Published in final edited form as:

Contemp Clin Trials. 2018 August ; 71: 63–69. doi:10.1016/j.cct.2018.05.020.

Partners-based HIV treatment for seroconcordant couples attending antenatal and postnatal care in rural Mozambique: A cluster randomized trial protocol

Carolyn M. Audet^{a,b}, Erin Graves^a, Ezequiel Barreto^c, Caroline De Schacht^c, Wu Gong^d, Bryan E. Shepherd^d, Arifo Aboobacar^l, Lazaro Calvo^{c,e}, Maria Fernanda Alvim^c, Muktar H. Aliyu^{a,b}, Aaron M. Kipp^{a,f}, Heather Jordan^a, Rivet Amico^g, Matthew Diemer^h, Andrea Ciaranello^{i,j}, Caitlin Dugdale^{i,j}, Sten H. Vermund^k, and Sara Van Rompaey^l

^aVanderbilt University Medical Center, Vanderbilt Institute for Global Health, 2525 West End Ave, Suite 750, Nashville TN 37203 USA; Phone (615) 343-7643; Fax: (615) 343-7797

^bVanderbilt University Medical Center, Department of Health Policy, 2525 West End Ave, Suite 1200, Nashville, TN 37203 USA; Phone: (615) 322-1324; Fax (615) 322-0265

^cFriends in Global Health, Avenida Maguiguana, 32 R/C, Maputo, Mozambique - CP 604; Office phone: +258 21328310; Fax: +258 21328311

^dVanderbilt University School of Medicine, Department of Biostatistics, 2525 West End Ave, Suite 11000, Nashville TN, 37203 USA; Phone (615) 322-2001; Fax (615) 343-4924

^eVanderbilt University Medical Center, Department of Pediatrics, 2200 Children's Way, Nashville, TN 37232 USA; Phone (615) 936-1000; Fax: (615) 936-3330

^fVanderbilt University Medical Center, Division of Epidemiology, Nashville, TN 37203, USA

^gUniversity of Michigan, Department of Health Behavior and Health Education, School of Public Health, 1415 Washington Heights, Ann Arbor MI USA, 48109-2029; Phone (734) 763-0051

^hUniversity of Michigan, Combined Program in Education and Psychology & Educational Studies, School of Education, Room 4120, Ann Arbor MI USA, 48109; Phone (734) 647-7369

ⁱDivision of Infectious Diseases, 100 Cambridge St, Room 1670, Massachusetts General Hospital, Boston MA USA, 02114; Phone (617) 726-3812; Fax (617) 726-2691

^jHarvard Medical School, Harvard University, 25 Shattuck St, Boston, MA USA, 02115

^kYale School of Public Health, 60 College St. Suite 212, New Haven CT USA, 06510-3201; Phone (203) 785-2867; Fax (203) 785-6103

^lMinistry of Health, Zambézia, Quelimane, Mozambique; +(258) 824 2984

Abstract

Background—In resource-limited rural settings, scale-up of services to eliminate mother-to-child transmission of HIV has not been as effective as in better resourced urban settings. In sub-Saharan Africa, women often require male partner approval to access and remain engaged in HIV care. Our study will evaluate a promising male engagement intervention (“*Homens para Saúde*”

Mais” (HoPS+) [Men for Health Plus]) targeting the elimination of mother-to-child transmission in rural Mozambique.

Design—We will use a cluster randomized clinical trial design to engage 24 health facilities (12 intervention and 12 standard of care), with 45 HIV-infected seroconcordant couples per clinic. The planned intervention will engage male partners to address social-structural and cultural factors influencing eMTCT based on new couple-centered integrated HIV services.

Conclusions—The HoPS+ study will evaluate the effectiveness of engaging male partners in antenatal care to improve outcomes among HIV-infected pregnant women, their HIV-infected male partners, and their newborn children. Our objectives are to: (1) Implement and evaluate the impact of male-engaged, couple-centered services on partners’ retention in care, adherence to antiretroviral therapy, early infant diagnosis uptake, and mother-to-child transmission throughout pregnancy and breastfeeding; (2) Investigate the impact of HoPS+ intervention on hypothesized mechanisms of change; and (3) Use validated simulation models to evaluate the cost-effectiveness of the HoPS+ intervention with the use of routine clinical data from our trial. We expect the intervention to lead to strategies that can improve outcomes related to partners’ retention in care, uptake of services for HIV-exposed infants, and reduced MTCT.

Keywords

HIV/AIDS; Antenatal care; Partners-based clinical services; Mozambique; Male partner engagement

1. Background

Mozambique has one of the highest HIV/AIDS burdens in the world, and is home to one of the nation’s poorest and most medically underserved provinces, Zambézia province. Adult HIV prevalence in 2015 in Zambézia was estimated at 15%, with a substantially higher prevalence among pregnant women.[1] According to the 2013 Demographic and Health Survey, 79% of pregnant women in Zambézia attended at least one prenatal visit.[2] In 2014, only 77% of pregnant women who attended an antenatal clinic (ANC) in Zambézia were tested for HIV, and only 80% of those women who tested HIV+ initiated antiretroviral therapy (ART).[3] Further, half of HIV-infected pregnant women abandoned care within six months of ART initiation. Fewer than 40% of HIV-positive mothers who attended clinic returned with their infants for early infant diagnosis (EID) services. Among returnees, only 70% of infants received a polymerase chain reaction (PCR) test to determine their HIV status, and only 30% of HIV-infected infants were enrolled on ART (Alvim, unpublished data 2015).

Women living in this region have identified a lack of support from husbands or male partners as a principal barrier to engagement in ANC and HIV testing services.[4–6] Qualitative [5–8] and clinical data [9] across sub-Saharan Africa reveal that women are reluctant to accept HIV testing or treatment if their partners are not supportive, highlighting the importance of partner engagement and programmatic adaptation to account for prevailing social gender norms. The male partner is the most influential family member affecting a woman’s health decisions in many rural Mozambican provinces,[10] yet long-standing community norms

inhibit men from engaging in the prenatal care of wives or partners.[11] Mozambique is not unique; improving social acceptability of engagement of male partners in HIV counseling during ANC has resulted in increased testing and treatment uptake across sub-Saharan Africa (SSA).[12–17]

By engaging the HIV-infected male partner, we can address patient-reported barriers to retention in care in rural Mozambique, notably lack of partner support.[18, 19] In addition, the couple receiving services together becomes a de facto adherence group.[20–26] 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.[10] In addition, partners exist in one's living environment. Through the provision of partner-based ART services, adherence to treatment becomes entwined with lived experiences – instead of messages only delivered when at clinic. Thus, to achieve the 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.

2. Objectives

The principal objective of the *Homens para Saúde Mais* (HoPS+) (“Men for Health Plus”) project is to develop and assess the impact of a partner-based ART delivery intervention among HIV-positive expectant couples. Our first objective is to implement, monitor, and evaluate the impact of couple-based services on HIV-related outcomes for all three members of the mother-male partner-infant triad from first ANC visit to 18 months post-partum through a cluster randomized control trial (RCT). Our second objective is to investigate the impact of the intervention on hypothesized mechanisms of change, including (1) partner social support [27]; (2) HIV stigma[28]; (3) relationship empathy[29]; (4) HIV knowledge[30]; (5) patient trust in provider[31]; and depression[32], through quantitative surveys with participants at baseline and 6 months. For our third objective, we will use validated simulation models to evaluate cost-effectiveness of the HoPS+ intervention, accounting for clinical and economic outcomes among pregnant and lactating women, their male partners, and their infants (Figure 1). Our results will inform culturally-appropriate HIV care and treatment during pregnancy and beyond. In order to succeed, eMTCT efforts in rural SSA require effective innovation for culturally-appropriate adherence support at all stages of the care continuum.

2.1 Outcomes of Interest

Our primary outcome is 12-month retention in clinical care. Our secondary outcomes include viral suppression among HIV-infected pregnant/lactating women and their HIV-infected male partners at 18 months and MTCT among infants at 18 months.

3. Procedures

This study is an unblinded, two-arm, cluster RCT that compares usual care to couple-based HIV care and treatment among expectant and post-natal seroconcordant couples in rural Mozambique. The trial will be conducted in 24 health facilities throughout Zambezia. The

study protocol and informed consent documents have been approved by Vanderbilt University Institutional Review Board and the *Comité Institucional de Bioética para a Saúde da Província da Zambézia* (Institutional Committee for Bioethics in Health in Zambézia Province) in Mozambique. The study was deemed to present minimal risk to participants. The study team will document all adverse medication side effects and experiences that occur. A safety and monitoring board will review results every six months. The trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03149237) (NCT03149237).

3.1 Site Selection

The 24 sites (clinics) were 1:1 matched by an optimal non-bipartite matching algorithm. Each of the 24 sites was assigned a study identification (ID) number. Five site-specific variables were used as covariates in the matching, including the number of women in the ANC population, the adult HIV+ male retention rate from 2016, the number of positive male partners, and the longitude and latitude (location) of the site. A matrix of Mahalanobis distances across all sites was computed on the five covariates with weight of 2, 2, 2, 1.5, and 1.5, respectively. Then the 12 matched pairs were selected by minimizing the overall sum of the distances between pairs. After matching, each pair was assigned a pair ID. The matching procedure was implemented with R “nbpMatching” package [33]. Randomization was conducted by randomly assigning one clinic within each pair to either the SOC group (12 sites) or the intervention group (12 sites).

3.2 Participant Selection

We will enroll 1,080 HIV-infected couples (2,160 individuals) who present for care at one of the 24 clinical sites. Couples (one pregnant woman and her male partner) will be eligible to participate if: both partners are HIV-positive; if the woman’s due date is >2 weeks from the time of study enrollment; and both persons are 18 years or older, able to give informed consent, be willing to consent to an infant medical record search, and willing to enroll in ART together. Participants do not necessarily need to be newly diagnosed with HIV, but they must either: test and receive positive results together at ANC visit; or clinical staff must be able to confirm their HIV-positive status from clinical records. Participants also do not necessarily need to be treatment naïve, but they cannot be on ART at the time of study enrollment (defined as more than 60 days from last missed medication pick-up appointment). Given that legal marriage is uncommon, all couples who self-identify as “married” or “living together” will be enrolled in the study. Eligible couples will be referred to the study’s couples counselor by the ANC health care staff; the couples counselor will confirm eligibility and obtain consent from each partner for study participation.

3.3 Participant Assessments

All participants who complete the consent process will complete assessments at baseline and six months via a counselor-facilitated questionnaire (Table 1). Assessments will consist of: (a) demographics (e.g., age, sex, education, marital status, and occupation), home community, and contact information for each partner; (b) partner social support [27]; (c) HIV stigma[28]; (d) relationship empathy[29]; (e) HIV knowledge[30]; (f) patient trust in provider[31]; and (g) depression[32, 34]. These assessment results will be collected on paper forms by the couple’s counselor and transferred into REDCap® by a study assistant.

The preceding psychosocial factors and HIV knowledge were selected because they have been associated with poor retention in HIV care [19, 35, 36] and are directly related to the social context within which we wish to evaluate couples-based ART. Furthermore, poor HIV knowledge and high HIV stigma continue to be present in Zambézia. Measures of HIV knowledge and depression have been previously validated in this population. [30] Measures of social support, HIV stigma, and clinician trust are currently being used in a different study in the province and are being evaluated for validity, though initial reports suggest good psychometric properties. Attendance in clinic-based couples counseling sessions, community-based couples support sessions, and clinic appointments will be recorded by the study team and the OpenMRS clinical database. Medication pick-up will be recorded in individual sheets for ART pick-up (*FILA*) and the clinical files and that information will be encoded in the Electronic Patient Tracking System (EPTS) in OpenMRS.

A small subsample (n=60) of participants in the intervention arm will complete in-depth interviews about their experience receiving the intervention, including their thoughts on the implementation of the intervention, relationship with couples counselors and peer support couples, and the impact of this partner-based support on interpersonal communication, family support for their well-being, and satisfaction with HIV clinical services.

3.1 Clinical Intervention Arm

The 12 clinics randomly assigned to the intervention arm will receive a combination of community and clinical prevention of MTCT (PMTCT) services, including: (1) Couple-based treatment enrollment in ANC and care for seroconcordant HIV+ expectant couples; (2) couple-centered treatment in the postpartum and breastfeeding periods at the clinic for children at risk; (3) couple-based education and skills building during the ANC and lactating/breastfeeding periods; and (4) treatment continuity support during the ANC and lactating/breastfeeding periods by expert patient (peer) educators selected among couples who have successfully navigated PMTCT.[37–39]

Couples-based enrollment and treatment in ANC and postpartum period—

Couples are a proven, effective unit of intervention in the African HIV prevention and care context.[3, 12, 13, 15, 17, 37, 40–49] Continuously engaging the man, however, has proven challenging within ANC, as men feel superfluous to ANC and PMTCT.[17] Our community outreach program has already increased the number of male partners markedly who test during the first ANC appointment. Given our ability to recruit >60% of male partners into ANC, we believe enrolling HIV+ partners into HIV care and treatment in ANC is a feasible strategy. The space for couples counseling in ANC has already been created, and can be used for couple-based HIV treatment delivery. Expectant HIV+ couples are eligible for ART enrollment regardless of their CD4+ cell count in Mozambique, but this guideline has rarely been followed in the past. Couples will receive joint monthly clinical visits from ANC through 18 months post-partum (at the child at risk clinic), thus avoiding any separation of clinical services.

Couple-based education and skills building—HIV-positive expectant couples enrolled in intervention sites will receive six monthly couples counseling and skills

development sessions throughout the ANC and postpartum/lactating periods to provide a venue for couples to: (1) share thoughts and feelings about their HIV diagnosis; (2) discuss and make decisions related to health, HIV care and treatment; (3) discuss relationship issues that may emanate from HIV diagnosis; and (4) discuss relationship issues unrelated to HIV. [50] Couples may experience the process of HIV treatment differently than persons enrolled individually. Providing skills to navigate the inherently complicated process of couples-based treatment is essential to retention and adherence.[43, 51] Based on an adaptation of the *CoupleConnect* curriculum[52], couples counselors will be trained in cognitive-behavioral strategies for promoting couple connectedness and strengthening couples' communication, to help couples maintain higher levels of functioning, prevent marital problems, and equip couples with effective and accessible coping strategies. These sessions will be provided by trained couples counselors employed by the study and assigned to work at respective clinics in the intervention arm.

Treatment continuity support from expert peer couples—Participating couples will be matched with an expert peer couples that 1) who successfully completed the PMTCT cascade in the past two years (i.e., since Option B+ was initiated in the region), and 2) are trained to deliver couple-based adherence support (based on the Adherence Support Worker program).[53] 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 (at minimum) 18 months postpartum. Couples will have the opportunity to choose the expert peer couple of their choice from trained volunteers living within a 2-km radius of their community. This peer mentorship will begin the first week of enrollment; monthly community-based support sessions will be held (at an agreed upon location) until infant prophylaxis is complete. Peer couples will discuss their experiences with prevention of mother-to-child transmission (PMTCT) services, provide advice for handling HIV diagnosis and treatment (e.g., if the couple experiences adverse effects of ART), and help the participating couple deal with social stigma, specifically enacted and internalized stigma related to HIV. Matching the 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: provider support continuity and community-based peer support. Continuity of care has been traditionally assessed based on clinical measures of provider continuity.[54–56] We propose to improve this model by adding a level of continuity of support at the community level. In Mozambique there is a history of patient-provider conflict and distrust. [19, 57] We believe that expert peer support will help address this barrier to quality care by allowing personal testimony from peers of how PMTCT care affected their health and that of their infant. In addition to promoting continuity of care, expert peer couples can provide community-based support for participating couples enrolled in PMTCT services. HIV stigma remains a significant barrier to retention in care and adherence to ART.[58, 59] These experienced couples have navigated these personal and social realities and can provide advice, assurance, and support if participating couples perceive, experience, or internalize HIV-related stigma.[60–62]

3.2 Control Arm

The 12 clinics randomized to the control arm will continue to provide standard of care ANC PMTCT services which include: invitation of male partner to ANC services, opt-out rapid HIV testing of all pregnant women and/or couples testing with male partners attending ANC, HIV-specific counseling and support for all pregnant women who test positive, provision of cotrimoxazole prophylaxis, and universal ART, as per World Health Organization (WHO) Option B+ national guidelines (Figure 1).[63] HIV-positive male partners will receive separate clinical and counseling services as well as relevant medications free of charge in the adult HIV/ART clinics. Postpartum women and their exposed infants will continue PMTCT follow-up after delivery at the CCR in a “one-stop point of care” model. In CCR, postpartum/lactating women will continue their HIV care and treatment follow-up, including provision of cotrimoxazole and isoniazid prophylaxis, as well as counseling and support; infants will have access to HIV testing by dried blood spot (DBS) PCR as early as 4 weeks after birth. Follow-up at the CCR for both mother and infant will continue for up to 18 months, unless the infant is diagnosed HIV-positive and the dyad is referred to respective adult and pediatric HIV treatment services.

3.3 Cost-effectiveness

The potential long-term clinical impact and cost-effectiveness of the HoPS+ intervention will be assessed using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model. CEPAC is a validated, patient-level (Monte Carlo) simulation model of HIV testing, disease progression, and treatment.[64] We will use the CEPAC-Adult model to project clinical and economic outcomes for HIV+ pregnant and postpartum women and their HIV+ male partners under both the SOC strategy and HoPS+ strategy for care delivery. [65–69] The CEPAC-Adult model will simulate HIV disease progression, including viral load and CD4 count trajectories, incidence of opportunistic infections, ART initiation and adherence, loss to follow-up, and return to care for mothers living with HIV and their male partners. Results from the CEPAC-Adult model will then be linked to the CEPAC-Pediatric model to capture clinical and economic outcomes for their HIV-exposed infants.[70–72] The CEPAC-Pediatric model includes the key events in the PMTCT “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; retention in care; maternal mortality during pregnancy; HIV testing in labor for women with unknown/negative HIV status; intrauterine, intrapartum, and postpartum MTCT with risks stratified by breastfeeding status and maternal virologic suppression; EID uptake, and linkage to pediatric postnatal care and ART. Further details regarding the linked CEPAC-Adult and CEPAC-Pediatric model structures can be found on the CEPAC website (<http://www.massgeneral.org/mpec/cepac/>).

4. Statistical Analysis

Objective 1: The primary trial endpoint is adult loss to follow-up (LTFU), defined as >60 days late for the scheduled ARV pickup at any time during 12 months post-treatment enrollment. Secondary endpoints include adult HIV viral suppression during the pre and post-natal period, infant seroconversion, infant LTFU, and mortality (mother, male partner or infant). Adult 12 month retention will be compared between arms using a generalized linear

mixed effects model, including random effects for the matched clinic pairs and for individual clinics nested within pairs to account for correlation due to clustering. [73] Separate models will be used to assess the impact of intervention on outcomes in each population (men, women, infants). An intent-to-treat approach will be employed for all analyses. All models for adult patients will include the following baseline covariates: age, education, depression scale score, social support score, provider trust score, stigma, HIV knowledge, relationship empathy, and distance from clinic. For infant HIV infection, we will include baseline maternal and male partner data as covariates. Missing covariate information will be multiply imputed using standard techniques. Sensitivity analyses will be conducted to investigate the effect of having no EID test result on HIV infection status; 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).

Objective 2: Generalized linear mixed effects models will be used as described for Objective 1, replacing the logit transformation of the outcome with an untransformed linear outcome because the 6-month self-reported outcomes are continuous (e.g., HIV knowledge score, HIV stigma score, social support, provider trust, empathy). Intervention status will remain the exposure variable of interest. As with Objective 1, gender-specific models will be used to measure each outcome of interest, adjusting for individual level covariates including baseline scores on survey items. Interactions between intervention status and the baseline values of each endpoint will be used to assess for effect modification. All outcomes 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 while examining the potential mediating role of each outcome on retention (Figure 2). Direct, indirect, and total effects of the intervention through the mechanisms identified in the first step of Objective 2 will be estimated using SEM and causal meditation analysis techniques [74, 75].

Objective 3: These models will be populated with inputs derived from the HoPS+ trial, as well as from the published literature. Trial-derived inputs will include: partners' ages, CD4+ cell count, and HIV viral load at ART initiation; maternal and male partner longitudinal retention in care through 18 months; maternal and male partner virologic suppression at 6 months, 12 months, and 18 months; EID uptake at birth, 4-8 weeks, and 18 months (or the end of breastfeeding); MTCT rates among those in care and receiving EID testing; and estimated intervention-related costs. In comparing the HoPS+ strategy to the SOC strategy, we will consider an ICER less 1x the *per-capita* GDP of Mozambique (approximately \$380 in 2016 USD) to be cost-effective.[76]

4.1 Power and sample size determination

Sample sizes were chosen to ensure adequate power to detect an effect of the intervention on the primary outcome, adult retention. Power calculations were based on preliminary, 2016 data from clinics in Zambézia. In these data, an estimated 31% of pregnant women were started and retained on ART after 6 months (55% of women started ART and 56% of those starting were retained); estimates were comparable for men. With 24 clusters and 45 couples per cluster, we anticipate having approximately 85% power to detect an improvement in retention from 31% to 48%. (Forty-eight percent corresponds to a 30% improvement in ART

initiation from 55% to 72% and a 20% improvement in retention among those who initiated ART from 56% to 67%.) These power calculations assume a type I error rate of 0.05, an intracluster correlation coefficient of 0.07, and that the correlation from matched sites is equal to 0.20.

4.2 Limitations

Our trial will have several limitations. The lack of blinding to the intervention introduces several potential biases. First, participants in the intervention arm will receive more structured contact time and attention by couple counselors and peer supporters than their control arm comparison group. We think this formal structured support is essential to prevent any negative effects of partner-based treatment (gender-based violence, for example). However, it is possible that additional counseling (beyond current standard of care) could be useful to patients independent of the intervention itself. Somewhat enhanced counseling is not likely to make a substantial difference in uptake,[77] so we still think that attribution of benefit, if any, can be assumed to be our package rather than merely somewhat extended counseling. Second, given the cluster RCT design, inter-clinic contamination is possible. This bias will be reduced by selecting geographically separate clinics >1.5 hours driving distance apart where patients very rarely visit both clinics. Third, three of our six measures (relationship empathy, social support, and trust of clinicians) have not been validated in this population. We plan to validate each of these three measures during the study and will be open to adapting the measures in future studies if it is found they are not accurately measuring the intended constructs. Fourth, with only 12 clinics in each arm, it is possible that observed differences between the intervention and control clinics could be due to characteristics of the clinics and not the study intervention. To minimize this possibility, we matched clinics prior to randomization based on similarity of characteristics. Matching of clinics or clusters is never perfect and there may be other key differences between clinics that were not incorporated into the matching algorithms. We will examine and report balance on observables after randomization. As our primary outcome is retention, there will be missing data for secondary outcomes (e.g., infant infection and 6-month psycho-social outcomes) among those participants who are not retained. We will perform sensitivity analyses that make various assumptions on the values of these missing outcomes (e.g., analyses only among those with complete data, analyses imputing missing outcomes based on the literature and/or characteristics of lost participants). Missing baseline covariates will be multiply imputed. Finally, because inclusion in the study requires seroconcordant couples being willing to enroll in ART programs together, it is likely that we are testing the intervention in a subset of patients who have better retention outcomes than the general seroconcordant population.

5. Conclusions/summary

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.[3] In our new project, “HoPS+”, we will implement and rigorously evaluate a novel partner-based ART enrollment immediately after both partners receive concurrent HIV-positive diagnoses in ANC. Our intervention will create an integrated structure to

provide couple-based ART and adherence support within comprehensive HIV care and treatment services. Anchored on professional and peer couples counseling and support, this intervention will seek to ensure that partners are engaged and retained in care throughout pregnancy and the postpartum/breastfeeding period. We expect the results of this trial to inform implementation of PMTCT and male engagement strategies in a wide range of settings. Our identification of individual characteristics and relationship dynamics impacted by the intervention will allow future implementers to identify appropriate populations in which to introduce HoPS+ strategies.

Acknowledgments

Disclosures

Funding: This work is supported by the National Institute of Mental Health grants R01MH113478. CMA is also supported by K01MH107255 and SHV is supported by P30MH062294. The authors are solely responsible for the design and conduct of this study, study analyses, and the drafting of this manuscript.

References

1. Ministerio da Saude (MISAU), Instituto Nacional de Estatística (INE), and I. International Inquérito de Indicadores de Imunização, Malária e HIV/SIDA em Moçambique (IMASIDA) 2015 INS, INE e International; Maputo, Mozambique: 2015
2. Ministerio da Saude (MISAU), Instituto Nacional de Estatística (INE), and ICF International (ICFI) Moçambique Inquérito Demográfico e de Saúde 2011 MISAU, INE e ICFI; Calverton, Maryland, USA: 2013
3. Audet CM, et al. Engagement of Men in Antenatal Care Services: Increased HIV Testing and Treatment Uptake in a Community Participatory Action Program in Mozambique. *AIDS Behav.* 2016
4. Dahl V, et al. Acceptance of HIV testing among women attending antenatal care in south-western Uganda: risk factors and reasons for test refusal. *AIDS Care.* 2008; 20(6):746–52. [PubMed: 18576178]
5. Bajunirwe F, Muzoora M. Barriers to the implementation of programs for the prevention of mother-to-child transmission of HIV: a cross-sectional survey in rural and urban Uganda. *AIDS Res Ther.* 2005; 2:10. [PubMed: 16255776]
6. Sarker M, et al. Determinants of HIV counselling and testing participation in a prevention of mother-to-child transmission programme in rural Burkina Faso. *Trop Med Int Health.* 2007; 12(12): 1475–83. [PubMed: 18076555]
7. Kempf MC, et al. A qualitative study of the barriers and facilitators to retention-in-care among HIV-positive women in the rural southeastern United States: implications for targeted interventions. *AIDS Patient Care STDS.* 2010; 24(8):515–20. [PubMed: 20672971]
8. Walcott MM, et al. Facilitating HIV status disclosure for pregnant women and partners in rural Kenya: a qualitative study. *BMC Public Health.* 2013; 13:1115. [PubMed: 24294994]
9. Becker S, et al. Comparing couples' and individual voluntary counseling and testing for HIV at antenatal clinics in Tanzania: a randomized trial. *AIDS Behav.* 2010; 14(3):558–66. [PubMed: 19763813]
10. Campbell TL. The effectiveness of family interventions for physical disorders. *J Marital Fam Ther.* 2003; 29(2):263–81. [PubMed: 12728782]
11. Audet CM, et al. Barriers to Male Involvement in Antenatal Care in Rural Mozambique. *Qual Health Res.* 2015
12. Aguiar C, Jennings L. Impact of Male Partner Antenatal Accompaniment on Perinatal Health Outcomes in Developing Countries: A Systematic Literature Review. *Matern Child Health J.* 2015

13. Auvinen J, Kylma J, Suominen T. Male involvement and prevention of mother-to-child transmission of HIV in Sub-Saharan Africa: an integrative review. *Curr HIV Res.* 2013; 11(2): 169–77. [PubMed: 23432492]
14. Auvinen J, Suominen T, Valimaki M. Male participation and prevention of human immunodeficiency virus (HIV) mother-to-child transmission in Africa. *Psychol Health Med.* 2010; 15(3):288–313. [PubMed: 20480434]
15. Brusamento S, et al. Male involvement for increasing the effectiveness of prevention of mother-to-child HIV transmission (PMTCT) programmes. *Cochrane Database Syst Rev.* 2012; 10:CD009468. [PubMed: 23076959]
16. Chomba E, et al. Evolution of couples' voluntary counseling and testing for HIV in Lusaka, Zambia. *J Acquir Immune Defic Syndr.* 2008; 47(1):108–15. [PubMed: 17984761]
17. Conkling M, et al. Couples' voluntary counselling and testing and nevirapine use in antenatal clinics in two African capitals: a prospective cohort study. *J Int AIDS Soc.* 2010; 13:10. [PubMed: 20230628]
18. da Silva M, et al. Patient Loss to Follow-Up Before Antiretroviral Therapy Initiation in Rural Mozambique. *AIDS and behavior.* 2014:1–13. [PubMed: 23321946]
19. Groh K, et al. Barriers to antiretroviral therapy adherence in rural Mozambique. *BMC Public Health.* 2011; 11:650. [PubMed: 21846344]
20. Decroo T, et al. Four-year retention and risk factors for attrition among members of community ART groups in Tete, Mozambique. *Trop Med Int Health.* 2014; 19(5):514–21. [PubMed: 24898272]
21. Decroo T, et al. Lessons learned during down referral of antiretroviral treatment in Tete, Mozambique. *J Int AIDS Soc.* 2009; 12:6. [PubMed: 19419543]
22. Decroo T, et al. Distribution of antiretroviral treatment through self-forming groups of patients in Tete Province, Mozambique. *J Acquir Immune Defic Syndr.* 2011; 56(2):e39–44. [PubMed: 21084990]
23. Decroo T, et al. Effect of Community ART Groups on retention-in-care among patients on ART in Tete Province, Mozambique: a cohort study. *BMJ Open.* 2017; 7(8):e016800.
24. Jobarteh K, et al. Community ART Support Groups in Mozambique: The Potential of Patients as Partners in Care. *PLoS One.* 2016; 11(12):e0166444. [PubMed: 27907084]
25. Rasschaert F, et al. Sustainability of a community-based anti-retroviral care delivery model - a qualitative research study in Tete, Mozambique. *J Int AIDS Soc.* 2014; 17:18910. [PubMed: 25292158]
26. Rasschaert F, et al. Adapting a community-based ART delivery model to the patients' needs: a mixed methods research in Tete, Mozambique. *BMC Public Health.* 2014; 14:364. [PubMed: 24735550]
27. SchwarzerR, , SchulzU. Berlin Social Support Scales (BSSS)2013[cited 2016 July 5, 2016]; Available from: <http://www.midss.org/content/berlin-social-support-scales-bsss>
28. Van Rie A, et al. Measuring stigma associated with tuberculosis and HIV/AIDS in southern Thailand: exploratory and confirmatory factor analyses of two new scales. *Trop Med Int Health.* 2008; 13(1):21–30. [PubMed: 18290998]
29. Davis MH. A multidimensional approach to individual differences in empathy. *Journal of Personality and Social Psychology.* 1983; 44(1):113–126.
30. Ciampa PJ, et al. Comprehensive knowledge of HIV among women in rural Mozambique: development and validation of the HIV Knowledge 27 Scale. *PLoS One.* 2012; 7(10):e48676. [PubMed: 23119087]
31. Hall MA, et al. Measuring patients' trust in their primary care providers. *Med Care Res Rev.* 2002; 59(3):293–318. [PubMed: 12205830]
32. Kroenke K, et al. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord.* 2009; 114(1–3):163–73. [PubMed: 18752852]
33. R package version 1.5.1. *nbpMatching: Functions for Optimal Non-Bipartite Matching.* 2016
34. McMahon AB, et al. PHQ-8 minor depression among pregnant women: association with somatic symptoms of depression. *Arch Womens Ment Health.* 2017; 20(3):405–409. [PubMed: 28175993]

35. Bond V, Chase E, Aggleton P. Stigma, HIV/AIDS and prevention of mother-to-child transmission in Zambia. *Evaluation and Program Planning*. 2002; 25:347–356.
36. Ferrando S, et al. Fatigue in HIV illness: relationship to depression, physical limitations, and disability. *Psychosom Med*. 1998; 60(6):759–64. [PubMed: 9847037]
37. Byamugisha R, et al. Male partner antenatal attendance and HIV testing in eastern Uganda: a randomized facility-based intervention trial. *J Int AIDS Soc*. 2011; 14:43. [PubMed: 21914207]
38. Kululanga LI, et al. Striving to promote male involvement in maternal health care in rural and urban settings in Malawi - a qualitative study. *Reprod Health*. 2011; 8:36. [PubMed: 22133209]
39. Ndong I, Steele C, Mahony E. Involving men in reproductive health: making the mandate a reality. *Sex Health Exch*. 1998; (2):14–5.
40. Aluisio A, et al. Male antenatal attendance and HIV testing are associated with decreased infant HIV infection and increased HIV-free survival. *J Acquir Immune Defic Syndr*. 2011; 56(1):76–82. [PubMed: 21084999]
41. Farquhar C, et al. Antenatal couple counseling increases uptake of interventions to prevent HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2004; 37(5):1620–6. [PubMed: 15577420]
42. Haas AD, et al. Retention in care during the first 3 years of antiretroviral therapy for women in Malawi's option B+ programme: an observational cohort study. *Lancet HIV*. 2016; 3(4):e175–82. [PubMed: 27036993]
43. Remien RH, et al. Couple-focused support to improve HIV medication adherence: a randomized controlled trial. *AIDS*. 2005; 19(8):807–14. [PubMed: 15867495]
44. Wall KM, et al. Promotion of couples' voluntary HIV counselling and testing in Lusaka, Zambia by influence network leaders and agents. *BMJ Open*. 2012; 2(5)
45. Allen S, et al. Promotion of couples' voluntary counselling and testing for HIV through influential networks in two African capital cities. *BMC Public Health*. 2007; 7:349. [PubMed: 18072974]
46. Cremin I, et al. Seasonal PrEP for partners of migrant miners in southern Mozambique: a highly focused PrEP intervention. *J Int AIDS Soc*. 2015; 18(4 Suppl 3):19946. [PubMed: 26198340]
47. Hoffman RM, et al. Benefits of PrEP as an Adjunctive Method of HIV Prevention During Attempted Conception Between HIV-uninfected Women and HIV-infected Male Partners. *J Infect Dis*. 2015; 212(10):1534–43. [PubMed: 26092856]
48. Murnane PM, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. *AIDS*. 2013; 27(13):2155–60. [PubMed: 24384592]
49. Ndase P, et al. Successful discontinuation of the placebo arm and provision of an effective HIV prevention product after a positive interim efficacy result: the partners PrEP study experience. *J Acquir Immune Defic Syndr*. 2014; 66(2):206–12. [PubMed: 24828268]
50. El-Bassel N, Wechsberg WM. Couple-Based Behavioral HIV Interventions: Placing HIV Risk-Reduction Responsibility and Agency on the Female and Male Dyad. *Couple and Family Psychology: Research and Practice*. 2012; 1(2):94–105.
51. Crepaz N, et al. Are couple-based interventions more effective than interventions delivered to individuals in promoting HIV protective behaviors? A meta-analysis. *AIDS Care*. 2015; 27(11):1361–6. [PubMed: 26608175]
52. EngenderHealthCoupleConnect: A Gender Transformative HIV Prevention Curriculum for Tanzanian CouplesEngenderHealth/CHAMPION PROJECT; Dar Es Salam: 2014
53. Family Health International. Adherence Support Worker Training: Facilitator's Guide2007[cited 2014 March 4]; Available from: http://www.aidstar-one.com/sites/default/files/promising_practices/g3p_docs/ASWFacilitatorsGuideHVenhv.pdf
54. Van Walraven C, et al. The association between continuity of care and outcomes: a systematic and critical review. *Journal of Evaluation in Clinical Practice*. 2010; 16(5):947–956. [PubMed: 20553366]
55. Van Walraven C, et al. Continuity of Care and Patient Outcomes After Hospital Discharge. *Journal of General Internal Medicine*. 2004; 19(6):624–631. [PubMed: 15209600]
56. Dreier J, et al. The association between continuity of care in the community and health outcomes: a population-based study. *Israel Journal of Health Policy Research*. 2012; 1(1):1–12. [PubMed: 22913408]

57. Audet CM, et al. Poor-quality health services and lack of programme support leads to low uptake of HIV testing in rural Mozambique. *Afr J AIDS Res.* 2012; 11(4):327–35. [PubMed: 25860191]
58. Pearson CR, et al. One year after ART initiation: psychosocial factors associated with stigma among HIV-positive Mozambicans. *AIDS Behav.* 2009; 13(6):1189–96. [PubMed: 19639405]
59. Micek MA, et al. Loss to follow-up of adults in public HIV care systems in central Mozambique: identifying obstacles to treatment. *J Acquir Immune Defic Syndr.* 2009; 52(3):397–405. [PubMed: 19550350]
60. Turan JM, et al. HIV/AIDS Stigma and Refusal of HIV Testing Among Pregnant Women in Rural Kenya: Results from the MAMAS Study. *AIDS Behav.* 2011; 15(6):1111–20. [PubMed: 20827573]
61. Rankin WW, et al. The stigma of being HIV-positive in Africa. *PLoS Med.* 2005; 2(8):e247. [PubMed: 16008508]
62. Mukolo A, et al. Correlates of social exclusion and negative labeling and devaluation of people living with HIV/AIDS in rural settings: evidence from a General Household Survey in Zambezia Province, Mozambique. *PLoS One.* 2013; 8(10):e75744. [PubMed: 24146771]
63. The Interagency Task Team, UNICEF, and World Health Organization. Toolkit, expanding and simplifying treatment for pregnant women living with HIV: Managing the transition to Option B/B +2013[cited 2014 March 7]; Available from: http://www.who.int/hiv/pub/mtct/iatt_optionBplus_toolkit/en/
64. Cost-Effectiveness of Preventing AIDS Complications (CEPAC)[cited 2016 January 16]; Available from: <http://web2.research.partners.org/cepac/mainpage.php>
65. Walensky RP, et al. The Anticipated Clinical and Economic Effects of 90-90-90 in South Africa. *Ann Intern Med.* 2016; 165(5):325–33. [PubMed: 27240120]
66. Walensky RP, Cohen MS, Freedberg KA. Cost-effectiveness of HIV treatment as prevention in serodiscordant couples. *N Engl J Med.* 2014; 370(6):581–2.
67. Walensky RP, et al. The cost-effectiveness of pre-exposure prophylaxis for HIV infection in South African women. *Clin Infect Dis.* 2012; 54(10):1504–13. [PubMed: 22474224]
68. Walensky RP, et al. Cost-effectiveness of HIV treatment as prevention in serodiscordant couples. *N Engl J Med.* 2013; 369(18):1715–25. [PubMed: 24171517]
69. Hyle EP, et al. The clinical and economic impact of point-of-care CD4 testing in mozambique and other resource-limited settings: a cost-effectiveness analysis. *PLoS Med.* 2014; 11(9):e1001725. [PubMed: 25225800]
70. Ciaranello AL, et al. Cost-effectiveness of first-line antiretroviral therapy for HIV-infected African children less than 3 years of age. *AIDS.* 2015; 29(10):1247–59. [PubMed: 25870982]
71. Ciaranello AL, et al. WHO 2010 guidelines for prevention of mother-to-child HIV transmission in Zimbabwe: modeling clinical outcomes in infants and mothers. *PLoS One.* 2011; 6(6):e20224. [PubMed: 21655097]
72. Francke JA, et al. Clinical Impact and Cost-effectiveness of Diagnosing HIV Infection During Early Infancy in South Africa: Test Timing and Frequency. *J Infect Dis.* 2016; 214(9):1319–1328. [PubMed: 27540110]
73. Fitzmaurice GM, , Laird NM, , Ware JH. *Applied longitudinal analysis* 2nd. Vol. xxv. Hoboken, N.J.: Wiley; 2011 701 Wiley series in probability and statistics
74. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods.* 2010; 15(4):309–34. [PubMed: 20954780]
75. VanderWeele T. *Explanation in Causal Inference: Methods for Mediation and Interaction* New York, NY: Oxford University Press; 2015
76. Marseille E, et al. Thresholds for the cost-effectiveness of interventions: alternative approaches. *Bulletin of the World Health Organization.* 2014; 93:118–124. [PubMed: 25883405]
77. Maman S, et al. Efficacy of enhanced HIV counseling for risk reduction during pregnancy and in the postpartum period: a randomized controlled trial. *PLoS One.* 2014; 9(5):e97092. [PubMed: 24824050]

Figure 1.
Flow diagram summarizing the HoPS+ study, Zambézia province, Mozambique

Figure 2.
Structural equation model (SEM), HOPS+ study, Zambézia province, Mozambique

Table 1

Summary of baseline and follow up assessments for the HoPS+ trial

		Previously Validated in Mozambique
Relationships Empathy	28 item scale with focus on interpersonal reactivity	No
HIV knowledge	27 item scale previously validated in Mozambique	Yes
HIV Stigma	20 item stigma scale with focus on community perception of HIV stigma	No
Social Support	17 item scale including perception of emotional and instrumental support	No
Provider Trust	26 item trust in clinician scale	No
PhQ-9 Depression	9 Item depression scale for clinic-based screening	Yes