

COVER PAGE

Title: Happy Homes, Healthy Families: A Relationship Strengthening Intervention for Pregnant Couples Affected by HIV in Zambia

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STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

I. Hypotheses and Specific Aims:

The overall objective of this application is to test the preliminary efficacy of a refined couples' counseling intervention through a pilot randomized controlled trial (RCT) at the University Teaching Hospital in Lusaka, Zambia, with 238 pregnant women living with HIV (WLWH) and their male partners (119 couples per arm). The central hypothesis is that pregnant WLWH in couples with better relationship functioning and more social support have greater odds of achieving and sustaining viral suppression across the PMTCT continuum of care through better ART adherence and engagement in PMTCT care. I additionally hypothesize that the couples-based intervention will improve interpersonal dynamics, such as communication, and in intrapersonal factors, such as women's mental health, which will mediate intervention effects on adherence and viral suppression. I plan to objectively test these hypotheses and attain the objectives of this application through the following two specific aims using an RCT study design:

Aim 1: Compare service utilization and PMTCT outcome indicators in two study conditions.

Approach: I will compare the percent of female participants with viral suppression (viral load <1,000 copies/mL) at 6 weeks postpartum (intermediate outcome) and at 24 weeks postpartum (primary outcome) between the intervention and control (enhanced standard of care) groups. I will compare the percent of female participants reporting ART adherence (using validated instruments); facility birth; exclusive breastfeeding; pediatric HIV testing, diagnosis, and treatment uptake; and postpartum family planning (intermediate outcomes) between the intervention and control groups via behavioral surveys at baseline and at 6 and 24 weeks postpartum.

Aim 2: Establish the effect of the intervention on intra- and inter-personal mechanisms influencing PMTCT outcomes. *Approach:* I will measure critical intrapersonal factors among female participants (mental health, self-esteem, perceived stigma) and relationship dynamics (IPV, conflict resolution, communication, coping) that are hypothesized to be on the causal pathway between the intervention, PMTCT-related behaviors, and viral suppression. Data will be collected through behavioral surveys at baseline and at 6 weeks and 24 weeks postpartum. I will compare these dynamics between the intervention and control groups and will use mediation analysis and structural equation modeling to test whether these relationship dynamics are affected by the intervention and if they are underlying mechanisms linked to the study outcomes.

II. Background and Significance:

Prevention of mother-to-child transmission (PMTCT) programs have the potential to make substantial gains towards the UNAIDS 90-90-90 goals among pregnant and postpartum women living with HIV (WLWH).¹ However, progress in PMTCT has recently stagnated.⁸ Retention on lifelong antiretroviral therapy (ART), for instance, among pregnant and breastfeeding WLWH in sub-Saharan Africa is far too low; 20% of pregnant women who start ART drop out of care before delivery.⁸ In 2018, it was estimated that 16,000 pediatric HIV infections could have been averted if mothers in Southern Africa were retained on ART (out of 130,000 new pediatric HIV infections that year).⁸ Zambia is one of the countries in Southern Africa with the greatest burden of HIV among women of reproductive age³⁵ and accounts for 3% of the total new global pediatric HIV infections.⁸ In the country, more than 90% of pregnant women attend at least one antenatal care (ANC) visit and receive HIV testing (16% test positive).^{35, 36} Across the additional steps in the PMTCT continuum of care, however, women drop-off at alarming rates (Figure 1).^{3, 20, 21} Even among those who remain engaged in care, optimal viral suppression – a key predictor of mother-to-child transmission (MTCT) and HIV treatment success²²⁻²⁵ – is challenging, especially during the postpartum period.⁷ **Accelerated progress in keeping mothers alive and reducing the incidence of pediatric HIV is dependent on overcoming the critical challenges of ART adherence and sustained retention in care among pregnant and postpartum WLWH.**^{4, 20, 26, 27}

Contextual factors, such as relationship dynamics with male partners, are a long-overlooked influence on women's HIV-related behaviors during and after pregnancy, and subsequent PMTCT outcomes. There is evidence that well-functioning relationships (e.g., relationship satisfaction, problem-solving and coping skills, communication, and conflict resolution skills) can promote HIV prevention behaviors in heterosexual couples, such as condom negotiation^{9, 10} and disclosing one's HIV status.^{11, 12} Moreover, social support within close interpersonal relationships like marriages is an important predictor of HIV-related health outcomes, likely because it reduces the stress of living with HIV.³⁸ Conversely, when there is a deficit in relationship functioning and social support, HIV-related health is adversely affected, including PMTCT.^{14, 15, 21, 28-31} My prior research from Zambia indicates that intimate partner violence (IPV) against WLWH, a strong indication of poor relationship functioning, hinders PMTCT adherence across the cascade of care, including ART adherence during and after pregnancy, safe infant feeding, and pediatric HIV testing.^{21, 28, 32} **Evidence-based strategies are urgently needed to address modifiable dynamics in couples to strengthen relationship functioning, promote social support, and improve PMTCT adherence and retention.**

Couples counseling is a promising approach to strengthen relationships and promote HIV health behaviors. Numerous studies indicate that psychoeducational interventions with couples can improve healthy relationship skills, reduce conflict, and increase relationship satisfaction.^{33, 34} Moreover, there is increasing evidence from sub-Saharan Africa that addressing relationship functioning improves sexual and reproductive health outcomes. Hartmann et al. (2012) report that a couples-focused intervention in Malawi resulted in greater shared decision-making around family planning through improved spousal communication and relationship quality.³⁵ In South Africa, Pettifor et al. (2014) found that improved communication and problem-solving skills within couples resulted in more effective engagement in HIV prevention behaviors.³⁶ Two recent trials from Kenya and South Africa, have also shown that couples-focused HIV interventions aimed at improving relationship skills can enhance the uptake of couples HIV testing^{17, 18} and maternal and child health outcomes.¹⁷ These prior studies indicate that relationship strengthening interventions through couples counseling are a feasible and acceptable approach to improving HIV outcomes in couples. **The proposed study will test if a couples counseling approach can extend to PMTCT outcomes in Zambia.**

I hypothesize that pregnant WLWH in couples with better relationship functioning are more likely to be adherent to ART, remain engaged in PMTCT care, and achieve and sustain viral suppression. In order to test this hypothesis, **I propose to assess the preliminary efficacy of a novel couples-based intervention through a a randomized controlled trial (RCT) in Lusaka, Zambia.** The intervention (three couples counseling visits paired with group health education) will target specific relationship dynamics in the context of HIV that emerged as priorities during the K99 phase, including communication, trust, respect, love, and support. Couples will also receive group education on key health topics during pregnancy and postpartum.

Recent studies have documented that relationship-strengthening interventions can improve certain HIV prevention behaviors in couples.^{22, 23, 43} This proposal builds upon previous studies and explores whether a couples counseling intervention with pregnant WLWH and their male partners can improve longitudinal viral suppression and other PMTCT outcomes in Zambia. The proposed research is innovative and represents a substantive departure from the status quo in the following ways:

1. Novel focus on the critical time period surrounding pregnancy. The WHO has called for a renewed emphasis on couples to enhance PMTCT efforts,³⁷⁻⁴³ but few evidence-based interventions exist for pregnant couples in low-resource settings.⁴⁴ For WLWH in sub-Saharan Africa, pregnancy is often the time of HIV diagnosis and ART initiation, and unfortunately, a subsequent high loss to follow-up and inadequate adherence.^{26, 45} Pregnancy is a unique opportunity for a couples counseling intervention that fosters a more supportive home environment to help women establish optimal ART adherence behaviors, likely to continue into the postpartum period and beyond. Pregnancy also often heightens men's interest in family health,⁴⁶ making it the ideal time to engage men in such an

intervention. Lastly, pregnancy can exert significant influence on relationship dynamics, improving unity and mutuality for some, but increasing conflict and violence among others.¹³ The proposed intervention is the first, to our knowledge, to use an adaptive relationship strengthening couples counseling approach to promote PMTCT adherence and retention.

2. Addressing the concomitant problem of high rates of IPV. Despite alarming high rates of IPV among WLWH,²¹ existing couples-focused HIV interventions in the region are not designed to specifically target IPV, and often, explicitly exclude couples who report IPV. My previous research in Zambia, found that over 60% of postpartum WLWH experienced IPV, which in turn, negatively affected their PMTCT adherence.²¹ Other scholars have found that IPV against women reduces the likelihood of HIV testing uptake, ART use, and viral load suppression.¹⁴ During the K99 phase, IPV emerged as a highly prioritized topic for the women and men we interviewed. Incorporating a focus on IPV, in addition to other relationship dynamics, has the potential for the intervention to have an even greater impact on PMTCT adherence, as well as improve the quality of life among WLWH.
3. Using a unique adaptive intervention design. Although there is increasing recognition that adaptive intervention designs have significant potential for use in health research,⁴⁷ very few trials have actually examined their effectiveness in promoting health outcomes and even fewer, have been applied to HIV.⁴⁸ Adaptive approaches use the dynamics of the “system” of interest (e.g., the couple) via a sequence of decision rules and tailoring variables to determine when and how the intervention should be modified to optimize effectiveness.⁴⁷ I propose to adapt specific intervention content delivered based on baseline data related to engagement in HIV care and relationship dynamics using pre-established guidelines. For instance, couples that report IPV will receive increased training in conflict negotiation skills. This adaptive approach has the potential to better meet the needs of heterogeneous couples participating in the intervention.

III. Preliminary Studies/Progress Report:

Refining a couples counseling intervention for pregnant WLWH and their male partners (K99 phase): To inform the content and delivery of the proposed R00 intervention, in Years 1-2 of the K99/R00, I conducted qualitative interviews with pregnant WLWH (n=30) and their male partners (n=18) in the target community. We also held three focus group discussions with service providers (lay health workers and community leaders; n=27). We asked participants to do a pile sorting activity prioritizing specific relationship skills they would want in a couples-based intervention, additional desired health and relationship content, and delivering the intervention in acceptable ways. This project provided key data on ways to ensure that the intervention will be acceptable and feasible in the community, and subsequently, have the greatest likelihood of efficacy. It also highlights my ability to conduct research in this setting with the target population (pregnant WLWH and their male partners).

IPV as a barrier to PMTCT adherence and retention: For my PhD dissertation and NIMH-funded F31 award, I led a mixed methods study in Zambia examining the relationship between gender power dynamics and HIV-positive women’s PMTCT adherence and retention. The results of this study indicate that HIV-positive pregnant and postpartum women in Zambia experience disproportionately high rates of IPV (>60%) compared to the general population of women.⁸ Moreover, women who experienced IPV, particularly emotional IPV, have reduced odds of adherence to ART during and after pregnancy,⁸ safe infant feeding,²⁷ and early infant HIV testing.¹⁸

Engaging men in PMTCT interventions: For my postdoctoral fellowship, I am leading a mixed methods study in western Kenya within the framework of my mentors' community randomized trial (R01HD0808477; PIs: Abuogi, Turan.). My sub-study examines the importance of specific male behaviors and relationship dynamics for PMTCT and ways to engage male partners in HIV care. The results from this research will help inform the specific content of the proposed K99/R00 couples counseling intervention.

IV. Research Methods

A. Outcome Measure(s):

The Primary outcome is the percent of female participants with HIV viral suppression (viral load <1,000 copies/mL) at 24 weeks postpartum between the intervention and control groups. The **Secondary outcomes** are the percent of female participants with HIV viral suppression (viral load <1,000 copies/mL) at 6 weeks postpartum; the percent of female participants reporting ART adherence (using validated instruments); facility birth; exclusive breastfeeding; pediatric HIV testing, diagnosis, and treatment uptake; and postpartum family planning between the intervention and control groups.

B. Description of Population to be Enrolled:

Couples are eligible if: female is <36 weeks pregnant (to have time to deliver at least one counseling visit during pregnancy); female is diagnosed as HIV-positive; both partners are >18 years of age and willing to participate; both partners live in the clinic catchment area and plan to reside there for at least six months; a long-term stable relationship (sleep under the same roof at least once a week) that has existed for ≥ 6 months; and no severe IPV in the past 6 months.⁶³

C. Study Design and Research Methods

This is a minimal risk study using a behavioral intervention to enhance HIV-related health behaviors and biomedical outcomes. The PI will be working with engaged staff at the University of North Carolina Global Projects Zambia (UNC GPZ) to implement the study. The proposed study uses a randomized controlled trial design (Phase II clinical trial) to test the efficacy of a couples counseling and health education intervention to change HIV-related health behaviors and biomedical outcomes (viral suppression) among pregnant and postpartum women living with HIV in Lusaka, Zambia. Our sample includes 238 heterosexual couples (n=476 individuals) recruited from the population of pregnant women living with HIV attending antenatal care at Chipata Clinic in Lusaka, Zambia. All enrolled couples (intervention and control groups) will be exposed to two group health education events. Couples in the intervention (n=119 couples) will additionally be exposed to three couples counseling visits. Biospecimen collection will take place in the form of three research-only blood draws to test viral loads among the female participants (n=238). We will also conduct face-to-face behavioral interviews using a standardized questionnaire. Recruitment and initial screening will take place during routine antenatal care (see Figure below). Local Zambian research assistants will work with nurses (relationship already established during the K99 phase) to conduct the initial screenings and recruit participants. Research assistants will arrange with interested, eligible women a convenient time and place to meet with them and their male partners (either the clinic or a private community venue) to complete the informed consent process, full screening, and enrollment. A letter will be offered to take home to the male partner explaining the study (women's HIV status will not be conveyed). Screening and informed consent will be done in separate locations for WLWH and their male partners (preferably at the same time) with gender-matched research assistants. Women with severe IPV will be offered support and referrals but will not be enrolled. Enrolled couples

will attend the first group education session (“baby shower” event) together during an upcoming weekend. Randomization into the intervention or control (n=119 couples per arm) will take place following the first group session using labeled envelopes.

Procedures: We will schedule a series of 24 group education sessions across three months to take place on the weekends at community venues with an expected 10 couples in each group. The first baseline behavioral questionnaire will be administered during the group education session. All research assistants will be present at the scheduled group sessions to assist with the educational activities and administer the behavioral questionnaires. At this same time, we will collect baseline viral loads of pregnant WLWH. Couples in the intervention arm will subsequently receive three additional couples counseling sessions at a private community venue or the clinic (depending on participant preference): one during pregnancy (3rd trimester) and two postpartum (12 weeks and 18 weeks). Lay health workers will deliver the intervention and be supervised by a local study coordinator and the PI throughout the entirety of the project. The paired male-female counselors will work with each couple in the intervention. At 6 weeks postpartum, there will be a series of second group education sessions for all couples (intervention and control arms) and the mid-line behavioral questionnaire. The mid-line viral load will also take place at 6 weeks postpartum. At 24 weeks postpartum, we will collect the end-line behavioral questionnaires and viral load. Once data collection is complete, we will offer couples in the control arm the option to participate in a condensed (one-session) counseling intervention. We will not be assessing outcomes in the condensed intervention but thought it ethical to provide.

COVID-19 Considerations: We are working with the University of North Carolina Global Projects Zambia (UNC-GPZ) to implement the proposed study. They have in place a written workplace policy detailing controls to mitigate the risk of exposure to the COVID- 19 virus. All study procedures will occur in accordance with the policy, including hand washing, wearing masks, cleaning and disinfecting workspace, avoiding group gatherings of more than 10 people, keeping a physical distance of 2 meters with individuals outside one’s household, and working remotely when feasible. In addition, all study staff will be required to complete a COVID screening form prior to starting every workday and anyone who is sick is required to stay home (this will not affect their pay as they are salaried). We will also minimize the number of research staff on site at any given time through the use of rotations/shift work. Face masks which cover the mouth and nose are required for all persons entering a GPZ workplace. This applies to employees, visitors, and study participants. All study staff will be provided with facemasks. All participants will also be provided with a facemask if they do not have one. All group sessions will occur at a private outdoor community venue that we are renting with social distancing (2 meters apart) with a maximum of 10 individuals, including all study staff and participants. The community venue is vacant and will not be used by others outside of the study team during any study activities. Counseling visits will occur at either the clinic or an outdoor community venue with social distancing and a maximum of four individuals present, including study staff and the participating couple.

The intervention: The proposed intervention is theory-driven and draws upon examples of other effective couples-based interventions in sub-Saharan Africa.^{17-19, 56, 57} The intervention consists of three counseling visits with each couple by a pair of male-female counselors beginning in pregnancy and spanning 18 weeks postpartum. Couples in the intervention, along with couples in the control arm, will also receive 2 group health education sessions (one that is gender discordant and one gender-concordant). Each couple counseling visit will include education on healthy relationships and a relationship-skills building exercises (e.g., role playing), as well as discuss identified health and relationship priorities by the couple (see table below). The intervention will use baseline tailoring variables from the behavioral questionnaire to adapt specific content in order to best meet the couples’ needs (status disclosure, male HIV status, relationship satisfaction, IPV).

Description of Intervention Components

Intervention Component	Attendees	Session Theme	Component description
Group education session 1	All couples	Healthy pregnancy	<ul style="list-style-type: none"> ➤ Gender-discordant groups (couples together) ➤ Half-day workshop ➤ Co-lead by male and female facilitators ➤ Discussion of pregnancy-related health followed by a “baby shower” event where the couple is given a small baby gift
Couples counseling visit 1	Intervention couples	Communication skills	<ul style="list-style-type: none"> ➤ Couple meets with a male-female pair of counselors ➤ 90-minute session focused on communication related to sexual and interpersonal negotiation
Group education session 2	All couples	Postpartum health	<ul style="list-style-type: none"> ➤ Gender-concordant groups (men and women meet separately) ➤ Half-day workshop ➤ Co-lead by male and female facilitators ➤ Discussion of postpartum-related health followed by a “baby reception” event where the couple is given a small baby gift
Couples counseling visit 2	Intervention couples	Trust and respect	<ul style="list-style-type: none"> ➤ Couple meets with a male-female pair of counselors ➤ 90-minute session focused on enabling trust and showing respect, including resolving conflict respectively without the use of IPV and issues related to HIV
Couples counseling visit 3	Intervention couples	Love and support	<ul style="list-style-type: none"> ➤ Couple meets with a male-female pair of counselors ➤ 90-minute session focused on how couples can show love and support for one another

Data Collection: The following service utilization and PMTCT outcome data will be collected at baseline (pregnancy), 6 weeks postpartum, and 24 weeks postpartum: (1) women’s viral load testing (i.e., research-only blood draws at the University Teaching Hospital (UTH) laboratory); and (2) behavioral surveys.

Viral load testing (female participants only): we will collect research-only blood draws at baseline, 6 weeks postpartum (mid-line), and 24 weeks postpartum (end-line) to determine HIV treatment success via viral suppression (<1000 RNA copies/ml). Blood will be collected by health care workers at the UTH laboratory, which has an existing infrastructure capable of drawing blood and testing viral loads.

Behavioral questionnaires (all participants): We will administer face-to-face behavioral surveys to both female and male participants at baseline, 6 weeks postpartum (mid-line), and 24 weeks postpartum (end-line) to capture self-reported service utilization and PMTCT outcomes, hypothesized mediating variables (intrapersonal and interpersonal factors, including relationship dynamics), sociodemographic characteristics, and intervention experiences (if applicable). The surveys will be verbally administered to all enrolled WLWH (both control and intervention arms) and their male partners by trained Zambian research assistants in the local languages. Survey data will be entered on pre-programmed tablets using the REDCap (Research Electronic Data Capture) mobile application and sent to the secure host server at the University of Colorado Denver. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data can be entered and securely stored on the tablet and subsequently sent to the server upon internet connectivity, which makes its use ideal for low-resource settings.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Viral load testing: For research purpose, blood will be drawn at three times from female participants (once during pregnancy and twice postpartum). This will be done by trained, experienced health care

providers with sterile equipment at the UTH laboratory. There is an extremely low risk of infection or any other physical repercussions from the procedure. Research-only blood draws may cause some physical discomfort to participants during the process. This procedure is routinely done for patients living with HIV.

Behavioral questionnaires: One potential risk to participants involved in this study is emotional discomfort, such as embarrassment or sadness when asked sensitive questions during the survey. These risks may occur, but we do not anticipate the risks resulting in any long-term psychological or physical distress or impairments. There are no physical, legal, or financial risks involved in the survey. The only potential risk is an emotional response to the sensitive questions being asked, including intimate partner violence experiences and issues related to living with HIV. Another potential risk could be social risk (e.g. risk to reputation) if information revealed during the course of the survey were to be disclosed outside of the research team (e.g., participants' HIV-positive status was revealed to family or the community).

Recruitment of couples for the study will begin by recruiting female participants (pregnant WLWH) at Chipata Clinic during routine ANC. Nurses at the facility will make the initial contact with pregnant women during their routine health care visit. After a pregnant woman has finished her health care visit, nurses will invite eligible women to meet with an on-site research assistant to provide the initial screening and discuss with each interested woman the enrollment process. The research assistant will provide a letter for the male partner discussing the study and inviting his participation. The research assistant will arrange with the women a time and place (either at the clinic or the community venue) to meet with her and the male partner to conduct the full screening, informed consent, and enrollment. Potential participants will either arrange a specific time and place or provide their contact details and a good time for the research assistant to follow-up. It is likely that many women will need to discuss with the male partner participation before agreeing. Women and their male partners who are interested in participation will then meet with a male-female pair of research assistants, who will discuss the study, complete the full screening, enroll the couple if eligible, and invite them to attend the first group education session and baby shower event on the weekend. Women and their male partners will complete screening and informed consent ideally at the same time but in different locations (separate private rooms). If the couple is unable to meet together, the research assistants will arrange separate appointments.

The informed consent process will explain all study procedures and include the following: why the study being done; how many people will take part in the study; why they have been chosen to participate in the study; what will happen if they take part in the study; how long they will be in the study; if they can stop being in the study; what side effects or risks to expect from being in the study; benefits to taking part in the study; their choices if they do not take part in the study; how information will be kept private; the costs of taking part in the study; payment and compensation for taking part in the study; their rights if they take part in the study; and who can answer questions about the study. Participants will have the opportunity to ask questions and voluntary participation will be emphasized. After this information is conveyed to the participant, they will be asked to sign a statement indicated they provide consent to participate.

Numerous studies indicate that couples' counseling within HIV interventions do not result in increased social harms. Nonetheless, careful effort has been made to minimize, monitor, and address potential social harms. The intervention has been designed to minimize conflict within couples and ensure privacy. First, women's HIV status will not be conveyed to the male partner (or anyone outside the study team). Second, couples in the intervention group will select the location (clinic or community venue) they feel most comfortable to have the couple counseling sessions. Third, because we are including women who have potentially experienced IPV, all activities have been designed in accordance with the WHO recommendations for conducting research on violence against women. A local safety monitoring manager in Lusaka will be hired to monitor data and any adverse events. He/she will follow-up with any participants who report IPV or major depression on the behavioral questionnaires and offer referrals to medical, legal, or psychosocial services.

All research assistants and counselors will participate in a 10-day training on the study design, the couples counseling intervention, research ethics, how to minimize discomfort to the participants, and preventing social harms. The HIV-status of woman in the study will not be known or reported to anyone other than the nurses (who are already aware from the woman's medical records), the research assistants conducting the surveys, the trained counselors, and the study investigators. Data will be de-identified prior to analysis using participant ID numbers. Women will NOT be told that they have been selected based on their HIV-status to minimize participants being able to determine other participants' HIV status. We will be following IRB protocol for minor deception in the study. The study will be approved by the Colorado Multiple Institutional Review Board (COMIRB), the University of Zambia Biomedical Research Ethics Committee, and the Zambian National Research Authority.

Data-related risks: Data-related risks to participants could result from (1) circumstances where an insufficient amount of data was collected to effectively answer the specific aims and research questions; or (2) data was not kept confidential and secure.

Data monitoring procedures: Recruitment goals will be carefully monitored by the Study Coordinator and the PI. We will also monitor the presence of any missing data and loss to follow-up to ensure the validity and integrity of the data. We will closely track incoming numbers of participants via ongoing recruitment activities, and weekly and monthly reports will be compiled by the study staff. We will utilize similar procedures to monitor any missing data or missed follow-up assessments. All study data (questionnaires and viral loads) will be coded with a participant study ID to maximize confidentiality. The codes that link the name of the participant and the study ID will be kept confidential in a secured database accessible only by the PI and limited research staff. All study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages. The database is hosted at the University of Colorado–Denver Development and Informatics Service Center, which will be used as a central location for data processing and management. Laptops and handheld devices will be encrypted, password protected, and backed up daily. Tablets will be used to collect much of the data via the REDCap mobile application, which allows data to be entered and securely stored on the device, and later, upon internet connectivity, sent to the host server. The PI and Study Coordinator will provide ongoing monitoring of the study progress. All data will be kept confidential with exception of limits to confidentiality legally required to be reported to law enforcement in Zambia (child abuse).

Data-related risk reporting and action plan: We will closely track incoming numbers of participants via ongoing recruitment activities, and weekly and monthly progress reports will be compiled by the study staff and reviewed by the Study Coordinator and the PI. We will utilize similar procedures to monitor any missing data. Recruitment and missing data reports will be monitored weekly by the Study Coordinator and monthly by the PI. All data will be protected on firewall-protected servers at the University of Colorado. Any identification of recruitment rates or follow-up rates that represent threats to our ability to sufficiently answer the research questions will be met with action by the PI to intervene to remedy the shortcomings, including adding additional recruitment sites (antenatal clinics). Should a situation arise of insufficient power or early detection of research questions, the PI will review and discuss with NIMH halting the study, when and if needed, and would report such action to all monitoring bodies. Completion rates of intervention activities will be monitored in parallel fashion using study logs.

Safety-related risks: Safety-related risks to participants could consist of: 1) emotional discomfort or distress resulting from sensitive questions being asked on the behavioral questionnaires pertaining to HIV and/or relationship issues; 2) social risk (e.g. risk to reputation) if confidential information revealed during the course of the study were to be disclosed outside of the research team; 3) tension, conflict or violence between the partners 4) risks related to biospecimen collection (research-only blood draws), such as physical discomfort, and the unlikely potential for infection or other physical repercussions from

the procedure; and 5) risks associated with participation in the intervention activities (group education sessions and/or couples counseling visits). Pregnant and postpartum women and infants also face risks of adverse pregnancy outcomes (e.g., preterm birth, miscarriage) and infant/maternal mortality, which are common in the study community but are not likely to be related to study participation but will be monitored during the course of the study. There is one exception to confidentiality: this study does not anticipate any mandatory reporting information being revealed in the course of the study; however, if child abuse is disclosed, Zambian law requires a report to law enforcement. Detailed protocols will be in place regarding the possibility of tension, conflict or violence between partners during or outside the counseling sessions. Protocols will be in place to monitor and respond to any instances reported by the participants of any type of negative relationship or other social event, and proper action will be taken, including the provision of referral for services depending on the specific event and participant preferences.

Safety-monitoring procedures: All safety-related risks will be monitored routinely, including during recruitment and enrollment, intervention sessions, and data collection (questionnaires, medical record reviews, and biospecimens). All participants will complete an informed consent process emphasizing their rights and the voluntary nature of the study, which will be read aloud from an information sheet (due to low literacy levels in the target population) and followed by participant signature/thumbprint. The intervention has been carefully designed to minimize conflict within couples and ensure privacy, including protecting confidential information (e.g., HIV status) from one's partner and to monitor all confidential information to protect subject privacy and inadvertent social harms. During study procedures, at any sign of participant discomfort or distress, or by request, the activity will be halted and applicable support and referrals (e.g., mental health or domestic violence services) will be provided. Confidentiality will be assured to all participants at the time of consent; they will be assured their answers or responses cannot be used against them for any reason, or for denial of any medical treatment.

Safety-related risk reporting and action plan: The PI will be responsible for executing the DSMP, conforming to rigorous standard monitoring procedures for participant safety, and complying with reporting requirements. The PI has primary responsibility for the overall conduct of the study, including the safety of human subjects. The PI will ensure appropriate (1) conduct of the informed consent process (e.g. that informed consent is obtained before proceeding with study procedures); (2) enrollment of study subjects; (3) collection and analysis of data; (4) implementation of study procedures to ensure consistent monitoring of subjects for possible adverse events; (5) immediate receipt and review of standardized and detailed adverse reports and reporting of to the Institutional Review Boards; and (6) maintenance of the privacy and confidentiality of study subjects. The PI will be in contact with the local Zambian research team (calls biweekly) throughout the study to review progress and address any human subject safety concerns. The PI will also review all electronic study data monthly from REDCap to ensure that the DSMP and all protection of human subject protocols are followed. The PI will conduct in-person reviews of the study procedures and data collection biannually in Lusaka. If any increased risks are identified during the study, the PI will review and determine the adequacy of human subject protections, making recommendations for enhancing these protections if deemed necessary.

Any adverse events, serious adverse events, unanticipated problems involving risks to subjects, or other participant safety or data concerns will be reported to the on-site study coordinator and the PI by study staff within 48 hours of becoming aware of the event. Serious adverse events that could be related to the study and any study deaths (extremely unlikely) will be reported by the PI to the NIMH Program Officer immediately. In addition to serious adverse events, the following will be reported by the PI to the NIMH Program Officer: unanticipated problems involving risks to subjects, protocol violations (significant divergences from the IRB-approved protocol), non-compliance, and suspensions or terminations by monitoring entities (IRBs and the Zambian National Health Research Authority). Non-serious adverse events and unrelated serious adverse events will be reported in the annual progress report to NIMH. The PI will oversee follow-up on any safety concerns that arise and work with the Study Coordinator to ensure that participants in need of medical, legal, or psychosocial services receive

appropriate, timely referrals. The PI will adhere to the NIMH Reporting Policy (<https://www.nimh.nih.gov/funding/clinical-research/nimh-reportable-events-policy.shtml>).

E. Potential Scientific Problems:

Prior work indicates that couples' counseling interventions do not result in increased social harms.⁶³ Nonetheless, careful effort has been made to minimize, monitor, and address potential social harms. The intervention has been designed to minimize conflict within couples and ensure privacy. Because we are including women who may have experienced IPV, all activities have been designed in accordance with the WHO recommendations for conducting research on violence against women.⁶⁴ All potential risks will be described in the informed consent process. Participants in need of medical, legal, or psychosocial services will be given referrals. If recruitment at Chipata Clinic is not meeting enrollment targets, we will expand to other clinics in a step-wise manner. To address the potential problem of low male participation, we will offer group sessions on the weekends and the couples counseling sessions at flexible times to accommodate men's schedules; frame the intervention as "family health promotion;" and offer incentives at all sessions. Loss-to-follow-up could impact study success; however, we have accounted for this in our power analysis and applied key findings from the K99 phase to ensure that the intervention is acceptable to maximize retention.

F. Data Analysis Plan:

1. Statistical analysis: In order to evaluate if the intervention has an effect on women's viral suppression (<1000 RNA copies/ml),⁶⁰ all female participants will have their research-only blood drawn at baseline (pregnancy), 6 weeks postpartum, and 24 weeks (6 months) postpartum. Blood will be collected at UTH, which has an existing infrastructure capable of testing women's viral loads in their laboratory. In addition, we will conduct behavioral surveys with female and male participants, separately, at baseline and at 6 weeks and 24 weeks postpartum. The survey draws upon existing validated measures, such as the ART visual analog scale⁶¹ and the Revised Conflict Tactics Scale⁶² and is informed by my extensive preliminary work during the K99 phase. All data will be entered into pre-programmed tablets by trained research assistants using REDCap. Data will be exported into STATA 14 and MPlus for analysis (see table below).

Data Analysis Plan

Aim	Indicators		Data source	Analytic method
Aim 1: Compare service utilization and PMTCT outcome indicators in two study conditions	<i>Primary outcome:</i> female viral suppression at 24 weeks postpartum (<1000 RNA copies/ml)	<i>Intermediate outcomes:</i> <ul style="list-style-type: none"> ➤ female viral suppression at 6 weeks postpartum ➤ female self-reported ART adherence (visual analog scale using 3-day, one-week, and one-month recall periods) ➤ facility birth ➤ exclusive breastfeeding to six months ➤ uptake of pediatric HIV testing (and treatment if positive) ➤ postpartum family planning 	Research-only blood draws (female partner), + Behavioral surveys	Independent t-tests and Pearson's chi-square tests; logistic regression models with generalized estimating equation; survival analysis with cumulative incidence across time, Kaplan-Meier curves, mixed-effects Cox proportional hazards models
Aim 2: Establish the effect of the	<i>Intrapersonal mechanisms:</i> <ul style="list-style-type: none"> ➤ mental health 	<i>Interpersonal mechanisms:</i> <ul style="list-style-type: none"> ➤ IPV past month ➤ Intimacy and trust 	Behavioral surveys	Mediation analysis with structural equation modeling

intervention on intra- and inter-personal mechanisms influencing PMTCT outcomes	<ul style="list-style-type: none"> ➤ self-esteem ➤ perceived stigma ➤ perceived partner acceptance 	<ul style="list-style-type: none"> ➤ Communication skills ➤ problem-solving skills ➤ joint decision-making ➤ Conflict resolution skills ➤ Relationship satisfaction ➤ Perceived social support ➤ Communal coping 		(SEM)
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2. Sample size calculation: Based on the primary outcome (viral load) and a projected 25% loss to follow-up (10% due to break-ups and 15% due to other causes), we require 238 total couples (119 couples per arm) to achieve the sample size target of 178. This target is based on a Pearson's chi-squared two-sample proportions test with a power of 0.80 and alpha of 0.05, assuming a delta of 0.20 at the 6-month follow-up between the intervention and control arms. Based on recent studies from the region,⁵⁸⁻⁶⁰ we estimate viral suppression at 6-months to be 55% in the control arm and 75% in the intervention arm. For the intermediate and mediating variables on the behavioral survey, the proposed sample size will enable us to detect a hazard ratio of 0.75, power of 0.80, and alpha of 0.05, using a two-sample comparison of survivor functions exponential test.

G. Summarize Knowledge to be Gained:

The expected research contribution is to test a culturally appropriate, scalable couples-based intervention that strengthens relationships, improves PMTCT outcomes, and establishes underlying intra- and inter-personal mechanisms. Moreover, this study, along with the K99 findings, will afford the necessary data and infrastructure for an R01 proposal to expand the intervention and test efficacy in larger RCT with longer-term HIV outcomes. If the proposed intervention is successful, it will promote maternal health through women's optimal treatment adherence, reduce pediatric and female-to-male sexual HIV transmission, as well as improve the quality of life and reduce the burden of disease among women and families affected by HIV.

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