Figure 1).[4] Couple as well as relevant medications are also offered free of charge in the HIV clinic to male partners. Post-partum women and their exposed infants continue EMTCT follow-up, after delivery, at the EID clinic in a “one-stop point of care model”. Post-partum women continue their HIV care and treatment follow-up, including provision of cotrimoxazole prophylaxis, and counseling and support; infants have access to HIV testing by dried blood spot (DBS)-PCR as early as 4-6 weeks after birth,. Follow-up at the EID clinic for both mother and infant continues for 18 months, unless an infant is diagnosed HIV positive and referred to HIV treatment services (Table 2).

Intervention arm: “*Homens para Saúde +*” (HoPS+) – (Men for Health+) (Objectives 1 & 2):

The 12 clinics randomly assigned to the **intervention arm** will receive a combination of community and clinical EMTCT services, including: (1) ANC-based couples HIV testing, couples-based treatment enrollment, and care for sero-concordant HIV+ expectant couples; (2) couple-centered treatment in the post-partum period at the EID clinic; (3) couples-based education and skills building during the ANC and post-partum period; and (4) treatment continuity support by expert-patient (peer) navigators selected among couples who have successfully navigated EMTCT (Figure 4).[27, 31, 54, 55]

Couples education and skill development- HIV+ expectant couples will receive six counseling and skill development sessions throughout the ANC and post-partum period (every other month) to provide a venue for couples to: (1) share thoughts and feelings about their HIV diagnosis; (2) make decisions related to HIV care and treatment; (3) discuss relationship issues that emanate from HIV; and (4) discuss relationship issues unrelated to HIV.[56] Couples may experience the process of HIV treatment differently than those enrolled individually. For example, one partner may constantly seek the other partners point of view (with positive or negative impact), there may be verbal, physical or sexual abuse, or one person may disclose information without the others consent. Providing skills to navigate the inherently complicated process of couple-based treatment is essential to retention and adherence.[57, 58] Based on an adaption of the “PREP approach”, counselors will be trained in cognitive-behavioral marital therapy and communication –oriented marital strategies, to help couples maintain high levels of function and prevent marital problems from developing (Appendix 1: Curriculum description). These sessions will be provided by a trained couple’s counselor (already in place) at the clinic.

Expert Peer Couple Partner- Couples will be matched with an expert peer couple trained to deliver couple-based adherence support (based on the Adherence Support Worker program)[59] who have successfully completed the PMTCT cascade in the past two years (since Option B+ was initiated). Couples will be eligible to act as expert peer couples if they are both living with HIV, the male partner attended at least one ANC appointment and the mother was retained in HIV care 9 months post-partum. Couples will have the opportunity to choose the expert peer couple of their choice from a “Facebook”-style book of trained providers living within

a 2km radius of their community. This peer-mentorship will begin the first week of enrollment; monthly meetings (at an agreed upon location in the community) will be held until infant prophylaxis is complete (~ 9 sessions). Peers will discuss their own experiences with PMTCT services, provide community-based advice if the couple experiences adverse effects of ART, and help the couple deal with the social stigma, specifically enacted and internalized stigma related to HIV. Matching the newly diagnosed HIV-infected couple with “expert peer support” by another couple that has successfully navigated the PMTCT cascade will provide two essential components of quality care, including provider continuity and community-based peer support. Continuity of care has been traditionally assessed based on clinical measures of provider continuity.[60-62] We propose to improve this model by adding a level of continuity of care at the community level. In Mozambique there is a history of patient-provider conflict and distrust.[34, 63] We believe that expert peer support will help address this barrier to quality care by allowing personal testimony from peer participants of how PMTCT care affected their health and that of their infant. In addition to ensuring continuity of care, expert peer partners can provide community-based support for couples enrolled in PMTCT services. HIV stigma remains a significant barrier to retention in care and adherence to ART.[64, 65] These experts have navigated this social reality and can provide advice, assurance, and support if couples perceive, experience, or internalize HIV-related stigma.[46, 66-70]

Cost-effectiveness Analysis (Obj. 3):

We will use detailed models of HIV in women, their partners, and children to project the long-term clinical outcomes, costs, and cost-effectiveness of the HoPS+ program. We will link 3 published, validated models to simulate a cohort of mother-father-infant pairs throughout pregnancy, breastfeeding, and their lifetimes: 1) a decision analytic model simulating a cohort of women through pregnancy and delivery (the “MTCT model”);[71-73] 2) a model of HIV disease among postpartum women (the “CEPAC-Adult model”);[74, 75] and 3) a model of perinatal and postpartum HIV infection (the “CEPAC-Pediatric model”).[76, 77]

To inform cost inputs related to the HoPS+ program during the study period (ANC enrollment through 12 months postpartum), we will collect data on healthcare and non-healthcare RU for both the SOC and HoPS arms. These will include number of clinic, laboratory, and pharmacy visits, as well as inpatient admissions and length of stay. We will gather data on patient time and costs, including days missed from usual activities, such as work, school, or housework, for illness; time spent attending clinic visits; time and costs of transport to clinic visits; and costs of childcare and food/beverages during clinic visits or counseling sessions. We will ask patients about formal and informal work, and costs will be assigned to patient time based on missed wages. To include program and provider costs, we will collect data on the provider time required to implement the interventions, as well as to lead or undergo training. Costs will be assigned based on average salaries. Additional intervention costs, such as transport costs for home visits, will also be included. For longer-term projections (5-year, 10-year, and lifetime), we will use published data on HIV-related healthcare resource utilization and costs.[78] We have derived these data for adult HIV care with collaborators in Mozambique, and we will use a similar approach to derive HIV care costs for children.[75]

b. Measurement of Results

Objective 1: 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.

Objective 2: Individuals consented in the study will complete interviewer-assisted, quantitative study measures at baseline and by 6 months post-study enrollment, including measures of: 1) partner social support;[45] (2) HIV stigma;[46] (3) empathy [47]; (4) HIV knowledge;[48] and (5) patient trust in provider.[49]

Objective 3: Clinical outcomes of the linked models include MTCT risk at birth and weaning, pediatric life expectancy from birth, maternal and paternal life expectancy from presentation to care, and combined (maternal + paternal + pediatric) life expectancy. Economic outcomes, from the healthcare system perspective, include antenatal and postnatal program costs, lifetime maternal HIV-related healthcare costs, lifetime pediatric healthcare costs, and 1 to 5-year maternal and pediatric health care costs. We will use these outcomes to calculate incremental cost-effectiveness ratios (ICERs) in \$/life-year (LY) as the difference in combined healthcare costs (program + maternal lifetime + paternal lifetime + pediatric lifetime costs) between the two strategies, divided by the difference in combined projected life expectancy (maternal + paternal + pediatric life expectancy). For ICERs, all outcomes will be discounted at 3%/year.[79-81] We will consider a strategy to be “cost-saving” if it leads to greater combined life expectancy and lower combined costs than an alternative strategy. Following WHO guidance and evolving consensus in the field of cost-effectiveness analysis, we will consider a strategy to be “cost-effective,” compared to its alternative, if its ICER is <0.5-1.0x Mozambique *per-capita* gross domestic product (GDP: \$525 in 2015)/LY. Recognizing the limitations of this approach, we will also compare ICERs to other HIV interventions in Africa, e.g., first line ART (\$500-\$5,500/LY).[82-86]

The primary data from the HoPS+ program (Objectives 1& 2) will be used as inputs to the MTCT model. These data will include the proportion of mother-infant pairs accessing each step in the EMTCT cascade under the HoPS+ and SOC service-delivery models: ANC, HIV testing, HIV test results, offer and receipt of ART, viral suppression, delivery in a healthcare facility, and linkage to maternal and pediatric care (including EID) after delivery. Data reflecting the biology of HIV infection, including MTCT risks and HIV disease progression (stratified by CD4 and ART use) will be derived from published data, as in previous work,[71] and will be primarily incorporated into the CEPAC-Pediatric and Adult models. We use published data to inform these parameters because EID and ART program data are limited by small patient numbers and by differential loss to follow-up (i.e., higher MTCT, disease progression, and death among those lost to care).

Cost inputs to the models are derived in two steps. First, we estimate healthcare and non-healthcare resource utilization (RU), including inpatient days, outpatient visits, laboratory and pharmacy, and patient and provider time. Next, we assign a unit cost to each resource used (e.g., cost per inpatient day, or wages per hour of provider time), and calculate total costs as the product of RU*unit cost.[79]

c. Instruments used in the study

We will use the following instruments in the study: (1) partner social support;[45] (2) HIV stigma;[46] (3) empathy scale [47] (4) HIV knowledge;[48] and (5) patient trust in provider[49] (see Appendix 2). These instruments are quantitative scales, which provide closed ended options for patient response. We will also utilize the Patient Health Questionnaire (PHQ-9) depression screening tool [87] with all participating adult patients (Appendix 3). This instrument is also a quantitative scale with closed ended response options; scores collected at baseline and 6 months will be used as covariate variables in data analysis (see Section 10).

d. Anticipated end date of study:

This study is expected to be concluded in June 2022.

9. Locations of Study

Friends in Global Health supports HIV care and treatment services to 88 clinical sites in the province. Our trial will involve 24 of these clinics. These sites range from small district-level hospitals to rural health posts. All provide Option B+ services free of charge to HIV-infected pregnant women and their partners. In 2015, FGH clinics tested 95% (114,857) of the pregnant women presenting for ANC for HIV and provided Option B+ ART services to 87% (8,137 newly diagnosed women); 3,000 HIV-infected men were identified through ANC-based couples counseling.

Table 2: Study Sites by intervention Status

	Intervention sites		Control sites	
	Health Facility	District	Health Facility	District
1	Muiane CS III	Gilé	Mocubela CS III	Mocubela
2	Mixixine CS III	Namacurra	Inhassunge CS I	Inhassunge
3	Palane-Mucula CS II	Inhassunge	Mugubia CS	Namacurra
4	Gurai PSA	Mocubela	Bingagira PS	Inhassunge
5	Muebele PS	Namacurra	Gonhane CS III	Inhassunge
6	Maganja da Costa CS III	Maganja dC	Gilé CS II	Gilé
7	Naburi CS III	Pebane	Tapata CS III	Mocubela
8	Nante CS III	Maganja dC	Malei PS	Namacurra
9	Tomeia PSA	Pebane	Pebane CS II	Pebane
10	7 de Abril CS III	Pebane	Magiga PSA	Pebane
11	Pele-Pele CS	Pebane	Alto Maganha CS	Pebane
12	Madal CS	Quelimane	M'Baua CS III	Namacurra

10. Data Management and Analysis

Data Management and Security

The data collected will be kept in a database housed in Mozambique. 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 a REDCap 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 Study Manager 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 OpenMRS 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, de-identified data will be extracted into a restricted dataset by FGH employees from the existing OpenMRS databases and sent to a VUMC Biostatistician for analysis. 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 1: *Statistical analysis plan for Objective 1.* We propose a generalized linear mixed effects model, with random effect for clinic.[88] A simple model for $E(Y_{ij})$, the probability of ART initiation in the i th clinic at the j th time-point is given by:

$$\text{logit } E(Y_{ij}) = \beta_1 + \beta_2 \text{Group}_{ij} + b_i + e_{ij}$$

where b_i is a random effect for clinic i which accounts for clustering of patients within clinics, due perhaps to similarities in health-seeking behavior and/or access to care. β_1 is a fixed effect

corresponding to time j , Group_{ij} is an indicator of intervention, and β_2 is the treatment effect (difference in log odds of ART receipt). We test the hypothesis, $H_0: \beta_2 = 0$. The mixed effects model will be extended to allow for covariate adjustment, such as: age, education, and distance from clinic. Separate models will be used to assess each outcome in each population (men, women, infants). For example, ART initiation among pregnant women ($n=1,080$) and then ART initiation among male partners ($n=1,080$). All adult patient models will include depression scale scores as covariates in attempts to control for potential presence of depression symptoms among participant groups. Female-specific models allow for inclusion of covariates unique to pregnant women, such as prior ANC, parity, etc. We also expect the intervention odds ratio to differ between women and their male partners. For infant HIV infection, sensitivity analyses will be conducted to investigate the effect of no EID test result on HIV infection; infants of mothers who did not initiate ART or were not retained in care at delivery will be assigned probabilities of infection (with definitions based on latest research). Then, infant HIV status will be multiply imputed using the Bernoulli distribution and estimates from the multiple regressions will be combined with multiple imputation techniques. An intent-to-treat approach will be employed for all analyses.

Due to the potential for false positive results when many comparisons are performed, we will report test results in all abstracts, manuscripts, and presentations in a pre-determined order as ascertained by the HoPs+ investigators. For example, the order of reporting results could be male initiation, male retention, female initiation, female retention, etc.; the final order will be selected *a priori*. Because we are interested in answering multiple questions but will report all analyses in the context of the aforementioned ordering, no adjustment for multiplicity will be performed, an approach consistent with recommendations for clinical trials.[89] Analyses will be conducted using R software (www.r-project.org), and scripts will be accessible on our Vanderbilt project website.

Objective 2: Generalized linear mixed effects model will be utilized as described for Objective 1, replacing the logit transformation of the outcome with an untransformed linear outcome because the outcomes are continuous. Intervention status remains the exposure variable of interest and β_2 is the treatment effect (difference in mean levels of knowledge, stigma, etc.). As with Objective 1, gender specific models will be used to model each outcome of interest, adjusting for individual level covariates such as age, education, depression scores, and distance from clinic. Interactions between intervention status and the baseline value of each endpoint will be used to assess for modification of the intervention effect. All potential mediators found to be associated with the intervention at $p<0.20$ in Objective 2 will be included in a multi-level structural equation model (SEM) to account for clustering within clinics (Figure 2). SEM is well-suited to examining mediating and moderating processes over time [90-94]. Specification of the potential mediators as latent variables in SEM allows for better specification of measurement error, potentially reducing bias.[91, 94] Further, the capacity to detect and adjust for potential reporting bias in key study measures (e.g., does social desirability lead male partners to systematically report lower stigma) ensures that true differences in parameter estimates are not inflated by

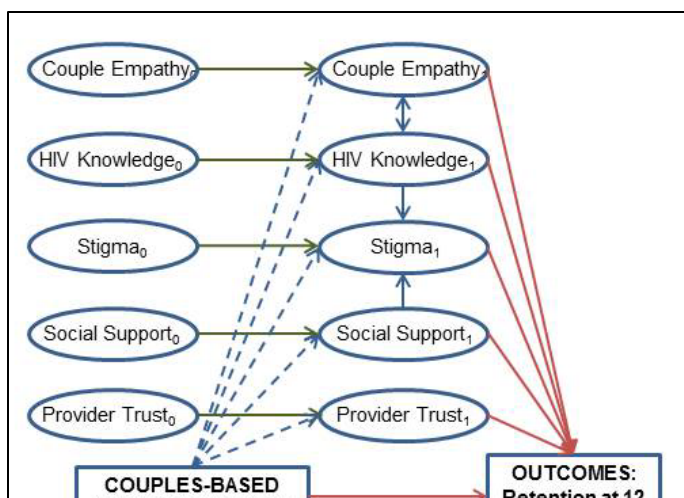


Figure 2: Mechanisms of Intervention Effect

reporting bias.[95] Specific to this objective, SEM yields precise estimates of mediating and moderating relationships that adjust for the presence of all other variables in the model, more precisely capturing the complex reality of these processes. Direct (including controlled and natural), indirect (including natural), and total effects of the intervention through the mechanisms identified in Aim 2a will be estimated. Further, SEM allows for the flexible respecification and modeling of alternative mediating pathways, such as whether improved levels of social support may be associated with reduced stigma, which is in turn predictive of retention.[94] It also allows for exploring the impact of omitted variables, providing a post-hoc estimate of how robust the parameter estimates are.

Objective 3: The MTCT model is a simulation model of a cohort of pregnant women, from the time of conception through delivery. The model is a deterministic model, with a decision-tree structure, coded in TreeAgePro® software (Williamstown, MA); validation and sensitivity analyses are published.[72, 73, 96-98] Modeled events include the key steps in the EMTCT "cascade of care:" presentation to ANC; offer and acceptance of HIV testing; receipt of HIV test results; offer of, acceptance of, and adherence to ART; maternal mortality during pregnancy; HIV testing in labor for women with unknown/negative HIV status; live birth; infant HIV infection at delivery; and linkage to postnatal care and ART for mothers and infants.[99] After delivery, model outcomes for infants include vital status and HIV infection/exposure (infected, exposed-uninfected, or unexposed); model outcomes for mothers include vital status, CD4 ($>$ or $\leq 350/\mu\text{L}$) and current ART receipt. These outcomes at the time of delivery are translated into long-term survival, life expectancy, and costs by simulating the lifetimes of mothers, fathers and infants in the CEPAC models.

The CEPAC-Adult model is a first-order, patient-level (Monte Carlo) simulation of adult HIV infection. People with HIV are simulated individually from delivery through death, and HIV disease progression is characterized by monthly health state transitions. Health states include acute opportunistic infections (OIs), chronic HIV infection, and death. Monthly risks of OIs and HIV-related death are estimated by CD4 count, OI prophylaxis and history of OIs, and availability of and response to ART. The model uses clinical events and monthly costs over each patient's lifetime; model outcomes include average per-person costs and life expectancy.[74, 100-102]

The CEPAC-Pediatric model is a Monte Carlo simulation of HIV infection in children, calibrated to African settings.[76] Infants enter the model at birth. HIV-uninfected infants face a monthly risk of postpartum infection if breastfed. Infants with *in utero*, intrapartum, or postpartum HIV are assigned an initial CD4% and HIV RNA level. Disease progression follows monthly transitions among health states as for adults, and these transitions are dependent upon current CD4/CD4% and age.[103] Each ART regimen confers a probability of suppressing HIV RNA to <400 copies/ml, which leads to an increase in CD4% or CD4 and a reduced risk of OIs and death. ART failure can occur at any time, and simulated patients can be switched from first- to second-line ART after observed clinical, immunologic, or virologic failure. Model outcomes include survival and costs, as for the adult model. The CEPAC website (<http://web2.research.partners.org/cepac>) provides details of the CEPAC-Pediatric and Adult model structures.

11. 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.

Recruitment and Consent of HIV+ Couples: Couples who test positive for HIV during an ANC visit at one of the study sites will be asked whether they would be willing to participate in a research study. If the couple is interested, they will be provided a 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 survey sessions.

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.

Consent Procedures

The consent procedures are detailed above and the consent form can be found in the annex (Appendices 4 and 5). The signed consent forms will be kept in a lock box at the FGH office in Quelimane, separate from the transcripts of the interviews. The consent forms will be kept for 7 years, at which point they will be burned to ensure that no one will be able to link any consents to participants.

Evaluation of benefits and risks

Adverse events

Risks to the subjects (both intervention and control group): The level of risk associated with this research is expected to be minimal for all participants. Potential psychological discomfort may occur when administering the survey as many of the questions are personal and have to do with

a stigmatized infectious disease. Participants are able to decline to answer any question that they deem uncomfortable.

Participants who enroll in couples HIV care and treatment will have the potential for interpersonal conflict, given that they will receive their care and treatment together. To mitigate this concern we are providing couples based counseling at the facility and peer support in the community.

Adverse Experience: We do not anticipate any adverse events as a result of this study, however study participants will be provided with a telephone number and instructed to contact study clinicians to report any serious AEs they experience.

Protection against risks: The study protocol and training manuals will include strict guidelines for conducting the survey and recording the data in a confidential manner. All study staff will receive formal responsible conduct of research training per NIH, Vanderbilt, and Mozambican Ministry of Health guidelines. Participants may withdraw from the study for any reason at any time.

Benefits

For HIV-infected couples there is a possibility that couple-based HIV care and treatment will result in them gaining additional psychosocial support and education for their HIV treatment. For these patients, they could experience improved health outcomes. The results of this evaluation may help us to offer better services for HIV-infected couples living with HIV who access services at the study clinics and throughout Mozambique. This could benefit Mozambican society through improved health programs for people living with HIV.

12. Limitations

Given the cluster RCT design, inter-clinic contamination is possible but will be eliminated by selecting geographically isolated clinics >1.5 hour driving distance apart where patients very rarely visit both clinics.

13. 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.

14. Budget

Description	TOTAL USD	MZM	Study Details	
Human Resources	60,000	4,200,000	Price per unit/person	Number of people/units
Project Officer (TBD)	30,000	2,100,000	30,000	1
Study Assistants	30,000	2,100,000	1,250	24
TRAVEL & TRANSPORT	14,670	1,026,900		
maintenance for car/gas (per day 44USD)	6,750	472,500	\$45	150
cell support for study assistants	2,880	201,600	10	24
basic nokia phone for each study assistant	960	67,200	40	24
bicycle repair kit	720	50,400	30	24
bicycles for peer supporters	3,360	235,200	140	24
TRAINING/PROJECT ACTIVITIES	5,980	418,600		
Training for Peer supporters				
per diem (food)	2,880	201,600	15	96
Venue hire	1,100	77,000	50	12
Training Materials	2,000	140,000	2,000	1
OTHER	2,500	175,000		
Laptop and accessories for Project Officer plus internet via movital	2,000	140,000	140,000	1
Photocopies of consent forms and questionnaire	500	35,000	0.25	
Total of all costs	83,150	5,820,500		
Contingency 10%	8,315	582050		
TOTAL	91,465	6,402,550		

15. Timeline

	Year 1	Year 2	Year 3	Year 4	Year 5
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Study Activities	1	2	1	2	1	2	1	2	1	2
Staff and counselor hiring and (re)-training										
Enrollment of pregnant women & partners										
3, 6 , 12, and 18 month follow up										
Survey collection										
Fidelity assessments										
CEPAC model expansions										
Last study participant visits										
Data collection & management										
Data analysis										
CEPAC model inputs from trial data										
Model-based cost-effectiveness analyses										
Manuscript preparation										

Timeline of Study Activities

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Appendix 1: Couples Education and Training Sessions

Sessions	Why is this so important?	What will couples do?	What are the results?
1. Personality	<p>Personality conflicts can serve as barriers to healthy communication and camaraderie—personally and professionally. Understanding offers a beginning to working with different personality types more effectively, especially when it comes to our primary romantic relationship.</p> <p>Unit at a Glance</p> <p>Lesson 1: Personality Differences</p> <p>Lesson 2: Exploring My Type</p> <p>Lesson 3: Understanding Our Differences</p>	<p>Individual Activity: <i>The Primary Colors Personality Tool</i></p> <p>Couple Activity: <i>Discussing the Differences in personality types</i></p> <p>Individual Activity: <i>Looking at the Bright Side</i></p> <p>Couple Activity: <i>Talking about the Positives</i></p>	<p>Participants:</p> <ul style="list-style-type: none"> Assess their own personality for an improved sense of what individual needs they bring to the relationship. Acknowledge the value that each different personality style brings to a relationship. Explore the positives and the pitfalls of their personality style. Practice showing appreciation for their partner's personality style.
2. Danger Signs & Time Out	<p>Several key studies indicate that patterns of ineffective communication-- Communication Danger Signs-- can ultimately defeat the good intentions of couples by negating the feeling of safety.</p> <p>Chronic negative patterns of interaction, in fact, are indicators of longevity, strongly differentiating happy couples from unhappy couples</p> <p>Unit at a Glance</p> <p>Lesson 1: The First Three Danger Signs</p> <p>Lesson 2: The Fourth Danger Sign</p> <p>Lesson 3: The Power of the Danger Signs</p> <p>Lesson 4: Time Out</p>	<p>Couple Activity/Skit: <i>What's for Dinner?</i></p> <p>Individual Activity: <i>Negative Interpretation or Benefit of the Doubt?</i></p> <p>Couple Activity: <i>Smart or Not-so-Smart Time Out?</i></p> <p>Individual Homework Activity: <i>Creating Your Time Out Strategy</i></p> <p>Couple Activity/Skit: <i>The Power of Humility</i></p>	<p>Participants:</p> <ul style="list-style-type: none"> Recognize the Danger Signs of ineffective communication. Focus on minimizing stress on each other. Replace detrimental communicative habits with proactive talking strategies. Understand the value of taking a Time Out to discourage unhealthy exchanges.

<p>3. The Speaker Listener Technique</p>	<p>Research strongly indicates that when people feel safe enough to share their thoughts, as opposed to feeling attacked or ignored, they are better able and willing to talk about their issues honestly. The Speaker Listener Technique helps diffuse the Communication Danger Signs that breed animosity so that speakers can feel safe enough to slow down and listen carefully to one another.</p> <p style="text-align: center;">Unit at a Glance</p> <p>Lesson 1: What is Good Communication?</p> <p>Lesson 2: The Speaker Listener Technique</p> <p>Lesson 3: Skillful Speaking & Listening</p> <p>Lesson 4: Speaker Listener Technique Practice</p>	<p>Couple Activity: <i>What is Good Communication?</i></p> <p>Couple Activity: <i>Practice with a Playful Disagreement</i></p> <p>Couple Activity: <i>Practice Sharing a Concern</i></p>	<p>Participants:</p> <ul style="list-style-type: none"> • Learn and practice a proven effective model of communication—the Speaker Listener Technique. • Reinforce Emotional Safety through honest and open discussion.
<p>4. Events, Issues & Hidden Issues</p>	<p>According to field research, couples often repeatedly fight about the same Incidents, or find themselves sliding into major arguments from simple beginnings. To avoid the “same old argument,” couples often fall victim to avoiding talk altogether.</p> <p>Understanding each other is an authentic starting point to solving the <i>real</i> problems more effectively.</p> <p style="text-align: center;">Unit at a Glance</p> <p>Lesson 1: Four Frustrating Situations</p> <p>Lesson 2: The Surface Layer--Events</p> <p>Lesson 3: The Middle Layer--Issues</p>	<p>Individual Activity: <i>Our Events</i></p> <p>Individual Activity: <i>Four Frustrating Situations</i></p> <p>Individual Activity: <i>Our Events</i></p> <p>Individual Activity: <i>Common Issues</i></p> <p>Couple Activity: <i>Me? Have Hidden Issues?</i></p> <p>Couple Activity: <i>Speaker Listener Technique for Discussing Hidden Issues</i></p>	<p>Participants:</p> <ul style="list-style-type: none"> • Learn that Events often trigger Issues. • Learn to recognize their Issues—from past experiences or current expectations. • Work on discussing their Issues, rather than letting them be triggered by Events. • Experience the normalization of conflict. • Learn to flag the warning signs of Hidden Issues disguised as an Event. • Enjoy more productive discussions that

	Lesson 4: The Core—Hidden Issues		can deepen intimacy.
5. Anger & Stress	<p>Anger & stress factors into our relationships from every angle of our lives, but romantically, stress and anger: (1) drains strength, (2) increases conflict, and (3) decreases trust. In turn, stress wears down our ability to give our partners the patience and attention they deserve, often increasing conflict and decreasing trust¹.</p> <p style="text-align: center;">Unit at a Glance</p> <p>Lesson 1: The Physiology of Stress & Anger</p> <p>Lesson 2: Two Reasons to Manage Amy</p> <p>Lesson 3: Assessing My Stress & Anger</p> <p>Lesson 4: Strategies to Manage Amy</p>	<p>Small Group Activity: <i>AMY and Your Health</i></p> <p>Individual Activity: <i>Assess My Stress</i></p> <p>Individual Activity: <i>Assess My Anger</i></p> <p>Group Activity: <i>The Thinking Strategy</i></p> <p>Group Activity: <i>The Muscle Strategy</i></p> <p>Couple Activity: <i>The Dealing-with-Stress-&-Anger-Together Strategy</i></p>	<p>Participants:</p> <ul style="list-style-type: none"> • Learn about the specific ways that stress affects the physical and emotional well-being of relationships. • Practice calming skills to control their own stress. • Identify ways to work as a team to deal with stress together. • Improve <i>all</i> relationships that see conflict/stress--parenting, work, sports teams. • Enact a relaxation exercise for improved awareness.
6. Problem Solving	<p>Most couples are looking for healthy ways to solve problems together. This unit offers a structure that couples can use so that they can approach their problems as a team. It also helps couples set realistic expectations that not all problems need to be solved in order to have a healthy happy relationship. The unit encourages couples to remember to protect all of the good stuff in their relationship even when problems come up.</p> <p style="text-align: center;">Unit at a Glance</p> <p>Lesson 1: XYZ Statements</p>	<p>Individual Activity: <i>Practice Using XYZ Statements</i></p> <p>Couple Activity: <i>Working Through the Problem Solving Model</i></p> <p>Couple Activity: <i>Problem Solving Night!</i></p>	<p>Couple Participants:</p> <ul style="list-style-type: none"> • Practice talking about a problem before solving it. • Identify what issues instigate the most conflict. • Engage in 4 steps of problem solving. • Begin to apply problem solving strategies to their own Issues. • Face productive approaches to handling “unsolvable” problems.

	(For the Small Problems) Lesson 2: The 4-Step Problem Solving Model (For the Bigger Problems) Lesson 3: Managing Expectations (For the Unsolvable Problems)		
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Appendix 2: Measures used in study

1. Stigma (Van Rie et al. TB and HIV/AIDS stigma scales)

1. Some people think that those with HIV are disgusting.
2. Some people do not want those with HIV playing with their children.
3. Some people feel uncomfortable being near those with HIV.
4. Some people do not want to talk with others with HIV.
5. Some people keep distance from people with HIV.
6. If a person has HIV, some community members will behave different towards that person for the rest of her or her life.
7. Some people try not to touch others with HIV.
8. Some people are afraid of those with HIV.
9. Some people think that people with HIV are unclean.
10. Some people prefer not to have those with HIV living in their community.
11. Some people think that people with HIV get what they deserve.
12. Some people who have HIV feel hurt because of how others react to knowing they have HIV.
13. Some people who have HIV feel alone. *
14. Some people who have HIV are afraid that other people in the community will talk about them having HIV. *
15. Some people who have HIV lose friends when they share with them they have HIV.
16. Some people who have HIV are afraid to tell those outside their family that they have HIV.

17. Some people who have HIV worry that others will reveal their secret. *
18. Some people who have HIV keep their distance from others to avoid spreading the HIV virus.
19. Some people who have HIV feel guilty because their family has the burden of caring for them.
20. Some people who have HIV will chose carefully who they tell about having HIV.

2. Physician Trust (Hall et al. /Measuring trust in Physicians)

1. Your doctor cares about your health just as much or more than you do.
2. Your doctor will do whatever it takes to get you all the care you need.
3. Your doctor's medical decisions are influenced by how much money [he or she] can make.
4. Your doctor is the kind of person who would fight hard to get your health insurance to pay for your treatment.
5. Sometimes you worry that [your doctor's] medical decisions are wrong.
6. Sometimes [your doctor] cares more about what is convenient for [him/her] than about your medical needs.
7. If [your doctor] asked you to be in a medical research study, you would worry that [he or she] care more about the research than about what is best for you.
8. No matter what health problem you might have, [your doctor] will always be able to figure out exactly what is wrong.
9. Your doctor's medical skills are not as good as they should be.
10. You think your doctor can handle any medical situation in [his or her] field, even a very serious one.
11. Your doctor does not always give you a chance to say everything you think [he or she] needs to know.
12. Your doctor is extremely thorough and careful.
13. You completely trust your doctor's decisions about which medical treatments are best for you.
14. Your doctor will listen with care and concern to any problem you might have, even problems that are small or silly.
15. Your doctor would never prescribe the wrong medication for you.
16. Your doctor is totally honest in telling you about all of the different treatment options available for your condition.

17. Your doctor has better medical skills than most other doctors in [his or her] field.
18. Your doctor sometimes pretends to know things when [he or she] is really not sure.
19. Your doctor only thinks about what is best for you.
20. Sometimes your doctor does not pay full attention to what you are trying to tell [him or her].
21. You worry that your doctor may share embarrassing information about you with people who have no business knowing it.
22. Your doctor always uses [his or her] very best skill and effort on your behalf.
23. You have no worries about putting your life in your doctor's hands.
24. Your doctor would never mislead you about anything.
25. Your doctor is the kind of person who would take care of you even if you could not afford to pay.
26. All in all, you have complete trust in your doctor.

3. Empathy

4. Social Support (Berlin Social Support Scales)

Perceived Emotional Support

1. There are some people who truly like me.
2. Whenever I am not feeling well, other people show me that they are fond of me.
3. Whenever I am sad, there are people who cheer me up.
4. There is always someone there for me when I need comforting.

Perceived Instrumental Support

1. I know some people upon whom I can always rely.
2. When I am worried, there is someone who helps me.

3. There are people who offer me help when I need it.
4. When everything becomes too much for me to handle, others are there to help me.

Need for Support

1. When I am down, I need someone who boosts my spirits.
2. It is important for me always to have someone who listens to me.
3. Before making any important decisions, I absolutely need a second opinion.
4. I get along best without any outside help. (-)

Support Seeking

1. In critical situations, I prefer to ask others for their advice.
2. Whenever I am down, I look for someone to cheer me up again.
3. When I am worried, I reach out to someone to talk to.
4. If I do not know how to handle a situation, I ask others what they would do.
5. Whenever I need help, I ask for it.

5. HIV Knowledge (Ciampa et al/ HIV Knowledge in Mozambique)

1. HIV and AIDS are the same thing.*
2. A person with HIV can look and feel healthy.*
3. A cure for AIDS exists.*
4. A blood test can tell if a person has been infected with HIV.*
5. A person who feels sick from AIDS can feel better by taking medicines
6. A woman who has HIV can give it to her infant during birth
7. A woman who has HIV can give it to her infant while breastfeeding
8. A pregnant woman who has HIV can prevent her baby from becoming infected by taking medicine
9. A person can get HIV by getting an injection with a needle that was already used on someone else.
10. A person can get HIV by sharing blades.
11. A person can get HIV from mosquito bites.
12. A woman can get HIV if she has sex with a man who has HIV.*
13. A person can get HIV by sharing forks, spoons or cups with a person who has HIV.
14. A person with HIV can cure the infection by taking medicine.

15. Eating healthy foods can keep a person from getting HIV.
16. Coughing and sneezing spread HIV.
17. A person can get HIV by shaking hands with someone who has HIV.
18. A person can get HIV by a curse.
19. A person who has HIV can use medicine to prevent becoming sick with AIDS.
20. A person can seek protection from a traditional healer to avoid getting AIDS.
21. A man can get HIV if he has vaginal sex with a woman who has HIV.
22. Bathing or washing one's genitals after sex keeps a person from getting HIV.
23. A person cannot get HIV by having oral sex, mouth-to-penis, with a man who has HIV.
24. Having sex with more than one partner can increase a person's chance of being infected with HIV.
25. A man wearing a latex condom during sex can lower his chance of getting HIV.
26. A person with another STD, such as syphilis, is more likely to get HIV.
27. Cleaning of the vagina with soap before or after sex will keep a woman from getting HIV.*

Appendix 3: Patient Health Questionnaire – 9 (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ DATE: _____

Over the last 2 weeks, how often have you been
bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

add columns + +

(Healthcare professional: For interpretation of TOTAL, TOTAL:
please refer to accompanying scoring card).

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

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PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.

Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying PHQ-9 Scoring Box to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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Appendix 4: Informed Consent (intervention arm)

This informed consent document applies to adults 18 years or older. This document is to be read aloud to the patients in the intervention arm.

Age of patient: _____

Introduction

This consent form contains information about a new study to provide couples-based HIV care and treatment to pregnant couples. This form describes your rights as a participant. It 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.

If you and your partner agree to participate in this program I will ask you to sign the form or make your thumbprint mark. Even if you agree to participate, you can stop participating at any time. I will give you a copy of this form. This form might contain some words that are unfamiliar to you. Please ask me to explain anything you do not understand.

Purpose of this study

This study is being done by staff from Vanderbilt University Medical Center (VUMC) and Friends in Global Health (FGH). We want to try a new way to offer HIV care and treatment to HIV positive couples who are expecting a child. Right now, couples can receive HIV testing together but can not enroll together in HIV treatment services. Pregnant women are enrolled in antenatal clinics (ANC) and men in adult HIV services.

Couples who are in the intervention group of this study will be able to get HIV services with their partner. This will happen first in ANC and then in the Child at-Risk (CCR) clinic after delivery. Couples in the intervention group will also receive additional couples counseling and community based support from peer educators. We want to see if couples who get these services together are better at staying on HIV treatment compared to couples in regular care.

Procedures to be followed and approximate duration of the study

This study will begin today and last for the next three years. If you and your partner agree to be part of this study, we will enroll you both into HIV care and treatment. All future clinical visits, counseling sessions, and drugs will be given to you at the ANC or CCR clinics. After you are enrolled in HIV treatment, you and your partner will be brought to meet with a couples' counselor.

We will also provide you both with a list of peer educators who successfully completed the steps of the prevention of mother-to-child treatment cascade. You will be able to choose the couple you wish to work with. Once you have made your choice, our study coordinator will arrange a meeting with you and your peer support couple in the next two weeks. Your peer supporters will

meet with you every month for the first seven months of your care. These meetings may be at your home or in another safe place you choose.

We will access your medical records to see what medications you are taking, medical data about your health (CD4 cell count and viral load), and the dates you pick up your medications.

A study staff person will also conduct two surveys at the beginning of your treatment and six months after you start treatment. You do not need to answer all the questions in the surveys 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 surveys at any time without any penalty.

Expected Costs:

None.

Possible Risks

The idea of providing HIV care and treatment together for couples expecting a baby is new and untested. While we will provide extra counseling for this, there is a chance that you and your partner will not agree on ways to take medication or talk together. This could make more problems in your relationship. If you feel any discomfort or have relationship problems please contact us as soon as possible so we can work to resolve it together.

We know that talking about your personal experiences with HIV with your partner or health care workers can be uncomfortable. We will try to have a comfortable, honest, and relaxed discussion. Still we know that some of the questions we ask might make you feel uncomfortable. We will try to limit embarrassment as much as possible. No study staff will tell anyone else your responses to the survey questions.

Possible Benefits

The information you share may help us to offer better services for couples living with HIV who come for ANC services. This could benefit Mozambican society by improving health programs for people living with HIV. If the project is successful, you may have better communication and trust with your partner after our counseling sessions.

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

Nothing. You are free to stop participating at any point without problem. You only need to say that you would like to stop being in the study. You can tell this to us at any time.

Confidentiality

We will make every effort to keep your personal information confidential. However, it's not possible to guarantee total confidentiality. The clinical information obtained during this study will be kept with your medical record. These medical records are stored securely at the health facility.

Privacy Information

Your information may only be shared if you or someone else is in danger, or if we are required to do so by law. If this occurs, your information may be shared with VUMC, or the U.S. and/or Mozambican government. This includes, for example, the VUMC IRB, U.S. Federal Government Office for Human Research Protections, or the Mozambican Ministry of Health.

Contact Information for Questions

If you should have any questions about study or wish to have additional counseling related to your care, please feel free to contact the evaluation activities coordinator, Lazaro Calvo, at the FGH office in Quelimane at +258 24217100.

For more information about giving consent or your rights, please feel free to contact the National Committee for Bioethics of Health in Mozambique at +258 824066350. You may also contact the VUMC Institutional Review Board (IRB) office in the U.S. at +001-615-322-2918.

Do you have any questions?

This form has been read and explained to me. I have been given an opportunity to ask questions I have about the study. I understand that I may decide at any time that I do not want to continue participating in the study. I understand that I will receive a copy of this consent form. By saying yes, you agree to participate in Partner-based HIV care and treatment for the next 18 months. You are agreeing to participate in our interviewer-administered surveys and that we can look at your medical records, and that of your unborn child. By saying no, you decline to participate in all parts of the study.

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

I give my consent to participate in the study.

Printed Name of Patient

Date

Signature of Patient

Date

Thumbprint of Participant

Signature of Witness (if thumbprint used)

Date

Signature of Person Who Explained This Form

Date

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.

Appendix 5: Informed Consent (control arm)

This informed consent document applies to adults 18 years or older. This document is to be read aloud to the patients in the control arm.

Age of patient: _____

Introduction

This consent form contains information about a new study to provide couples-based HIV care and treatment to pregnant couples. This form describes your rights as a participant. It 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.

If you and your partner agree to participate in this program I will ask you to sign the form or make your thumbprint mark. Even if you agree to participate, you can stop participating at any time. I will give you a copy of this form. This form might contain some words that are unfamiliar to you. Please ask me to explain anything you do not understand.

Purpose of this study

This study is being done by staff from Vanderbilt University Medical Center (VUMC) and Friends in Global Health (FGH). We want to try a new way to offer HIV care and treatment to HIV positive couples who are expecting a child. Right now, couples can receive HIV testing together but can not enroll together in HIV treatment services. Pregnant women are enrolled in antenatal clinics (ANC) and men in adult HIV services.

Couples who are in the intervention group of this study will be able to get HIV services with their partner. This will happen first in ANC and then in the Child at-Risk (CCR) clinic after delivery. Couples in the intervention group will also receive additional couples counseling and community based support from peer educators. Couples in the control group will complete two surveys, but otherwise will enroll in HIV care and treatment as they would normally. We want to see if couples who get these services together are better at staying on HIV treatment compared to couples in regular care.

Procedures to be followed and approximate duration of the study

This study will begin today and last for the next three years. If you and your partner agree to be part of this study, you will enroll into HIV care and treatment in ANC and Adult HIV care and treatment, respectively. After you are enrolled on HIV medication, you and your partner will be brought to meet with the study coordinator who will ask you and your partner to complete two surveys.

A study staff person will also conduct the same two surveys at six months after you start treatment. If you give us permission, we can complete this survey at the health facility or at your home (depending on your preference). You do not need to answer all the questions in the surveys 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 surveys at any time without any penalty.

Expected Costs:

None

Possible Risks

We know that talking about your personal experiences with HIV with your partner or health care workers can be uncomfortable. We will try to have a comfortable, honest, and relaxed discussion. Still we know that some of the questions we ask might make you feel uncomfortable. We will try to limit embarrassment as much as possible. No study staff will tell anyone else your responses to the survey questions.

Possible Benefits

The information you share may help us to offer better services for couples living with HIV who come for ANC services. This could benefit Mozambican society by improving health programs for people living with HIV. If the project is successful, you may have better communication and trust with your partner after our counseling sessions.

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

Nothing. You are free to stop participating at any point without problem. You only need to say that you would like to stop being in the study. You can tell this to us at any time.

Confidentiality

We will make every effort to keep your personal information confidential. However, it is not possible to guarantee total confidentiality. The clinical information obtained during study will be kept in your medical record. These medical records are stored securely at the health facility.

Privacy Information

Your information may only be shared if you or someone else is in danger, or if we are required to do so by law. If this occurs, your information may be shared with VUMC, or the U.S. and/or Mozambican government. This includes, for example, the VUMC IRB, U.S. Federal Government Office for Human Research Protections, or the Mozambican Ministry of Health.

Contact Information for Questions

If you should have any questions about this study or wish to have additional counseling related to your care, please feel free to contact the evaluation activities coordinator, Lazaro Calvo, at the FGH office in Quelimane at +258 24217100.

For more information about giving consent or your rights, please feel free to contact the National Committee for Bioethics of Health in Mozambique at +258 824066350. You may also contact the VUMC Institutional Review Board (IRB) office in the U.S. at +001-615-322-2918.

Do you have any questions?

This form has been read and explained to you. You have been given an opportunity to ask questions about the study. You know that you may decide at any time to not continue participating in the study. You understand that you will receive a copy of this consent form. By saying yes, you agree to participate in two surveys: one now and a second one in six months. You are agreeing that we can look at your medical records, and that of your unborn child. If you say no, you decline to participate in all parts of the study.

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

I give my consent to participate in the study.

Printed Name of Patient

Date

Signature of Patient

Date

Thumbprint of Participant

Signature of Witness (if thumbprint used)

Date

Signature of Person Who Explained This Form

Date

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.