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Developing and Assessing a Male Engagement Intervention in Option B+ in Malawi: A Randomized Controlled Trial in Lilongwe

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Developing and Assessing a Male Engagement Intervention for Option B+ in Malawi: A Randomized Controlled Trial in Lilongwe

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Study team

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PROTOCOL SUMMARY

Research Question

The overarching research question is whether a couple-based approach or an individual-based approach to Option B+ results in better maternal, paternal, and infant HIV outcomes one year after maternal enrollment.

Rationale

In sub-Saharan Africa, engaging HIV-infected men in HIV care and treatment and engaging HIV-uninfected men in prevention has proven challenging. Additionally, men rarely engage in the antenatal care-seeking of their female sexual partners, leading to worse maternal and infant outcomes. There is promising evidence that couple-based approaches within Option B+ prevention of mother to child transmission programs could address multiple outcomes simultaneously: poor male engagement in the HIV continuum of care, low male adoption of biomedical HIV prevention approaches, and poor uptake and retention in the continuum of care for women and infants. This is a randomized controlled trial to compare a couple-based intervention to an individual-based standard of care over a one year period. There are five objectives:
Objective 1: determine whether the intervention increases continuum of care outcomes for HIV-infected men.
Objective 2: determine whether the intervention increases prevention uptake in HIV-uninfected men.
Objective 3: determine whether the intervention improves continuum of care outcomes for HIV-infected women.
Objective 4: determine whether the intervention improves uptake of early infant diagnosis and explore its effects on mother-to-child transmission and child survival. (This is a secondary objective).
Objective 5: develop an in-depth understanding of transmission dynamics in Lilongwe.

Methods

Study design: This is a two-arm, non-blinded randomized controlled trial comparing a couple-based intervention to an individual standard-of-care approach to Malawi's Option B+ program.

Primary Population: The study will be conducted at Bwaila District Hospital and may move instead to Area 18 if enrollment is slow or other studies are recruiting there. Women will be eligible to participate if they are:

- HIV-positive and eligible for Option B+
- ≥18 years old or 15-17 years old and married (emancipated minor)
- Planning to remain in the relevant catchment area for the next year or notify the study team if they leave the area or change facilities
- In a committed heterosexual relationship with a male partner for ≥3 months
    - The partner is expected to be in Malawi for at least one week in the next six months
    - Able and willing to give locator information for that male partner
    - Willing to have study staff conduct phone and physical tracing of that partner
    - Willing and able to engage in a couple-based intervention with that partner
- Able and willing to provide informed consent

Enrolling pregnant women is essential as this is the primary population eligible for Option B+. The target sample size is 500 women randomized in a 1:1 ratio to two arms (250/arm), up to 500 of their partners, and up to approximately 500 infants (although more are possible due to non-singleton births). It is expected that 14,000 women will present for antenatal care at this hospital over a 12-month period. Approximately 700 (5%) will be newly diagnosed as HIV positive and 500 (71%) will meet eligibility criteria. Enrollment may take longer if there are fewer pregnancies, a lower HIV prevalence, or lower eligibility rates. Women will be actively followed for one year and their data will be abstracted for up to three years.

Male partners will be eligible if they present to the antenatal clinic, are ≥18 years old or 15-17 years old and married (i.e. an emancipated minor), and confirm that they have been in a relationship with the female partner for ≥3 months. They must be willing to undergo couple HIV testing and counseling (CHTC) with their female partner and be able and willing to provide

informed consent. They must believe participation will not result in intimate partner violence or abandonment. Men will be actively followed for one year and their data will be abstracted for up to three years.

Infants (singletons and twins) will be eligible if they are born during the study period or if the mother was identified as HIV-infected while delivering or breastfeeding that infant. Health information may be abstracted from clinic records for up to three years after maternal enrollment.

Control population: In addition, 350 HIV-uninfected pregnant women will be enrolled and frequency matched to the HIV-infected women based on pregnancy duration. The same eligibility criteria will be used.

Procedures and Interventions:

Study Procedures

Upon learning that the woman is HIV-positive, she will be screened and assessed for eligibility (**Screening**). She will provide oral consent for screening. Study staff will maintain a screening log with documented reasons for non-eligibility. Women interested in participating will be consented into the study, administered a brief survey, provide locator information and randomized to one of the study arms.

- **Female study visit 1:** Following those procedures, women will be administered a one-hour behavioral survey about demographics and socio-economic status, their sexual and care seeking behaviors, migration, and partnership characteristics. They will have a venous blood draw of approximately 20ml.
- **Female study visit 2:** The next visit, will occur approximately six months after visit 1. At this visit, women will fill out a comparable behavioral survey.
- **Female study visit 3:** The next visit, will occur approximately twelve months after visit 1. At this visit, women will fill out a comparable behavioral survey. They will have a venous blood draw of 20ml.

Men will provide or decline oral consent for screening, then be screened for the study, assessed for eligibility and consented at first presentation. They can refuse to provide informed consent and this will not affect their female partner's participation. For those in the couple arm, this will occur approximately one week after female study enrollment (visit 1). For those in the individual arm, this will occur approximately one year after female study enrollment (visit 2). For those where male partner consents:

- **Male study visit 1:** Only men in the couple intervention arm will have this visit, and this will coincide with couple intervention visit 1. This visit will occur approximately one week after the female intervention visit 1. At this visit, men will fill out a behavioral survey with similar information to the female survey. They will have a venous blood draw of approximately 20ml.
- **Male study visit 2**: This visit will occur approximately twelve months after the female's visit 1. At this visit, men will fill out a behavioral survey with similar information to the female survey. They will have a venous blood draw of approximately 20ml.

Standard of Care for Women, Infants, and Male Partners

Within the Option B+ program, all women are administered ART within one week of an HIV-positive test result (and typically on the same day). For the first six months, they receive a monthly supply of antiretroviral therapy and attend the clinic monthly. After six months, if they have good adherence, they receive a three-month supply of treatment, and attend the clinic every three months. Women who present with male partners receive standard of care CHTC, but this occurs for a minority of women (approximately 10%). Men identified as HIV-positive cannot initiate treatment in Option B+ settings. Additionally, condoms are available through the pharmacy, but not by the HTC counselors. Women have a first viral load test at six months. Infants undergo early infant diagnosis with DNA PCR six weeks after delivery and an HIV rapid test at twelve months. Those who are HIV-infected begin antiretroviral therapy immediately. This will not be altered by the study.

Study tracing procedures

Because this is a longitudinal study with relatively few visits, efforts will be made to maintain contact with all participants throughout the study. A community worker will collect locator information on all participants. To verify physical locations, participants will use electronic or paper maps or draw maps. Community workers may accompany participants home to learn

their physical address. The community workers will make routine contact with all study participants on a quarterly basis to update locator information. They will provide study participants with study contact information and ask participants to phone the study staff should they transfer facilities or change their locator information.

Individual arm (N=250)
No *intervention* procedures beyond standard of care procedures will be conducted in the individual arm. Women randomized to the individual arm will undergo the *study* procedures described above. At the twelve month visit, couples in this arm who present together will receive standard of care CHTC.

Couple arm (N=250)
In addition to the study procedures and standard of care procedures described above, women in the intervention arm will undergo the following procedures:

- **Female intervention visit 1 and partner tracing:** Women in the **couple arm** will be provided with study-specific partner referral cards and encouraged to bring male partners to antenatal care for important pregnancy information. The referral card will contain a specific time for male partners to present to the clinic, but note that this is flexible. The card will describe the purpose of the visit as pregnancy-related, not HIV-related to allow the woman the opportunity to disclose in the clinic if preferable. It will not contain information about the woman's HIV status or HIV care-seeking. Phone and physical tracing will be conducted with utmost regard for protecting the privacy of enrolled women and their partners through detailed standard operating procedures. They will receive brief disclosure support counseling.
- **Couple intervention visit 1 (day 0-30+):** Upon presentation, the couple will receive an enhanced CHTC intervention. The intervention will include pre-test counseling, return of joint results, and post-test counseling with differentiated messages for HIV-discordant and HIV-concordant couples. HIV-infected men can initiate cART and the couple will be offered condoms from the HTC counselor.
- **Couple intervention visit 2 (month 6):** Upon presentation, the couple will receive an enhanced couple-intervention similar to couple visit 1. It will be similar to visit 1, but will not include testing for HIV-concordant positive couples. In addition, EID will be provided if the infant has not had it yet, as these visits are likely to coincide. Counselor will discuss the importance of birth spacing and provide or refer for contraception. A small monetary or non-monetary nutritional supplement (approximately $5 equivalent) will be provided. This will coincide with female study visit 2.
- **Couple intervention visit 3 (month 12):** Upon presentation, the couple will receive an enhanced couple-intervention similar to couple visit 2. Conduct of or reminder of infant 1-year HIV test will be conducted. This will coincide with the female study visit 2 and male study visit 1.

Control Procedures
The 350 HIV-uninfected women will be screened, consented, and enrolled for participation. They will answer questions to the same interviewer-administered survey that HIV-infected women receive at their first study visit. Control participants will not have any additional visits, have blood drawn or enroll male partners. Their clinical information, including syphilis rapid test results will be abstracted.

Data collection, management, and analysis
Study staff will be responsible for data collection. Patient health information will be collected through the Baobob electronic medical record, when possible, and transferred from patient to study case report forms by study staff or downloaded. Study consents and surveys will be stored in locked filing cabinets. Data will be entered into a password protected Open Data Kit (ODK) database, Access database, or similar database by a trained data entry clerk.

- For **objective 1**, we will compare the individual to the couple arm for continuum of care outcomes for HIV-infected men. These outcomes include a) the proportion of HIV-infected men who learn that they are HIV-positive before the 12 month visit, b) the proportion of HIV-infected men who begin ART within a year of the woman's study enrollment, c) the proportion of HIV-infected men who remain in care one year after the woman's study enrollment, and d) the proportion of HIV-infected men who are virally suppressed one year after the woman's study enrollment. We have >99% power to detect a difference in the overall continuum (34% versus 73%).

- For **objective 2**, we will compare the individual to the couple arm for the proportion of HIV-uninfected men who a) are circumcised one year after study enrolment, b) had no unprotected sex with their study partner in the first six months after the woman initiated ART, and c) had a female partner who was virally suppressed at six and twelve months OR had no unprotected sex with their study partner in the second six months (7-12) after female ART initiation. We have 94% power to detect a risk difference of 85% in the couple intervention arm and 60% in the SOC arm.
- For **objective 3**, we will compare the individual to the couple arm for a) the proportion of HIV-infected women who are retained in care at one year, b) the proportion of retained women who are virally suppressed at one year, and c) the proportion of women who are both retained and suppressed at one year. To assess outcomes on the overall continuum (64% versus 81%), we have 97% power.
- For **objective 4,** we will compare the individual to the couple arm for a) the proportion of infants who had early infant diagnosis. To assess this outcome (0.6 versus 0.75), we have 87.5% power. We will also explore the rates of mother-to-child transmission and child survival in the two intervention arms.
- **Objective 5** is exploratory and analytic. We will learn use viral genetics, and multi-assay algorithms to learn about the timing, direction, and bio-behavioral context of HIV transmission. We will compare HIV-infected participants with recent HIV infection (~50 women) to HIV-uninfected controls.

For each outcome of interest, we will implement generalized linear models with an identity link and binomial distribution to estimate risk differences and ninety five percent confidence intervals.

Risks/Benefits

Risks: Participants may feel embarrassed to answer questions about sexual behavior. They can refuse to answer any questions at any time. Breach of confidentiality is another risk in this study. Measures will be taken to ensure this does not occur. If a participant's male partner is contacted in the community study staff will prevent other people (non-partners) from learning the reason for the community outreach worker visit. Once a partner is located, their identity must first be confirmed by the community outreach worker. The discussion with the community outreach worker must take place in a private place. During the blood draw or HIV test, participants may feel discomfort when blood is drawn. They may also feel dizzy or faint, or experience bruising or swelling at the blood drawing site. However, risk is minimal. Participants may become worried or anxious while waiting for HIV test results. Trained counselors will be available to help participants deal with these feelings. HIV partner notification may cause social, economic, legal or physical harm but these harms are rare. Our team will do everything in our power to help you resolve these problems if they arise. We will also systematically ask all female participants if these problems have occurred.

Benefits: The benefits to females from being in this study are to help notify sexual partners that they may have been exposed to HIV and to get couples HIV counseling and testing (either right away or one year later) and remain in care. This study may help male participants learn their HIV status. It will help couples learn each other's HIV status. If the male partner is HIV-infected, he may be able to start HIV care or treatment. If the couple is HIV-discordant, they may be able to use behavioral or biomedical prevention measures to remain HIV-uninfected. Female and infant Option B+ outcomes may improve. Malawi may benefit from the results of this research by learning new knowledge about partner notification and understanding of partner notification within the Option B+ program.

Costs/Compensation

Study and intervention visits will be compensated up to $5 per visit in Malawi kwacha or in kind equivalent.

Confidentiality Assurances

Sensitive information will be collected from male and female participants. Measures will be taken to ensure this information is not shared between partners. Community outreach workers will not disclose the HIV status of the female partners. They will simply suggest male partners report to the clinic for health information with female partners.

Both male and female participants will be assigned a study ID number. This number will be linked to the participant name and medical record at the antenatal clinic only through a separate log book that will be kept in a separate locked file. Data will be double-entered into a password protected Access database or uploaded to ODK by a trained data entry clerk. Only the study staff will be able to link the medical record that has the participant name on it with study information that has the study ID number on it. At the conclusion of the study, this link between the name and number will be destroyed.

No subjects will be identified in any report or publication about this study. In some cases, information in this research study could be reviewed by representatives of the University of North Carolina, research sponsors, or Malawi government agencies for purposes such as quality control or safety. We may present de-identified data for open access publications.

All electronic data will be collected on encrypted, password-protected devices and stored on encrypted, password- protected servers. All paper-based data will be stored in locked filing cabinets in locked rooms. Data will be stored following the termination of study completion and then destroyed.

Conflict of Interest

There are no conflicts of interest.

Collaborative Agreements

This is a single-site study. We will also seek approval from the University of North Carolina at Chapel Hill Institutional Review Board.

Intended use of results

The results of the study will be presented at international and local scientific meetings and published in scientific journals. The results will also be submitted to the NHSRC. The information collected in this study may lead to larger cluster randomized trials that will allow further evaluation of the impact of male participation on maternal, /infant, and male partner outcomes.

PROTOCOL

Title

Developing and Assessing a Male Engagement Intervention for Option B+ in Malawi: A Randomized Controlled Trial in Lilongwe

Abstract

In sub-Saharan Africa, engaging HIV-infected men in HIV care and treatment and engaging HIV-uninfected men in prevention has proven challenging. Additionally, men rarely engage in the antenatal care-seeking of their female sexual partners, leading to worse maternal and infant outcomes. There is promising evidence that couple-based approaches within Malawi's Option B+ prevention of mother to child transmission program could address all of these challenges: poor male engagement in the HIV continuum of care, low male adoption of biomedical HIV prevention approaches, sub-optimal female engagement in the continuum of care, and poor or uncertain infant outcomes. Our team has developed an intervention to address these challenges, and will conduct a randomized controlled trial (N=500 couples) to assess intervention effectiveness at one year. Through this work we aim to achieve four objectives: determine whether the intervention increases continuum of care outcomes for HIV-infected men (Aim 1); determine whether the intervention decreases the likelihood of male exposure to HIV over a one-year period (Aim 2); determine whether the intervention improves continuum of care outcomes for HIV-infected women (Aim 3) and their infants (Aim 4). Finally, we will develop an in-depth understanding of transmission dynamics in Lilongwe. Results are expected to inform how best to address family outcomes in an Option B+ program.

Background and Justification

In sub-Saharan Africa, engaging HIV-infected men in HIV care and treatment has proven challenging. Along all steps of the HIV care-seeking cascade, men exhibit worse care-seeking behaviors. They are less likely to seek HIV testing and counseling (HTC),[1-4] initiate combination antiretroviral therapy (cART),[5-8] and be retained in cART care.[9] Poor care-seeking has resulted in a lower prevalence of viral suppression[10] and earlier mortality.[9,11,12] Strategies to diagnose HIV-infected men earlier and improve their HIV care-seeking and adherence behaviors are urgently needed.

Similarly, HIV-uninfected men in HIV-discordant couples face challenges with HIV prevention. Without adopting any HIV prevention behaviors they are at very high risk for HIV infection.[13] Consistent condom use is one option, but new biomedical prevention options are also available, including medical male circumcision,[14-16] and "treatment-as-prevention" (having an HIV-infected sexual partner adhere to cART for viral suppression).[17,18] Helping men in HIV-discordant couples navigate this new HIV prevention environment is essential.

Additionally, men rarely engage in the antenatal care-seeking of their female sexual partners,[19] even though male engagement is associated with marked improvements in maternal and infant outcomes.[20-22] This low level of engagement has been noted in Malawi's Option B+ prevention of mother to child transmission (PMTCT) program, which provides all HIV-infected pregnant and lactating women with lifelong cART at the time of HIV diagnosis, regardless of CD4 count or clinical stage.[23,24] However, low levels of male engagement have been a critical barrier to female Option B+ uptake and retention,[19,20] and a missed opportunity for engaging men.

Couple-based approaches within Option B+ could address all of these challenges: poor male engagement in the HIV continuum of care, low male adoption of biomedical HIV prevention, sub-optimal female and engagement in the continuum of care, and poor or uncertain infant outcomes. Couple-based, approaches, especially couple HTC, have been encouraged by the World Health Organization (WHO), but implementation questions remain: 1) assessing strategies for recruiting couples, and 2) understanding the impacts of couple-based strategies on HIV treatment and treatment as prevention.[25] This proposal directly addresses both of these research areas.

In previous protocols our group has conducted formative work to guide the development of a couple-based intervention package for HIV-infected pregnant women and their male partners. Several key findings have emerged from this body of work that directly inform future interventions. First, it is feasible for three quarters of newly diagnosed HIV-infected pregnant women to recruit male partners for couple HTC using a combination of a written invitation, partner tracing, and a small incentive. Second, couple HTC identifies a substantial number of HIV-infected men who are not engaged in care, but additional approaches are required to support male care-seeking behaviors. Third, the majority of HIV-discordant couples initiate consistent condom use following couple HTC, but do not understand newer HIV prevention modalities. Fourth, couple HTC is associated with better CART uptake, but long-term retention has not been assessed. Within the framework of interdependence theory, these findings have informed a couple-based intervention to be assessed through a two-arm randomized controlled trial (N= 500 HIV-infected women and their partners).

Literature review

UNAIDS has recently set forth global "90-90-90" targets for control of the HIV epidemic. These targets refer to three HIV continuum of care indicators: 90% of HIV-infected persons tested and aware of their HIV status, 90% of these persons retained in care at one year, and 90% of these persons virally suppressed.[26] Some epidemic models have suggested that this level of suppression is needed to slow the spread of the HIV epidemic.[27] Couple-based approaches for achieving 90-90-90 targets are promising for Malawi where marriage occurs early and is nearly universal,[28] and a large share of transmission occurs within marriages.[29] Couple-based approaches have been used in a variety of settings to address HIV-related testing, prevention, and treatment behaviors.[22,30-33] Such approaches typically incorporate several effective elements: couple communication, joint problem solving and goal-setting;[34,35] sessions for individual couples rather than groups; and >1 intervention session.[35] In formative work, we have gained additional insight into how to implement couple-based approaches in an Option B+ setting.

Couple-based approaches for 90-90-90 targets in men: In SSA, the proportion of women who know their HIV status is higher than men, in part due to high rates of antenatal testing. Because nearly all HIV-infected pregnant women have an HIV-infected male partner, recruiting the partners of HIV-infected pregnant women is an appealing approach to achieving the first "90%" target. However, antenatal recruitment of male partners for couple HTC has proven challenging. In studies with patient-led approaches, male partner recruitment is typically <30%[36-38] However, health-sector led approaches or incentives typically lead to >50% uptake of couple HTC.[39-41] In a pilot assessment at Bwaila District Hospital, providing HIV-infected pregnant women with an invitation, clinic-led phone and physical tracing, and a research incentive led to 74% of couples seeking couple HTC.[42] Seventy-one percent were HIV-infected and 47% received an HIV-positive diagnosis for the first time. Although couple HTC was effective for identifying HIV-infected men, it was not sufficient for linking HIV-infected men to care. Busy schedules accounted for a large share of non-linkage and loss, and men indicated that availability of cART at the time of couple HTC would have led to initiation. Additionally, having partners pick up cART would alleviate care-seeking challenges. Thus, initiating both couple members in the antenatal setting, synchronizing their ART pickup, and allowing them to pick up drugs for one another is a promising strategy for improving the second "90%" target. For the third 90% target, adherent persons indicated that daily partner reminders, and synchronized pill-taking facilitate adherence, strategies that will be incorporated into the couple intervention.

Prevention behaviors for men in HIV-discordant couples: Couple HTC has been associated with consistent condom use in this population, as well as others throughout the region.[43-45] However, in our population there was confusion surrounding biomedical prevention approaches. Ensuring that couple-based approaches more clearly explain different HIV prevention options is important for helping couples remain protected. Through formative work, we have developed a greater understanding of the dyadic context in which condom use is occurring. Interdependence Theory, a dyadic model, identifies a combination of actor, partner, and joint effects for behavior change. Each person's behavior can be affected by that person (actor effects), his or her partner (partner effects), or a combination of both together (joint effects). The relationship context (i.e. commitment, intimacy, satisfaction, trust, communication, HIV communication, and sexual power) could account for these joint effects,[46-51] but varies by setting. [47,52-55] In this setting, we found that couple communication and social support improved following CHTC.

Couple-based approaches for 90-90-90 targets in women and infants: In ANC settings in Malawi, HIV testing and immediate ART initiation are nearly universal, but retention and adherence remain challenging.[56,57] Failure to disclose one's HIV status to a male partner is one key barrier to ART initiation.[58] In Bwaila District Hospital, we have found that women who received couple HTC are more likely to return for a first ART refill visit compared to those who do not receive couple HTC. Disclosure made it easier for some women to take pills openly and enabled social and financial support from partners. This support included couple-based routines, synchronized pill-taking, and daily reminders. These components have bene incorporated into the enhanced couple HTC intervention.

In summary, an emerging body of evidence in the region overall, and in our setting specifically, suggests that couple-based approaches could support a range of HIV testing, prevention, and treatment behaviors for HIV-infected pregnant women and their male partners. However, well-designed research is needed to determine the effect of couple-based approaches.

Rationale for enrolling HIV-uninfected women

HIV acquisition during pregnancy and breastfeeding leads to maternal morbidity and mortality and threatens to undermine elimination of mother to child transmission (eMTCT) efforts. This is due to the majority of pregnant women being HIV-negative,[59] high rates of maternal HIV acquisition during pregnancy and postpartum,[60,61] and elevated rates of vertical transmission at the time of maternal HIV acquisition. [62-66] As Option B+ test-and-treat programs have become more successful at reaching HIV-positive women at their first antenatal visit, a larger share of vertical transmissions will stem from maternal HIV acquisition after the first antenatal visit.[67,68] These elevated risks have been observed in Malawi where one third of vertical transmissions among infants <3 months stem from new undiagnosed maternal HIV infections during pregnancy.[69] Understanding the bio-behavioral characteristics of women most at risk for HIV acquisition and the male partners who transmit to them is critical for preventing maternal HIV acquisition and ultimately realizing eMTCT.

Initiating biomedical prevention, such as tenofovir-based oral pre-exposure prophylaxis (PrEP), during pregnancy is a promising approach for reducing maternal HIV acquisition.[70-72] Daily oral PrEP, in the form of tenofovir-emtricitabine (TDF-FTC), is safe in pregnancy[70] and highly effective for preventing HIV when adherence is high.[70-72] In Malawi, the provision of PrEP in antenatal settings is appealing due to high fertility (4.4 births per woman) and near-universal antenatal attendance.[59] However, offering PrEP to *all* HIV-uninfected Malawian pregnant women is not feasible or cost-effective[73] and, as such, is not supported by the Malawi Ministry of Health. PrEP is recommended for populations with annual HIV incidence above 3%,[74] but Malawi's estimated HIV incidence in young pregnant women is only 0.6%.[75,76] Thus, identifying a subset of pregnant women with HIV incidence above 3%, such as HIV-discordant couples, women with multiple sexual partners, or women with sexually transmitted infections, who would benefit most from PrEP, is a critical component of implementation. Such risk targeting is promoted by the World Health Organization as part of a comprehensive PMTCT package.[74]

Clinical risk scores are prediction tools for identifying sub-populations at higher risk for specific outcomes.[77-80] Recently, a risk score was developed to identify Kenyan pregnant and postpartum women with elevated risk for HIV acquisition.[81] When the score was restricted to clinically available information (Table 1), the area under the receiver operating characteristic curve (AUC) was 0.76 (95% CI: 0.67-0.85), moderate predictive ability. This study demonstrated that risk targeting was possible in this single setting, but with moderate performance—external validation and possibly updating are next steps. Geographical validation examines the transportability of an existing risk assessment tool to a new setting.[80] If the Kenyan model performs well in Malawi, this will enhance the generalizability of the tool. However, if it performs poorly, model updating may be needed. Updating can take several forms, including re-weighting the same variables, adding or removing variables, or developing a new tool. We have identified several variables that may be appropriate for consideration. In formative work in the antenatal setting (K99 MH104154),[82] comparing HIV-infected pregnant women and their primary sexual partners to HIV-uninfected women and their primary sexual partners, we identified three sets of risk factors associated with *prevalent* HIV-infection in pregnancy: 1) an HIV-positive primary sexual partner, 2) a primary sexual partner outside of Lilongwe for an extended period, and 3) male or female report of ≥2 lifetime marriages or ≥3 lifetime sexual partners (Table 1).[83] In Girl Power-Malawi, a cohort study among non-pregnant young women 15-24 years old (UK Aid),[84] we identified 11 female-reported individual, partner, and dyadic factors associated with HIV infection (Table 1).[85] Young women with ≥3 of these factors had a 4% annual HIV incidence rate, fourteen-times higher than those with ≤1 factor. Differences in these different approaches reinforce the need for external validation. By enrolling HIV-uninfected pregnant women and comparing them to recently HIV-infected pregnant women , we will validate and, if needed, update a risk assessment tool for Malawian pregnant women.

Hypotheses

The overarching hypothesis of this study is that a couple-based approach is superior to an individual-approach (standard of care) for achieving a range of maternal, male partner and infant outcomes within Malawi's Option B+ program.

Table 1. Risk factors of interest

Specific Aims/Study Objectives

This study has five sets of specific aims (study objectives), which relate to HIV-infected male partners, HIV-uninfected male partners, HIV-infected pregnant and breastfeeding women, and HIV-exposed infants. These are described below:

Aim 1: Determine whether the couple-based intervention increases new HIV-positive diagnoses among HIV-infected male sex partners, helps HIV-infected men engage and remain in care, and contributes to male viral suppression compared to individual standard of care. We will compare the couple-based intervention to standard of care for increasing the proportion of men who are aware of being HIV-infected, the proportion of these men who initiate and remain in cART care, and the proportion of these men with viral suppression at one year.

Aim 2: Determine whether the couple-based intervention identifies HIV-discordant couples and decreases the likelihood of male exposure to HIV compared to individual standard of care. We will compare the intervention to standard of care for increasing the number of men with non-HIV exposure from their female partner through consistent condom use, viral suppression, abstinence, or a combination of these methods over one year.

Aim 3: Determine whether the couple-based intervention improves female cART retention and viral suppression compared to individual standard of care. We will compare the intervention to standard of care for female cART retention and viral suppression at one year.

Aim 4: Determine whether the couple-based intervention improves infant early infant diagnosis uptake compared to individual standard of care. Explore uptake of early infant diagnosis and rates of mother-to-child transmission and child survival in the two intervention arms.

Aim 5: Develop an in-depth understanding of HIV transmission dynamics in Lilongwe. Using the biomarkers and behavioral survey, we will seek to understand transmission timing, direction, and context in Lilongwe. We will compare women with recent HIV infection to a population of HIV-uninfected controls to understand predictors of HIV acquisition in pregnancy in Malawi.

Methodology

Study Design:
A couple-based intervention will be compared to individual standard of care (SOC) in an un-blinded randomized controlled trial (RCT) (N=500 women) to assess identification of HIV-infected men, their one-year retention in care, and viral suppression (Aim 1); identification of HIV-discordant couples and adoption of non-exposure to HIV (Aim 2), female one-year retention in care and viral suppression (Aim 3), and infant ED (Aim 4). The trial will also compare the two arms for social harms. Additionally, the HIV-infected women with recent HIV infection will be compared to a control population of HIV-uninfected women.

Study Setting
The study will be conducted at Bwaila District Hospital and/or Area 18 Health Centre if enrollment is slow or other challenges arise. Bwaila District Hospital is a large maternity hospital serving the greater Lilongwe catchment area. Within Bwaila antenatal clinic (ANC) and labor and delivery (L&D), women are routinely screened for HIV infection using opt-out individual HTC, and immediately eligible for cART through Option B+ if found to be HIV-infected. Similar procedures are planned for Bwaila's immunization clinic which sees breastfeeding women. Women who are initiated on cART are seen monthly for the first six months and then every three months thereafter. Malawi has adopted a test-and-start model of care of all adults, but men cannot initiate cART in these Option B+ settings even though they can test there.

Study Population
The study will be conducted at Bwaila District Hospital and moved to Area 18 Health Center if needed. Women will be eligible to participate if they meet the following criteria:
Primary Population Inclusion Criteria

- HIV-infected and eligible for Option B+
- ≥18 years old or 15-17 years old and married (emancipated minors per Malawi law)
- Planning to remain in the Bwaila catchment area for the next year or notify the study team if they leave the area or change facilities
- Part of a heterosexual relationship for ≥3 months
    - Expects the partner to be in the relevant catchment area for at least one week in the next six months.
    - Able and willing to give locator information for this partner
    - Willing to have study staff conduct phone and physical tracing of that partner
    - Willing to undergo a couple-based intervention with this partner
- Able and willing to provide informed consent

Exclusion criteria

- Any condition that in the opinion of the study investigator would compromise the ability of the prospective participant to provide informed consent, undergo study procedures safely, or would prevent proper conduct of the study.

Enrolling pregnant women is essential as this is the primary population eligible for Option B+. The target sample size is 500 women randomized in a 1:1 ratio to two arms (250/arm), up to 500 of their partners, and up to approximately 500 infants (although more are possible due to non-singleton births). It is expected that 14,000 women will present for antenatal care at this hospital over a 12-month period. Approximately 700 (5%) will be newly diagnosed as HIV positive and 500 (71%) will meet eligibility criteria. Enrollment may take longer if there are fewer pregnancies, a lower HIV prevalence, or lower eligibility rates. The participant will be followed for one year and data may be abstracted from clinic records over a three year period.

Male partners will be eligible if they present to the antenatal clinic, are ≥18 years old or 15-17 years old and married (i.e. an emancipated minor), and confirm that they have been in a relationship with the female partner for ≥3 months. They must be willing to undergo CHTC with their female partner and be able and willing to provide

informed consent. They must believe participation will not result in intimate partner violence or abandonment. Men will be actively followed for one year and their data will be abstracted for up to three years.

Infants (singletons and twins) will be eligible if they are born during the study period or if the mother was identified as HIV-infected while delivering or breastfeeding that infant. The participant will be followed for one year and data may be abstracted from clinic records over a three year period from maternal enrollment.

Control population

HIV-uninfected women (N=350) will be enrolled as a control population using comparable inclusion criteria. These women will be enrolled for participation in a survey at their first antenatal visit. They will not have any additional visits or enroll male partners.

Randomization

Women will be randomized to Standard of Care (SOC), a predominantly individualized approach to Option B+, or to a couple intervention, a predominantly couple-based approach to Option B+. Permuted block randomization with block sizes of 2, 4 and 6 will be used to ensure approximately equal groups and mask the assignment procedures to the study staff. The allocation list will be generated using a random number generator in Stata or comparable program.

Schedule of visits

	Mo. 0	**Wk 0-4**	**Mo. 1**	**Mo. 2**	**Mo. 3**	**Mo. 4**	**Mo. 5**	**Mo. 6**	**Mo. 9**	**Mo. 12**
Pregnancy (pg)/ postpartum (pp) (Medians)	5 mo pg	5 mo pg	6 mo pg	7 mo pg	8 mo Pg	9 mo pg	1 mo pp	2 mo pp	5 mo pp	8 mo pp
Female standard of care	ART		ART	ART	ART	ART	ART	ART/VL	ART	ART
Female study activities	Female study visit1							Female study visit2		Female study visit3
Screening	x									
Enrollment	x									
Locator info	x									
Behavioral Survey	x							x		x
Blood collection	x							x		x
Locator info. Verification		x			X			x		x
Male study activities		M. study visit 1								M. study visit 2
Screening		x (C)								x (I)
Enrollment		x (C)								x (I)
Behavioral Survey		x (C)								x
Blood collection		x (C)								x
Couple Intervention Activities			Couple interv'n visit 1					Couple interv'n visit 2		Couple interv'n visit 3
Disclosure/invitation support to woman	x									
Phone/physical Tracing		x								
Couple counseling (and testing)		x						x		x
Provide condoms		x						x		x
Dispense ART to men		x (C)	x (C)	x (C)	x (C)	x (C)	x (C)	x (C)	x (C)	x (C)
Infant activities										
EID conduct								x		
Rapid test									(x)	
(C)=Couple arm only; (I)=Individual arm only										

Study Procedures
Upon learning that the woman is HIV-positive, she will be screened and assessed for eligibility (**Screening**) after providing oral consent. Study staff will maintain a screening log with documented reasons for non-eligibility. Women interested in participating will be consented into the study, administered a brief survey, provide locator information and randomized to one of the study arms.

- **Female study visit 1 (baseline):** Following those procedures, women will be administered a one-hour behavioral survey about demographics and socio-economic status, their sexual and care seeking behaviors, migration, and partnership characteristics. They will have a venous blood draw of approximately 20ml.

- **Female study visit 2 (midline):** The next visit**,** will occur approximately six months after visit 1. At this visit, women will fill out a comparable behavioral survey.

- **Female study visit 3 (endline):** The next visit**,** will occur approximately twelve months after visit 1. At this visit, women will fill out a comparable behavioral survey. They will have a venous blood draw of 20ml. Patient materials will be provided on family health information.

Men will be screened for the study and assessed for eligibility and consented. For those in the couple arm, this will occur upon first presentation (typically approximately one week after female study enrollment). For those in the individual arm, this will also occur upon first presentation (typically one year after female study enrollment).

- **Male study visit 1 (baseline):** Only men in the couple intervention arm will have this visit, and this will coincide with intervention visit 1. This visit will occur approximately one week after the female intervention visit 1. At this visit, men will fill out a behavioral survey with similar information to the female survey. They will have a venous blood draw of approximately 20 ml.

- **Male study visit 2 (endline)**: This visit will occur approximately twelve months after the female's visit 1. At this visit, men will fill out a behavioral survey with similar information to the female survey. They will have a venous blood draw of approximately 20ml.

Study tracing procedures
Because this is a longitudinal study with few visits, efforts will be made to maintain contact with all participants throughout the study. Ascertaining outcomes on the entire cohort is a challenge as many will not present to the clinic and this is expected to be differential by arm. Specifically, 1) male testing outcomes cannot be observed among men do not present to the clinic, 2) loss-to-care outcomes cannot be distinguished from informal transfer without review of clinic documentation, and 3) viral suppression cannot be ascertained without a blood draw. To address this challenge, we will collect data prospectively, when possible, and retrospectively otherwise. Rigorous tracing procedures will support retrospective data collection. First, at the initial visit, women will provide extensive phone and physical tracing information. To verify physical locations, participants will use Google Earth and draw maps. Community workers may accompany participants home to learn their physical address. The community workers will make routine contact with all study participants on a quarterly basis to update locator information. They will provide study participants with study contact information and ask participants to call the study staff should they transfer facilities or change their locator information. If one or both members of the couple does not come for their study visits, study procedures can be conducted in the community or by phone. Detailed standard operating procedures outlining such processes will be developed to protect privacy and confidentiality.

Standard of Care for Women, Infants, and Male Partners
Within the Option B+ program, all women are administered ART within one week of an HIV-positive test result (and typically on the same day). For the first six months, they receive a monthly supply of antiretroviral therapy and attend the clinic monthly. After six months, if they have good adherence, they receive a three-month supply of treatment, and attend the clinic every three months. Women who present with male partners receive standard of care CHTC, but this occurs for a minority of women (approximately 10%). Men identified as HIV-infected cannot initiate treatment in Option B+ settings. Additionally, condoms are available through the pharmacy, but not by the HTC counselors. Women have a first viral load test at six months. Infants undergo early infant diagnosis with DNA PCR six weeks after delivery and an HIV rapid test at twelve months. Those who are HIV-infected begin antiretroviral therapy immediately. Standard of care may evolve over the course of the study as it is being implemented over a 2-year period.

Individual arm procedures (N=250)
No *intervention* procedures beyond standard of care procedures will be conducted in the individual arm. Women randomized to the individual arm will undergo the *study* procedures described above. At the twelve month visit, couples in this arm who present together will receive standard of care CHTC. An intervention will be given to women, as needed to support inviting the male partners.

Couple arm procedures (N=250)
In addition to the study procedures and standard of care procedures described above, women in the intervention arm will undergo the following procedures:

- **Female intervention visit 1 and partner tracing:** Women in the **couple arm** will then be provided with study-specific partner referral cards and encouraged to bring male partners to antenatal care for important pregnancy information. The referral card will contain a specific time for male partners to present to the clinic, but note that this is flexible. The card will describe the purpose of the visit as pregnancy-related, not HIV-related. It will not contain information about the woman's HIV status or HIV care-seeking. Phone and physical tracing will be conducted with utmost regard for protecting the privacy of enrolled women and their partners through detailed standard operating procedures.

- **Couple intervention visit 1 (day 0-30):** Upon presentation, the couple will receive an enhanced CHTC intervention. The intervention will include pre-test counseling, return of joint results, and post-test counseling with differentiated messages for HIV-discordant and HIV-concordant couples. The counselor will follow a structured set of procedures that promote intra-couple communication, address gendered power dynamics, and encourage joint decision-making and goal setting. HIV-infected men can initiate cART at the antenatal clinic and the couple will be offered condoms from the HTC counselor. A small monetary or non-monetary allowance ($5 equivalent) will be provided.

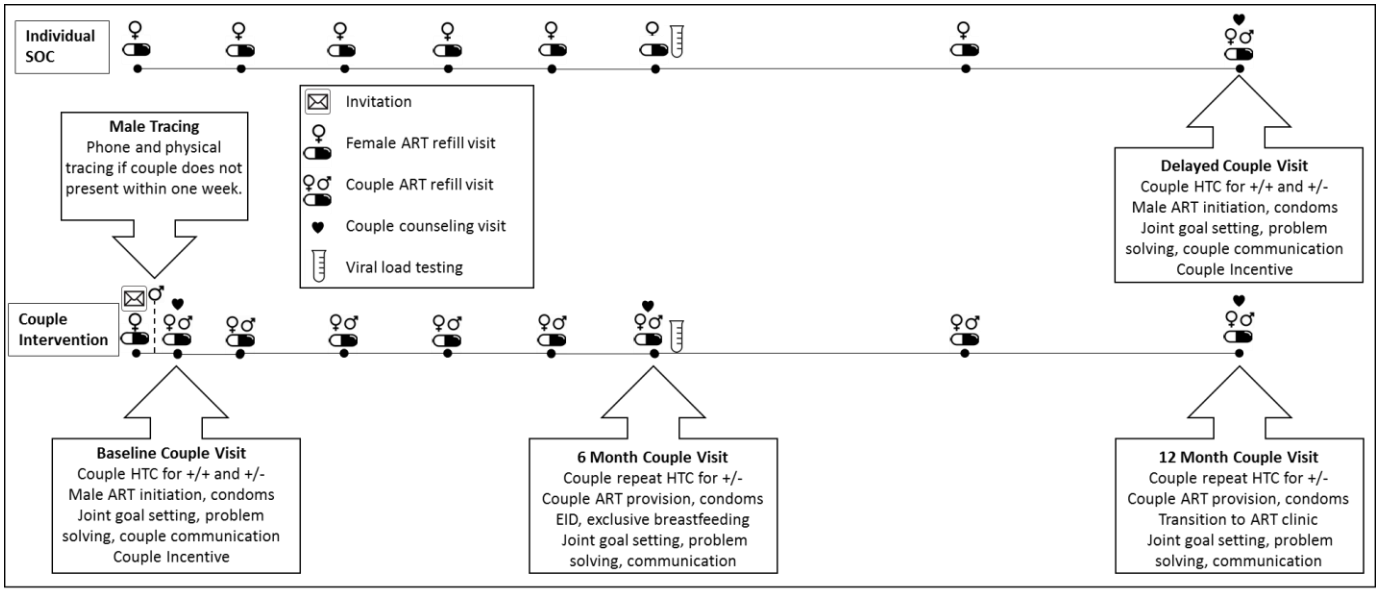
- **Couple intervention visit 2 (month 6):** Upon presentation, the couple will receive an enhanced couple-intervention similar to couple visit 1. It will be similar to visit 1, but will not include testing for HIV-concordant positive couples. In addition, EID will be provided if the infant has not had it yet, as these visits are likely to coincide. Counselor will discuss the importance of birth spacing and provide or refer for contraception. A small monetary or non-monetary allowance ($5 equivalent) will be provided. This will coincide with the female visit 2.

- **Couple intervention visit 3 (month 12):** Upon presentation, the couple will receive an enhanced couple-intervention similar to couple visit 2. Conduct of or reminder of infant 1-year HIV test will be conducted. This will coincide with the female study visit 3 and male study visit 2.

- **Between visits:** Between sessions, couple members can pick up condoms and cART for one another.

The following graphic depicts the differences between the two interventions. The standard of care may evolve over the course of the study.

Figure 1. Intervention Overview



Behavioral Survey
This will be administered to women and men at each study visit to assess demographics and socio-economic status, HIV care-seeking and prevention behaviors, sexual behavior, intimate partner violence, couple HIV communication, power, self-efficacy and social harms.

In-depth Interviews
In depth interviews will be conducted with a subset of the population. Up to 10% of women and their male partners may be selected to answer in-depth questions about their study participation at enrollment and baseline and endline. In-depth interview guides will be developed to support administration of these semi-structured interviews.

Biomarkers
Blood will be collected to conduct the following tests:

- **HIV rapid antibody tests:** Determine and Unigold are used in the national HIV program. They will be used to detect HIV among women and men in both arms. Although we do not anticipate changes, it is possible that Malawi will change its testing protocol: such changes would be considered acceptable and adopted in this study.

- **Viral load:** This will be conducted at female study visit 3 (12 months) and male study visit 1 among HIV-infected men (12 months). These will be study-related measures that exceed standard of care. They will be performed by UNC Project laboratory. This laboratory participates in the Virology Quality Assurance Laboratory that oversees QA/QC for assay and laboratory technologist performance for the HPTN/ACTG laboratory network. In addition, we will abstract results from standard of care routine viral load testing conducted at the 6 month visit.

- **Syphilis:** Point of care rapid syphilis tests will be offered to participants according to standard of care with results offered to participants—e.g. at the first antenatal visit. Additionally, blood specimens will be

collected, stored, and run in batch mode at the end of the study. These results will not be available to participants. This will be collected at female study visit 3 and male study visit 2.

- **HSV-2:** Blood specimens will be collected, stored, and run in batch mode at the end of the study. These results will not be available to participants. This will be collected at female study visit 1 and 3 and male study visit 1 and 2.

- **Viral genetic testing:** Blood specimens will be collected, stored, and run in batch mode at the end of the study. These results will not be available to participants. This will be collected at female study visit 1 and male study visit 1 or 2 (whenever HIV diagnosis occurs). These will be used to determine phylogenetic linkage to the partner and estimated duration of infection.

- **Multi-assay algorithm to classify HIV recent infection:** Blood specimens will be collected, stored, and run in batch mode at the end of the study. This will be collected at female study visit 1 and male study visit 1 or 2 (whenever HIV diagnosis occurs). Optimal algorithms continue to evolve and we will select the algorithm with the best performance characteristics. This will likely consist of BED capture immunoassay, an avidity assay using a modified version of the Genetic Systems ½+O ELISA, CD4 count, and HIV RNA concentrations to identify person with recent infection.

Testing on syphilis, HSV-2, viral genetic testing, and multi-assay algorithms are contingent on supplemental funding.

HIV-uninfected women: Controls will be frequency matched based on pregnancy duration at the first antenatal visit, a known confounder. Eligibility criteria will be comparable to the HIV-infected women. Eligible women will be enrolled, consented, and administered a comparable behavioral survey as HIV-infected women.

Primary outcomes and statistical power

The primary outcomes are organized by aim (Table 1). Based on historical data, we expect that 70% of male partners to be HIV-infected (N=350/500) and 30% (N=150/500) to be HIV-uninfected.

In Aim 1 the primary outcomes are the UNAIDS continuum of care indicators: the proportion of HIV-infected men aware of their HIV status, the proportion retained in care at one year, and the proportion virally suppressed (<1000 copies/µl). For all three outcomes, we have >90% power to detect a risk difference of 90% in the couple intervention arm and 70% in the SOC arm at each step of the continuum. We have >99% power to detect a difference in the overall continuum (34% versus 73%).

Table 2. Power calculations

	SOC Arm		Couple Arm		
	(n/N)	%	(n/N)	%	Power
HIV+ Men (estimated N=175/arm)					
HIV+ men diagnosed +	(123/175)	70%	(158/175)	90%	**>99%**
HIV+ men retained for one year	(86/123)	70%	(142/158)	90%	**99%**
HIV+ men virologically suppressed	(60/86)	70%	(128/142)	90%	**96%**
Overall cascade	(60/175)	34%	(128/175)	73%	**>99%**
HIV- Men (estimated N=75/arm)					
HIV non-exposure	(45/75)	60%	(64/75)	85%	**94%**
HIV-infected women (N=250/arm)					
Retained in care	(200/250)	80%	(225/250)	90%	**88%**
Virlogically suppressed	(160/200)	80%	(203/225)	90%	**83%**
Overall cascade	(160/250)	64%	(203/250)	81%	**97%**

In Aim 2 the primary outcome is the proportion of men without HIV exposure from their primary partner. This is a composite outcome based on abstinence, female viral suppression, and consistent condom use. Men will be considered non-exposed for one year if, during the first six months there are no unprotected sex acts, and, during the second six months, there are no unprotected sex acts or the woman is virally suppressed (<1000 copies/µl) at six and 12 months. We have 94% power to detect a risk difference of 85% in the couple intervention arm and 60% in the SOC arm.

In Aim 3 the primary outcomes are UNAIDS continuum of care indicators: the proportion of HIV-infected women retained in care at one year and the proportion virally suppressed at one year (<1000 copies/µl). For both indicators,

there is >80% power to detect risk differences of 80% (SOC arm) and 90% (intervention arm) at each continuum step. To assess outcomes on the overall continuum (64% versus 81%), we have 97% power. For all male outcomes and the female overall continuum outcome, even with 10% attrition, due to couple dissolution or other factors, we have >80% power to detect these expected differences.

In aim 4 we will compare the individual to the couple arm for a) the proportion of infants who had early infant diagnosis. To assess this outcome (0.6 versus 0.75 with 20% attrition), we have 87.5% power. We will also explore the rates of mother-to-child transmission and child survival in the two intervention arms.

Aim 5 is a primarily descriptive aim and we are therefore power calculations are not needed for descriptive variables. To identify predictors of recent HIV infection, we conducted a power calculation appropriate for detecting odds ratios. If 10% of HIV-infected women (N=50) have recent HIV infection (cases), we will need to enroll 350 controls to detect an odds ratio of 2.5, assuming an alpha level of 0.05, 80% power, and 20% prevalence of an exposure of interest in the control population.

Data collection, management, and analysis
All data will be collected by trained research assistants with certifications in humans subjects projections and good clinical practices. All female participants will be followed for one year with study assessments at baseline, 6 months, and 12 months. Data will be collected from participants or clinic records in Microsoft Access or Open Data Kit software on Android tablets, and stored on a secure server. Additionally, clinical data from the Baobob system or patient records will be collected or downloaded. Intervention fidelity will be obtained using intervention checklists completed by those delivering the intervention and observers.

The primary analysis for this study will be intention to treat. For each outcome of interest, generalized linear models with an identity link and binomial distribution to estimate risk differences and ninety-five percent confidence intervals. Per protocol analyses will also be conducted as well based on presence of at least one CHTC visit.

Ethical and human subjects considerations

Institutional Review Board oversight and informed consent
Approval for the study will be sought from UNC's IRB and Malawi's National Health Sciences Research Committee. These two bodies will provide oversight for the study. This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by both bodies. All procedures conform to US and Malawian ethical standards regarding research involving human subjects.

Written informed consent will be obtained. All study participants will sign an informed consent prior to enrollment. The consent form will describe the purpose of the study, the procedures to be followed, the contact information of the local study contact investigator, and the risks and benefits of participation in accordance with all applicable regulations. The informed consent forms will be translated into the local language (Chichewa) and accuracy will be confirmed. Partners will also provide informed consent prior to study participation.

Literate participants will document their provision of informed consent by signing their informed consent form. Non-literate participants will be asked to document their informed consent by marking their informed consent form (e.g., with an X, thumbprint, or other mark) in the presence of a literate third-party, impartial witness. Any other local IRB/ethics committee requirements for obtaining informed consent from non-literate persons also will be followed.

Participants will be provided with copies of their informed consent forms if they are willing to receive them and believe they will not lead to difficulties if found by partners or other persons. It will be stressed with each potential participant that participation in this study is completely voluntary. Potential participants will be told that if they choose not to participate, there will be no penalty; they can continue to participate in other research studies

or programs at the site and there will be no changes in the services they may receive at the clinic where they were contacted about this study. The consent will also inform participants that they have the right to refuse or withdraw from participation at any time.
The investigators have experience obtaining informed consent for trials in Lilongwe and thus the informed consent process has been designed to maximize understanding of potential risks.

Potential Risks
All potential risks for the patients must be weighed in the context of the current standard of care for patient management. Encouraging male partner attendance is already part of the standard of care at Bwaila Hospital and Malawi's national PMTCT program and when men do attend they are encouraged to receive couple HIV counseling and testing. Thus, many study procedures are consistent with clinic procedures. There are four types of potential risks that may occur: breach of confidentiality or privacy, reactions to sensitive topics, social harms, and physical harms.

Breach of confidentiality may occur through the partner notification procedures if the health worker accidentally discloses confidential information about one partner to the other. There could also be breach of privacy if the community has identified the health care worker as someone who works on HIV-related issues and presumes the male partner has HIV. Similarly, at the initial couple counseling session, the two members of the couple may not know each other's HIV status. Counselors may accidentally disclose HIV status before receiving consent to do so from both participants. Participants may also feel concerned that their one-on-one interview information will be shared with their partner.

The questionnaires will assess sensitive topics, including sexual behavior and intimate partner violence. Participants may have strong emotional reactions to being asked about this type of information. This is also a potential source of risk in both phases of the study.

Social harms are also a potential risk for participants in this research due to the sensitivity of these issues. Possible social harms include verbal or physical intimate partner violence, divorce, or abandonment, and their sequelae. In the Malawian context divorce or abandonment may also signify loss of income and social ostracism.

The primary physical harm pertains to risk from a venous blood draw. The risk of venous blood draw may cause bruising, pain, or make the client feel faint. However, quantities of blood collected are minimal and in line with that typically collected for routine medical procedures.

Adequacy of Protection against Risks
Female participants will be recruited form Bwaila District Hospital Option B+ program following routine HIV counseling and testing when they become eligible for Option B+. Males will be recruited for enrollment when they present to the clinic either alone or with their index sex partner.

Male partners may be recruited in the community by community recruiters. Standard operating procedures will be developed to ensure the protection of confidentiality. Community recruiters will be rigorously trained on these procedures. Training will include practical sessions so they not only learn what the procedures are but also how to appropriately operationalize them. We will apply lessons learned from the feasibility pilot assessment to both the procedures themselves and the training on these procedures.

In all aims, eligible persons will be recruited by trained research staff fluent in their native language to initiate the consent process. In order to protect persons against intimate partners, we will ensure that prospective participants do not believe that participation will lead to intimate partner violence or abandonment. This will screen out those at highest risk for intimate partner violence and other social harms. Research staff will go over the entire informed consent with the eligible persons and describe: the purpose of the study, the detailed procedures to be followed, the risks and benefits of participation, the duration of participation, and the steps taken to protect the participant. The eligible person will be given the opportunity to ask questions. No coercion will be placed on persons to enroll in the study. It will be explained that declining consent will not have any impact on the care they receive. Importantly,

the informed consent will detail the possible social harms that could occur as a result of the study. Trained research staff will be trained to discuss the pros and cons of participation with all prospective participants. They will discourage participation among those who anticipate a severe social harm. The consent will also inform persons that they can withdraw at any time should they change their mind. Written informed consent will be obtained from each participant and participants will be provided with a copy of their informed consent forms. Study staff will document the informed consent process. The entire consent process will be conducted in accordance with the relevant US-based institutional review board, as well as the National Health Sciences Research Committee, the local regulatory body.

Privacy of male and female partners is of highest importance. In both the clinic and the community, all study-related activities will occur in private locations. Health workers in the clinic and community will follow a rigorous set of procedures to ensure they are not intentionally or inadvertently disclosing HIV status or any other sensitive information from one partner to the other or to other members of the community.

Through the partner notification process, community health workers will not identify themselves as persons from an HIV-related activity. They will present themselves as general health workers or community members. Community health workers will not begin the notification process until they have confirmed the identity of the male partner. They will follow a script about why they are in the community and why they would like to recruit the men to the clinic.

At the couple counseling sessions, the two members of the couple may not know each other's HIV status or other personal information. Counselors will be trained not to disclose past HIV status or other information.

To protect participants against risks associated with sensitive topics, they will be reminded that the answer to their questions will be kept confidential and that this information will not be shared with anyone, including their sex partner. They will be allowed the opportunity to refuse to answer certain questions.

Social harms will be actively monitored in both phases of research through formal assessment. One key purpose of the formative work was to determine whether the prevalence for social harms is too high in this setting. This was not the case, so substantial modifications to the strategy have not been made. Among 300 HIV-infected women in this setting participating in similar studies, none reported intimate partner violence as a result of study participation and less than 2% reported abandonment. It is critical to monitor and appropriately address social harms. Social harm monitoring will occur through both routine and ad hoc screening. At all study visits, social harms will be assessed in both partners through a structured assessment form. This form will assess both the nature and the magnitude of the harm. Additionally, participants will be encouraged to come to the clinic when a social harm occurs. During these ad-hoc visits, the same social harm form will be filled out. When social harms do occur they will be reported according to ethical body regulatory procedures for adverse events. Social harms will be addressed through a set of standard operating procedures that includes referrals for medical, legal, or psychosocial services. We have begun a situational analysis that has already identified numerous resources in the catchment area. These include a special police unit for addressing domestic disputes, counseling on alcohol abuse, family counseling, marital counseling, HIV counseling, HIV support groups, rape crisis services, and inpatient and outpatient medical services. We will expand this situational analysis on an annual basis. Referrals will be documented and we will follow up on the outcomes. Social harms will be reported as a main outcome in the primary study manuscript so harms and benefits can easily be considered together.

The primary physical harm pertains to risk from a venous blood draw. The risk of venous blood draw may cause bruising, pain, or make the client feel faint. However, quantities of blood collected are minimal and in line with that typically collected for routine care. They will be collected in a health facility and near trained medical personnel should the patient become faint.

Potential Benefits of the Proposed Research to the Subjects and Others

There are potential benefits of the proposed research to the subjects themselves and to others. For HIV-infected women who participate in the intervention, it is possible that the involvement of their partner will lead to physical

or psychosocial health benefits for themselves or their infants. In formative work, we saw improvements in social support and couple communication following couple counseling. For HIV-infected men, it is possible that the intervention may help them link to care sooner than they otherwise would or become re-linked to care if previously lost. For HIV-uninfected men, there is the possibility that the intervention may help them take measures to effectively limit their exposure to HIV and prevent transmission. For women, there is the possibility that this can lead to improved retention in care or adherence. For infants, there is the possibility that the research will lead to earlier and more thorough HIV diagnosis—this can be life-saving.

This research is designed to benefit society by gaining new knowledge. Understanding how to optimize the implementation of Option B+ is critical given the high human and economic costs of the disease in this region. Research findings will be disseminated within Malawi and internationally.

Importance of the Knowledge to be Gained

There is considerable potential for the proposed research to generate findings of importance. Specifically, the activities proposed are designed to enhance the quality and effectiveness of the Malawi Option B+ program for women, linkage to HIV care for HIV-infected men, and prevention from HIV for men. This has implications not only for Malawi but also for other high prevalence countries. Results will be disseminated nationally, regionally, and internationally.

Reportable Events

All serious adverse events associated with the procedures will be appropriately reported to the UNC IRB and the Malawi NHSRC according to their reporting procedures. Field staff in Malawi will be trained to complete descriptions of adverse events that will then be sent electronically to both the PI and the co-PI. Thus, adverse events will be monitored at three levels; by the Principal Investigators, by the UNC IRB and by the NHSRC. Of course, efforts will be taken to minimize the potential for adverse events. Intervention and research staff training will stress ensuring confidentiality and avoidance of negative events, and quality assurance/quality control (QA/QC) will be performed regularly to ensure adherence to proper counseling techniques. Two types of reports will be made involving the conduct of the study. Adverse Events Reports will be made using standard forms available from the relevant IRBs for adverse events associated with the study procedures or subject participation. Serious medical adverse events are unlikely as the only medical procedure that will be conducted as part of HIV standard of care. Incident Reports will also be made of any incidents involving the conduct of the trial (eg, enrolling a participant who did not meet eligibility criteria, needle stick injuries of staff, etc.) These reports will be made in the form of a letter or memo to the Chairs of the relevant IRBs signed by a Principal Investigator. All reporting form study staff to the PI or co-PI should be made in real-time whenever possible (i.e. when the participant is still present). However, if this is not possible, a written report must be made within 24 hours.

Copies of adverse event reports will be stored at UNC and in the study offices at UNC Project-Malawi. Adverse events or incident reporting in this trial has been considered in the context of several important characteristics of the study. First, this is a minimal-risk study as defined in federal regulations—"the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

In addition we will provide contact information for participants: We will provide participants with information on how to contact the local research staff to report such events as breaches of confidentiality, HIV-related disruption of families, acts of discrimination, and physical harm. We will ask participants to return to the research site or otherwise contact research staff in order to make such reports as well as receive referrals to mitigate potential harm. This will not include identifying information about the study or references to HIV or HIV testing, so that the cards will not have the potential to jeopardize the confidentiality of participants.

Dissemination of results

The results of the study will be presented at international scientific meetings and published in scientific journals. The results will also be submitted to the NHSRC. The preliminary data collected in this study may lead to larger longitudinal studies that will enable us to further evaluate the impact of male participation on maternal, infant, and male partner outcomes.

Study team

Nora E. Rosenberg, PhD, MSPH, **Principal Investigator**
Dr. Rosenberg, as the Principal Investigator, is responsible for overall scientific direction and ethical conduct of the study.

Tiwonge Mtande, BA, Site Principal Investigator
Ms. Mtande, as the Site Principal Investigator, is responsible for overall operational function of the study. She is the in-country point of contact for all study activities, operations, and ethics. She will undertake study coordinator responsibilities. Half of her time will be dedicated to this study. She will supervise all study staff and ensure data integrity and ethical conduct of the study.

Mitch Matoga, MBBS, Co-Investigator
Dr. Matoga, as a Co-Investigator, is responsible for consultations on medical aspects of the study. He may use study data for his dissertation.

Twambilile Phanga, MBBS, Co-Investigator and Senior Research Officer
Ms. Phanga, as a Co-Investigator and Senior Research Officer will support procedures surrounding social harms and conduct periodic quality control activities.

Sam Phiri, PhD, MSc, Dip Clin Med, Co-Investigator
Dr. Phiri is the Director of the Lighthouse Trust, which employs many of the staff in the study clinic. He will ensure staff are appropriately allocated or trained.

Rose Kolola Nyirenda, Co-Investigator, Director Department of HIV and AIDS
Dr. Niyirenda is the Director of Malawi's Department of HIV and AIDS. In this role, she will serve as a liaison between the study and policy. She will be the knowledge-to-practice link in the study.

Mina Hosseinipour, MD, PhD, MPH, Co-Investigator
Dr. Hosseinipour is the Scientific Director of UNC Project. In this capacity, she will provide scientific direction to the study.

Suzanne Maman, PhD, Co-Investigator
Dr. Maman will provide guidance on qualitative aspects of the study.

William Miller, MD, PhD, MPH, Co-investigator
Dr. Miller will provide guidance on quantitative aspects of the study.

Work plan

Quarter	2017 Q2	2017 Q3	2017 Q4	2018 Q1	2018 Q2	2018 Q3	2018 Q4	2019 Q1	2019 Q2	2019 Q3	2019 Q4
Study preparation	×										
Implementation		×	×	×	×	×	×	×	×	×	
Enrollment period		×	×	×	×						
Six month visit				×	×	×	×				
Twelve month visit						×	×	×	×	×	
Analysis and publication										×	×

The study will have a one quarter preparation phase, a two-year implementation phase, and a half-year analysis and publication phase. During the implementation phase, each evaluation time point (enrollment, six-month visits, and twelve-month visits) is expected to last one year.

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