STUDY PROTOCOL

Adaptation of the Friendship Bench Mental Health Intervention for HIV-infected Perinatal Women in Lilongwe (Periscope)

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Full Research Protocol: UNCPM 21910 - Phase 2 - Adaptation of the Friendship Bench mental health intervention for HIV-infected perinatal women in Lilongwe.

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Appendices

Appendix 1 – English and Chichewa Informed consent forms (version 3.1, dated 09 September 2020)

Appendix 2 – English and Chichewa data collection instrument (version 1.0, dated 7 June 2019)

Abstract

The scale up of antiretroviral treatment (ART) to all pregnant and breastfeeding women, known as Option B+, has the potential to dramatically improve maternal health and end mother-to-child HIV transmission. However, lack of engagement in HIV care among peripartum women threatens to limit the positive impact of Option B+ on HIV care outcomes. Engagement in HIV care is likely to be adversely influenced by perinatal depression (PND), particularly in settings like Malawi where disengagement from HIV care and PND are common. Interventions that improve PND and address engagement in HIV care are urgently needed. Our **long-term goal** is to adapt, test, and scale up resource-appropriate interventions to reduce PND and improve engagement in HIV care among women taking ART under Option B+ in Malawi. Our **central hypothesis** is that the adaptation and further enhancement of the Friendship Bench intervention will reduce PND symptoms and increase HIV care engagement in this population. The **objective** of this proposal is to assess the feasibility, fidelity of delivery, and acceptability of an enhanced version of the Friendship Bench intervention in addressing PND and HIV care engagement among perinatal HIV-infected women. This proposal draws on our formative work on the experiences of PND and feasibility and acceptability of PND screening and treatment among HIV-infected perinatal women in Malawi. Our **specific aim** is to assess the feasibility, fidelity, and acceptability of the Enhanced Friendship Bench intervention to improve PND and engagement in HIV care among women taking ART under Option B+. Our multi-disciplinary team is uniquely positioned to address these aims given our expertise in PND, mental health, perinatal HIV and our extensive research experience in Malawi. The proposed work is **significant** because PND among HIV-infected women is common and likely to adversely affect perinatal engagement in HIV care. Mental health interventions exist, but their impact on PND and engagement in perinatal HIV care has not been explored. The proposed work is **innovative** because it is the first to assess how PND affects engagement in HIV care and gathers formative research needed to develop scalable treatment options. Completion of the proposed aims will directly lead to an adapted counseling intervention protocol to improve PND and perinatal engagement in HIV care among perinatal HIV-infected pregnant women in a subsequent R01 (large scale randomized controlled trial) application.

A. BACKGROUND AND JUSTIFICATION

The scale up of antiretroviral treatment (ART) to all pregnant and breastfeeding women, known as Option B+, has the potential to dramatically improve maternal health and end mother-to-child HIV transmission.[1] However, lack of engagement in HIV care among peripartum women threatens to limit the positive impact of Option B+ on HIV care outcomes. In Malawi, women who initiate ART during pregnancy under Option B+ are 5 times as likely to not return to HIV care after their initial visit, compared to non-pregnant women initiating ART.[2] For Option B+ to improve HIV care outcomes at a population level, women must remain engaged in HIV care.

Engagement in HIV care is likely to be influenced by perinatal depression (PND). Worldwide, PND (onset of depression during pregnancy or the first 3-6 months postpartum[3,4]) affects 10-15% of women during pregnancy and up to 20% of women postpartum, with higher rates seen in lower income countries.[5-7] PND causes potentially devastating consequences to women, their infants and families.[8-11] Depression also disproportionately affects people living with HIV,[12,13] leading to poor ART adherence, reduced retention in care, and ultimately worse clinical outcomes – all important aspects of engagement in HIV care.[14-20] Despite the high burden of PND and negative effects of depression on HIV outcomes in non-pregnant populations, the impact of PND on engagement in perinatal HIV care has received little attention.

Consequently, understanding how PND affects women's health and engagement in HIV care is a high priority.[21-23] Women in Malawi are not currently screened for PND and treatment is rare. Growing literature shows that counseling interventions delivered by non-specialists in resource-limited settings can improve depression outcomes.[24-31] Yet, the feasibility and acceptability of expanding such interventions to HIV-infected perinatal women has received limited attention,[32] and the possibility of enhancing mental health interventions to simultaneously address perinatal engagement in HIV care has not been explored.

Our **long-term goal** is to adapt a culturally and resource-appropriate intervention for HIV-infected women with PND.

B. HYPOTHESES

Our **central hypothesis** for this pilot study is that our enhanced Friendship Bench intervention will prove feasible and acceptable to providers and women, and will be delivered with fidelity by study staff. This will lay the groundwork for a future study that will test whether the intervention reduces PND symptoms and increases HIV care engagement among HIV-infected women with PND.

C. OBJECTIVES

The **objective** of this proposal is to adapt and enhance the Friendship Bench and assess its feasibility, fidelity of delivery, and acceptability in addressing PND and HIV care engagement among perinatal HIV-infected women. This proposal draws on our formative research on the experiences of PND and feasibility and acceptability of PND screening and treatment among HIV-infected perinatal women in Malawi. To address our main objective, our specific objectives are:

1. **To assess the feasibility of the Enhanced Friendship Bench intervention to improve PND and engagement in HIV care;**
2. **To assess the fidelity of the Enhanced Friendship Bench intervention to improve PND and engagement in HIV care, and;**
3. **To assess the acceptability of the Enhanced Friendship Bench intervention to improve PND and engagement in HIV care.**

D. LITERATURE REVIEW

PND is common among women worldwide, and is a leading cause of maternal morbidity.[6] PND is defined as onset of depression during pregnancy and/or within the first 3-6 months postpartum.[3,4] About 10-15% of women experience depression prenatally and ~20% of women become depressed postnatally, with higher rates seen in lower income countries.[5-7,33] PND, like depression generally, may be very common among HIV-infected women: our group's recent meta-analysis of PND among HIV-infected women in sub-Saharan Africa found a pooled prevalence of 42.5% for prenatal and 30.7% for postnatal depression.[34]

PND adversely affects the health of women, their infants and families. In the general population, PND has been associated with an increased risk for low birth weight and prematurity, impaired mother-infant attachment, and infant malnutrition during the first year of life.[5,10,11,35] Women living with HIV are already at an increased risk of adverse pregnancy and infant health outcomes,[36,37] and may be at particularly high risk of PND.[9,38] Consequently, addressing PND in HIV-infected women may have several maternal-child health benefits.[21,22]

PND may be a barrier to the success of Option B+, the rapidly expanding effort to initiate all HIV-infected pregnant women on lifelong ART.[39,40] Option B+ is expected to have major benefits by preventing vertical HIV transmission, improving maternal health, and reducing onward sexual transmission. However, the realization of these benefits requires engagement in HIV care, which has emerged as a major challenge and priority area of research for the National Institute of Mental Health (NIMH). In Malawi, up to 30% of women are lost to HIV care within 6 months of starting ART[2,41] and globally just 28% of HIV-exposed infants are tested for HIV within 2 months of birth.[42,43] Given the strong and consistent associations between depression and HIV outcomes in general (non-pregnant) HIV-infected populations[14-20], women with the dual burden of HIV and PND may be at particularly high risk for disengagement from HIV care.[44]

Evidence-based PND interventions exist, but they have not been adapted to the unique needs of HIV-infected women. We proposed to adapt The Friendship Bench, an evidence and theory-based counseling intervention that improves depression in the general population.[24,45] Friendship Bench uses problem-solving therapy[46,47] to help participants identify a problem they can address, such as barriers to attending their HIV visits, during counseling sessions with trained, supervised lay healthcare workers. The Friendship Bench has been adapted to address PND among postpartum women[32], but has not been adapted to the specific needs of HIV-infected women. HIV-infected women with PND face unique issues surrounding disclosure to their partner, stigma related to HIV and PND, concerns over perinatal HIV transmission, and barriers to ART adherence and retention in HIV care. For these reasons, PND among HIV-infected women may lead to suboptimal engagement in HIV care. Addressing these issues through evidence-based interventions is essential to address NIMH's research priorities of supporting engagement in HIV care and improving HIV care outcomes.

The goal of the proposed developmental award is to gather formative research for a R34 application to develop a scalable, culturally sensitive intervention to address PND among HIV-infected women. After the completion of our specific aims we will have gathered information on: 1) women's experiences pre and postnatally with PND, how PND affects perinatal engagement in HIV care, and preferences on counseling and pharmacological treatment; 2) the feasibility of provider screening for PND in high-volume antenatal/ART clinics; and 3) and adapted the Friendship Bench intervention to address PND and its possible impact on engagement in HIV care. Information gathered in this proposal will lead to a R34 application to pilot test our adapted intervention, and a subsequent R01 application to test our intervention in a randomized controlled trial.

E. INNOVATION

The proposed project is innovative in two important ways:

1) **This will be the first project to evaluate how PND affects engagement in HIV care during the peripartum period.** By gathering rich, qualitative data among HIV-infected women with PND in the prenatal and postnatal periods, we will explore women's experiences of PND and how those experiences influence ART adherence, retention in HIV care, and behaviors around infant HIV testing.
2) **We will gather the in-depth information needed to adapt a scalable perinatal counseling intervention for HIV-infected women,** with the goal of improving PND and engagement in HIV care.

F. METHEDOLOGY

F1. Environment and Team

Dr. Brian Pence, PI, is an Associate Professor of Epidemiology who has led research for 15 years on the identification and treatment of mental health disorders among people living with HIV in the US and Africa. He is supported in the US by **Dr. Samantha Meltzer-Brody**, a Professor of Psychiatry with particular expertise in perinatal mood disorders who recently launched an initiative to integrate depression screening into maternal waiting homes in Malawi, **Dr. Go,** Professor of Health Behavior, an expert in qualitative and mixed methods research, **Dr. Angela Bengtson**, epidemiologist and postdoctoral trainee at Brown University whose recently funded NIMH K99 award focuses on retention in HIV care among perinatal HIV-infected women, and **Dr.**

Bradley Gaynes, psychiatrist who has collaborated on several studies of mental health integration in Malawi. The team further includes **Dr. Mina Hosseinipour**, Scientific Director at UNC Project-Malawi, **Dr. Dixon Chibanda**, psychiatrist at the University of Zimbabwe, developer of the Friendship Bench and a leader in developing task-shifting models for treating mental health disorders in low-income countries; **Dr. Kazione Kulisewa**, Malawian psychiatrist leading mental health reform efforts in Lilongwe; and **Mr. Michael Udedi**, Assistant Director of Clinical Mental Health Services at the Malawi Ministry of Health. These team members have all collaborated together previously on mental health research and service initiatives in Malawi. Overall this impressive and experienced team is well positioned to successfully implement this high-impact project.

F2. Study Design: We will conduct a clinic-level pilot study among five clinics. Three of the five clinics initially served as primary study sites and were assigned to one of 3 conditions: 1) Adapted Friendship Bench (AFB; n=1 clinic/35 women), 2) Enhanced Friendship Bench (EFB; n=1 clinic/35 women) or 3) Enhanced Usual Care (n=1 clinic/35 women).

In June 2020, it was clear that due to both low patient volume and COVID-19 delays, recruitment targets would not be met at these three sites. Therefore recruitment is on hold at these sites and resources will be focused on launching activities at two new larger sites: Bwaila and Area 18. These sites will employ individual-level randomization of the study intervention. Participants will be enrolled at an ANC visit prior to or including 34 weeks gestation and followed through 6 months postpartum.

F3. Study Setting and Site: The proposed study will be at conducted at five public antenatal clinics in Lilongwe District, Malawi: Lumbadzi, Mitundu Nathenje, Area 18, and Bwaila health centers. Each of the five health centers provides ART services to HIV-infected women through the antenatal clinic during pregnancy, and also has separate ART clinics serving non-pregnant HIV-infected adults on the health center grounds. In Malawi, HIV-infected pregnant women typically initiate ART at an antenatal care clinic, and transition to an HIV clinic for care after delivery. Thus, the co-location of antenatal and ART services makes these health centers the ideal locations to serve HIV-infected women as they transition from receiving HIV care prenatally in an antenatal clinic, to postnatally in an ART clinic.

In Malawi, all pregnant women presenting for care receive opt-out HIV testing at their first antenatal care visit. Women who test HIV+ undergo adherence counseling and start ART the same day. PND screening and assessment are rare to nonexistent at antenatal/ART clinics in Lilongwe, as in most clinical settings in Malawi.

UNC Project in Lilongwe will serve as the administrative home for the study and has longstanding relationships with Bwaila FHU, antenatal/ART clinics in Lilongwe, and the Ministry of Health.

F4. Study Population:

Women (92 total): As of this protocol v3.2, we have recruited a total of 12 women from our original 3 clinics. As we launch activities at our two new clinics and reduce to 2 arms, we will seek to recruit 40 new participants per arm or 80 new participants total, for a total enrollment of 92 participants. All 92 women will contribute to analyses of feasibility and acceptability, but only the new 80 women will contribute to between-arm comparisons due to the differences in sites.

We will include 92 HIV-infected, depressed women initiating, re-initiating, or continuing ART who engage in ANC and are identified with antenatal depression at ≤34 weeks gestation to allow sufficient time for approximately 4 prenatal counseling sessions and approximately 2 postnatal counseling sessions. Women with a score ≥10 on the EPDS[48,49] and/or ≥ 8 on the SRQ-20 will be considered to be depressed and will be invited to participate.

Inclusion criteria:

- HIV-infected, pregnant women initiating, re-initiating, or continuing ART during antenatal care (ANC)
- ≤34 weeks gestation to allow sufficient time for approximately 4 prenatal counseling sessions and approximately 2 postnatal counseling sessions.

- Screened positive for depression with a score ≥ 8 on the SRQ-20
- At least 18 years of age

Feasibility of recruitment – Approximately 30 HIV-infected women initiate or re-initiate ART monthly at each of the study sites, or 150 women over 6 months, with ~90% presenting at ≤30 weeks. Based on our group's systematic review[34], we conservatively estimate 30% of HIV-infected women will have antenatal depression, suggesting that enrolling ~6 women per site per month is feasible. Utilization of two additional clinics will aid in timely participant recruitment should enrollment at the three primary sites lag behind expected targets.

Psychosocial counselors (n=4 total): Trained psychosocial counselors will be identified to administer counseling sessions for both the AFB and EFB arm. We will recruit 2 female counselors for each primary intervention arm clinic to complete up to 4 individual prenatal counseling sessions and up to 2 postnatal group sessions (approximately 100 counseling sessions per counselor total over 4-6 months, and ~ 20 counseling sessions per counselor per month). Group counseling will be offered on multiple days; each group will have 5-8 women attending 2 sessions.

Research Assistants (n=3): Trained research assistants will be hired to conduct participant screening and to complete baseline and 6-month data collection with all participants at each of the five study clinics. Research assistants will spend the majority of their time in each of the three primary study sites and rotate between the remaining two clinics as needed.

Supervisors (n=2): Supervision for counselor will be provided by the study mental health professionals (n=2).

F6. Pilot Trial Arms

We have adapted the Friendship Bench intervention to meet the particular needs of HIV-infected women with PND and enhanced it to additionally support engagement in perinatal HIV care. We will conduct a pilot trial, comparing Enhanced Friendship Bench (EFB), to enhanced standard care (ESC).

1. Arm 1: Adapted Friendship Bench (AFB - DROPPED) – [Note: This arm is no longer included in the trial as of protocol v3.1, but this text is retained to aid with understanding Arm 2.] The existing Friendship Bench intervention protocol has been adapted to address the unique needs of HIV-infected women. AFB will include 4 individual prenatal counseling session (in-person or by phone) and 2 group postnatal counseling sessions. No specific retention support will be provided, but participants may identify barriers to engagement in HIV care to address during their pre- or postnatal counseling sessions.

Prenatal counseling sessions (n=4) will be facilitated by psychosocial counselors and are designed to align with the WHO's recommended 4 antenatal care visits. However, since many women in sub-Saharan Africa do not attend all 4 antenatal sessions, prenatal counseling sessions can occur outside antenatal visits, including by phone. The first session includes three components called Opening the Mind, Uplifting, and Strengthening, with subsequent sessions building on the first. Opening the Mind refers to the therapeutic process by which, through asking questions, clients are encouraged to open their minds to identify their problems, choose one to work on, identify a feasible solution, and agree on an action plan through an iterative process guided by the counselor. Each structured session lasts 30-45 minutes and will be conducted in a private clinic room, or by phone, in participant's local language (Chichewa). Participants will receive up to 4 text messages, phone calls, or both during their treatment course to reinforce the PST approach and encourage them to follow their action plan. After 4 sessions of individual prenatal therapy, the counselor can refer participants not improving or with suicidal ideation to a supervisor trained in mental health to reassess and manage the case. Case management may include additional counseling or pharmacotherapy, at the discretion of the managing clinician.

Postnatal counseling sessions (n=2) will be facilitated by a psychosocial counselor. In Malawi, HIV-infected women transition from receiving HIV care at an antenatal clinic to an ART clinic, typically by 6 weeks postpartum. Postnatal group counseling session will occur after a woman has transitioned to receiving care at an HIV clinic. In the Adapted Friendship Bench arm, women will be invited to attend 2 postnatal group-counseling sessions. Postnatal group counselling sessions will be scheduled to coincide with a woman's

regularly scheduled ART visits. All sessions will include 5-8 women and will take place on a variety of days to accommodate women's varying ART clinic appointment schedules. Group counseling sessions will last ~60 minutes and will be conducted in a semi-private clinic location in Chichewa.

2. Arm 2: Enhanced Friendship Bench (EFB) - EFB will include all elements of AFB, but will additionally integrate retention strategies. Retention Strategy 1. Strengthening social support: To provide additional social support for participants, we will add one (optional, recommended) "person important to me" session to the AFB. At this session, the participant will be invited to bring with her to one session a person of her choice who can be a support to her in managing both her HIV and/or depression, such as a partner, friend, or companion. To reduce the risk of inadvertent disclosure of one's HIV or depression status, prior to this social support session, we will ask all participants beforehand whether the person that she identified knows her HIV and depression status. If they do not, we will discuss risks with her before proceeding as she wishes. The social support session may be conducted in person, in a private clinic room, or by phone. Retention Strategy 2. Home visits: In our formative research, perinatal women discussed their barriers to attend clinic visits to pick up their meds, especially during late stages of pregnancy and immediately following birth. One common suggestion the women discussed to support HIV care engagement was home visits when they were unable to attend clinic. To assist women with receiving their medication during late pregnancy and postpartum, we will conduct up to six home visits in the EFB arm. To preserve patient confidentiality, prior to initiating home visits the participant and her counselor will agree on a "cover story" for the counselor's identity when she comes to visit ("This is my aunt from…"). The counselor will be able to deliver her medications. The counselor will also conduct a counseling session, if they have enough privacy to do so. Home visits may begin monthly starting in the third trimester and continuing through up to 6 months postpartum. The participant may decline home visits, if for example she is concerned that the home visit would pose a risk for her with her community or family.

3. Enhanced Standard Care (ESC). Standard care for mental health in public facilities in Malawi includes options for basic supportive counseling by the primary provider or nurse, medication management by the primary provider, referral to the clinic psychiatric nurse or mental health clinic (most clinics have either an assigned psychiatric nurse or a mental health clinic that visits on a rotating basis), or in more severe cases referral to the psychiatric units at tertiary care hospitals (in the Lilongwe region, this is Bwaila Hospital). For this study, standard care will be enhanced by a trained study research assistant who will provide mental health screening; basic psychoeducation education on common mental disorders; and (if indicated) facilitation of referral to the clinic's psychiatric nurse or mental health clinic or to Bwaila Hospital. The RA will also ensure that the patient sees a nurse or clinical officer that day to evaluate whether the referral plan is appropriate and to ensure that the participant is safe to go home. The research assistant will have up to 3 follow-up contacts with the participant to assess whether she has followed up on recommended referrals or treatment plans and to assess whether any further outreach is indicated.[24]

F7. Intervention delivery and supervision – Our adapted and enhanced counseling interventions will be delivered by trained psychosocial counselors. Prior to study enrollment, counselors will be trained to deliver the Adapted Friendship Bench and Enhanced Friendship Bench interventions. During the pilot, counselors will be supervised by District Health Promotion Officers and the study psychiatrist.

- **Setting:** During the prenatal period, individual counseling sessions will be facilitated by counselors in a private location within the antenatal clinic, or via phone. Due to issues around stigma and disclosure for both HIV-infected and depressed women, individual, rather than group, counseling sessions will be preferable to ensure patient privacy in the antenatal clinic which serves the general pregnant population. During the postnatal period, group counseling sessions will be facilitated by counselors at a semi-private location on the grounds of ART clinics. The group counseling sessions will be described as "friendship groups", with no mention of PND, to reduce possible stigma associated with depression. ART clinics serve only HIV-infected women, reducing concerns about HIV-related stigma or disclosure.
- **Training**: counselors serving as counselors from both antenatal and ART clinics will attend a 2-week training. Topics included in the training will be PND, counseling skills, problem solving therapy, and self-care. Dr. Chibanda and members of his team will deliver the training. All training sessions will be audio-recorded for fidelity and assessed using a checklist to ensure the counselors had covered all the critical components.

- **Supervision**: counselors will be supervised and supported by the study's two mental health professionals (Dr. Kulisewa and Mr. Udedi) who will be contacted in the event that a client presents with very high scores on the EPDS or suicidality. A Friendship Bench trainer will provide weekly group supervision for counselors.

F8. Intervention Delivery and Data Collection. Prior to launch, each of the three primary clinics will be randomly assigned to Adapted Friendship Bench (AFB), Enhanced Friendship Bench (EFB) or enhanced standard care (ESC), with the exception of the fourth and fifth clinics which will individually randomize eligible participants to one of the two remaining study arms.

Screening and Enrollment HIV-infected women who are initiating, re-initiating, or continuing ART during pregnancy under the Option B+ will be informed about the study by their provider and invited to participate. Screening and enrollment procedures will take place on the same day as a woman's ANC visit. Women who consent to participate (Appendix 1) will be given an initial screening for perinatal depression or anxiety using the Patient Health Questionnaire (PHQ)-2 and/or the Generalized Anxiety Disorder (GAD)-2 as a part of routine antenatal care. Women who show symptoms perinatal depression or anxiety will be asked to complete the Edinburgh Postnatal Depression Scale (EPDS) and/or the Self-Reporting Questionnaire (SRQ)-20 with a trained psycho-social counselor to confirm symptoms (Appendix 2). Women who screen positively on either the PHQ-2/GAD-2, the EPDS ($\geq$10) or SRQ-20 ($\geq$8) will be invited to participate. Women screening positive for depression who choose not to participate will be referred to a mental health provider for care.

Study Visits (n=2 for participants in all arms)

Baseline Visit: At the baseline visit, women will be asked to fill out a questionnaire about their mental health, HIV, and reproductive health history. In addition to assessing depression with the EPDS, we will assess the prevalence of common mental disorders using the Self-Reporting Questionnaire (SRQ-20). The SRQ-20 was designed by the World Health Organization as a screening tool for common mental health disorders (CMD). The SRQ-20 has 20 questions exploring symptoms of depression, anxiety and somatic complaints, rather than a specific diagnosis of depression or anxiety. The SRQ-20 was validated in Malawi and is available in Chichewa.[50,51 50,51 50,51 50,51 50,51 50,51 50,51 50,51 50,51 50,51 50,51 48-51] A cut-point of 8 or above has been previously used in Malawi to identify probable CMD. The baseline interview will also assess socio-demographics, self-reported health, and key structural and psychosocial factors including trauma history, intimate partner violence (IPV), other violence in the home, socioeconomic measures, coping, social support, self-efficacy, and experiences of stigma related to HIV and mental health (Appendix 2). Measures of trauma, IPV, and other violence will be important for understanding participants' experience of depression in their broader socioecological context. We have used these measures previously in similar settings.

6-month Postpartum Visit: At 6 months postpartum, HIV-infected women will be asked to complete the EPDS and SRQ-20 either in-person of by phone. Viral load measures for all HIV-infected women will be collected by study personnel at 6 months postpartum. Information on HIV appointment attendance and infant HIV testing during the first 6 months postpartum will be collected from a participant's medical record, as we are doing in our ongoing USAID project. Information on infant anthropometry (length, weight, head circumference), infant physical health (presence of respiratory illness, diarrhea, and immunization records) and infant development, assessed using the Observation of Mother-Child Interaction (OMCI) guide, the PAMANED Study Family Care Indicators Questionnaire in Chichewa, and the WHO Indicators of Infant and Young Child Development (IYCD) Item guide, which have been validated for use in children as young as 4 months of age, will also be collected (Appendix 2).The OCMI portion of the 6 month postpartum visit will be video-recorded to review the fidelity rating after the visit has occurred. HIV-infected women, counselors and supervisors will be asked to complete a brief exit interview either in-person or by phone to assess the feasibility and acceptability of the intervention.

Counseling Sessions (EFB n= up to 7; ESC, n=0):
Women will be followed from study enrollment at their ANC visit through 6 months postpartum. Women in the

AFB and EFB arms will receive approximately 4 prenatal individual counseling sessions and approximately 2 optional, but recommended postnatal group counseling sessions (n=up to 6 counseling session). Women in the EFB arm will receive up to the same number of counseling sessions (4 prenatal and 2 postnatal) as women in the AFB arm, with an additional social support session described in section F6 (n=up to 7 counseling sessions). Women in the ESC arm will not receive counseling sessions, but will receive psychoeducation from a trained research assistant, referrals as needed, and follow-up calls to assess whether referrals were acted on and whether any further unmet mental health needs remain (n=0 counseling sessions). Counseling sessions will take place every 1-2 weeks at the antenatal care clinic, or via phone, during the prenatal period and approximately monthly during the postnatal period to coincide with routine ART refill visits.

Data Collection: At each counseling session (prenatal and postnatal) women will be asked to complete the EPDS and SRQ-20 to assess their mental health status.

F9. Outcomes – The primary goal of this R34 application is to evaluate the feasibility, acceptability, and fidelity of a counseling intervention to improve PND and engagement in HIV care among HIV-infected women. Recognizing the small sample size, indicators of preliminary effectiveness of the intervention for mental health and engagement in care outcomes will be reported as secondary outcomes. Primary and secondary outcomes will be assessed at 6 months postpartum and compared across the study arms.

F9.a. Primary Outcomes:
Feasibility will be defined as the ability to successfully enroll and retain HIV-infected, depressed women in the pilot intervention. Feasibility will be assessed as the number of women enrolled, a comparison of planned to actual enrollment and reasons for non-enrollment, and the proportion of women retained in each arm at 6 months postpartum.

Acceptability will be defined as the ability to deliver a culturally and resource-appropriate intervention. Acceptability will be assessed through brief exit interviews among a subset of HIV-infected women. Exit interviews will include both closed and open-ended questions and will assess how easy the intervention was to participate in or deliver, the perceived usefulness of the intervention, and suggestions for improvement.

Fidelity will be defined as adherence to the intervention protocol. Fidelity to session content for both individual and group counseling sessions will be assessed by members of the Friendship Bench team (DHO or study psychiatrist), by using a checklist of intervention characteristics either during direct monitoring or using audio recording of up to 3 randomly chosen sessions per counselors. Scoring either 'meeting expectations' or 'exceeding' expectations' on at least 80% of applicable checklist items during each session will be considered fidelity to the intervention protocol.

F9.b. Secondary Outcomes: Secondary outcomes will be used to provide preliminary information about effectiveness at 6 months postpartum, taking into consideration the limited sample size for the pilot project**.** Composite outcome: Retained in HIV care, with improved depression: We will assess a combined outcome at 6 months of whether a woman attended an HIV visit within the last 30 days and achieved remission (defined as ≥50% improvement in SRQ-20 score from baseline and an SRQ score <8). We will compare the following additional outcomes at 6 months postpartum: Self-Reporting Questionnaire (SRQ-20): The proportion of women reporting a score ≥8; Retention in HIV Care: (a) The proportion of women who attended an HIV care visit in the last 30 days; (b) considering the increase in visit spacing during the COVID-19 pandemic, we will consider a second definition of retention in HIV care of at least 2 visits at least 30 days apart in the first 6 months postpartum; Viral Load Suppression**:** The proportion of women with a HIV RNA level <1000 copies/mL; Infant health: the proportion of women whose infants received an HIV RNA test .

F10. Statistical Analysis – Baseline mental health, HIV, and reproductive health characteristics of women will be compared across 2 study arms using t-tests for continuous variables and chi-square tests for categorical variables to assess balance across study arms. **Primary Outcomes** – Quantitative measures of feasibility, acceptability, and fidelity will be summarized using means and standard deviations or proportions and compared across arms using statistical models for continuous or binary outcomes, as appropriate. Specifically,

we will compare the mean number of women enrolled and the proportion of women retained in EFB or ESC through 6 months postpartum (feasibility); the proportion of participants who found the intervention easy to administer and helpful (acceptability), and the proportion of counseling sessions scoring either 'meeting expectations' or 'exceeding' expectations' on at least 80% of applicable checklist items (fidelity) across study arms. **Secondary Outcomes** will be analyzed as above at 6 months postpartum across 2 study arms. In addition, statistical models examining differences in SRQ-20 scores at 6 months will be generalized linear models.

F11. Sample Size. The primary goal of this R34 proposal is to evaluate the feasibility, acceptability, and fidelity of the adapted and enhanced Friendship Bench intervention to improve PND and engagement in HIV care among HIV-infected women. In Aim 3, we will enroll 92 HIV-infected women with PND in a 2-arm pilot (n=12 total in the clinic-randomized phase, n=40 women per arm in the individually randomized phase) to compare enhanced standard care with the enhanced Friendship Bench intervention. Information on preliminary effectiveness of the intervention across a range of mental health and engagement in HIV care outcomes will be assessed, but interpreted cautiously as effectiveness is not the primary aim of this pilot study. Intervention effectiveness will subsequently be assessed in a large-scale clinic-randomized controlled trial. Given that the objective of this analysis is to estimate feasibility, acceptability, and fidelity of the described interventions, feasible sample sizes (n=40/arm; 92 including both the clinic-randomized and individually randomized phases) were determined according to clinic patient volumes and estimated perinatal depression among women living with HIV in the study setting. Precision estimates for the given sample size are based on two-tailed statistical significance tests and a Type 1 error probability (α) of 0.05. The sample of 92 women (40 per arm) will be sufficient to estimate quantitative measures of feasibility and acceptability with reasonable precision (e.g., confidence intervals around proportions of ±5-9 percentage points across all arms, and ±9-17 percentage points within a given arm). This margin of error was estimated using a desired sample size of 92 and population feasibility and acceptability proportions ranging from 10 to 50%.

E. Potential Challenges and Solutions

What if women are lost to follow-up (LTFU) between pre and postnatal care? Our proposal directly addresses the high rate of LTFU in the postnatal period[2,52] for women on Option B+ by providing linkage to care coordination from the antenatal to ART clinic and measuring engagement in care through 6 months postpartum. The information gathered at the pilot stage will help to inform the design of a large-scale randomized controlled trial to improve PND and engagement in HIV care during the peripartum period.

Will group counseling sessions be difficult to coordinate among multiple women? Our team has successfully coordinated group counseling sessions as a part of the original Friendship Bench intervention,[24] and among postnatal women.[32] Uptake of group counseling sessions has been very high and it has been feasible to integrate the group counseling sessions into routine clinical care.

What other retention support is available to HIV-infected women and how will this influence this study? During this pilot phase, we will carefully record what other retention support is available to HIV-infected women at the study sites and other area clinics, and how frequently women access these services. Currently at our five sites these services consist of tracing patients who have defaulted for >2 months. Tracing is done either by clinic personnel, depending on available MoH funding for transportation, or by staff of the local NGO Lighthouse Trust through PEPFAR and CDC funding. A time-updated understanding of available retention support services will be critical in order to design the subsequent RCT to test the effectiveness of the Friendship Bench in improving PND and engagement in HIV care.

G. Timeline for Work Plan

Timeline	2019					2020				2021	
	Aug	Sep	Oct	Nov	Dec	Q1	Q2	Q3	Q4	Q1	Q2
Continued planning and development	■										
Post job openings and hire staff		■									
Staff training			■								
Launch 3-arm pilot trial			■								
Pilot accrual and follow-up; Fidelity monitoring			■	■	■	■	■	■	■		

Exit Interviews								[redacted]		
Data analysis, manuscript preparation, RCT planning									[redacted]	

H. Dissemination of Results
Results from this study will be shared with the Community Advisory Board at UNC-Project and other key stakeholders, including HIV-infected women, community members, HIV and mental health providers, the National Health Sciences Research Committee, and Ministry of Health officials in Malawi. We will also disseminate our results through presentation at international scientific conferences focused on HIV, mental health, or women's health and through publication in peer-reviewed journals.

I. Impact and Future Directions: PND is extremely common in sub-Saharan Africa and negatively affects women, infants, and communities. For HIV-infected women, PND may also adversely affect perinatal engagement in HIV care, putting them at an even greater risk of poor HIV outcomes. Resource-appropriate interventions to address PND, and its possible impact on engagement in HIV care, are urgently needed. The information gathered in this proposal will lead to an R01 application to test our intervention in a randomized controlled trial.

J. Protection of Human Subjects
This Human Subjects Research meets the definition of clinical research. The data collection and analyses outlined in this proposal will be reviewed by the University of North Carolina Institutional Review Board, in the U.S., and the Malawi National Health Sciences Research Committee (HSRC) before any data collection or analysis occurs.

The study will also be reviewed and informed by the existing community advisory board (CAB) of UNC Project in Malawi. The CAB will review the study protocol prior to implementation and provide feedback. The CAB meets monthly.

1. Risks to Human Subjects

a. Human Subjects Involvement and Characteristics
In our pilot study, we will recruit 92 prenatal HIV-infected women who consent to participate and screen positive for mental health disorders during pregnancy on the EPDS or SRQ-20 questionnaires, indicating perinatal depression (PND) or common mental health disorders. Psychosocial counselors (n=4), research assistants (n=3), and supervisors (n=2) will be considered a secondary population. The goal of or study is to evaluate the feasibility, acceptability, and fidelity of the enhanced Friendship Bench intervention to improve PND and engagement in HIV care among HIV-infected women. Women will be recruited from the Lumbadzi, Mitundu, Nathenje, Area 18, and Bwaila healthcare centers in Lilongwe, Malawi when they present for prenatal care initiation and are HIV-positive. All women who screen positive for depression will be referred for mental health treatment to the nearest provider.

Rational for including pregnant women: Option B+ is a program of the Malawi Ministry of Health to provide lifelong ART to all HIV-infected women who are pregnant. A critical component to the success of Option B+ is keeping women engaged in HIV care – something that has emerged as a challenge since Option B+'s inception in Malawi. Women with PND may be at an increased risk of disengaging from HIV care. Our project includes pregnant women in an effort to improve treatment options for PND among this population, with the goal of also improving engagement in HIV care and ultimately the effectiveness of Option B+.

The study characteristics of the study population are expected to be similar to those of all HIV-infected, peripartum women with PND in public healthcare centers in Lilongwe, Malawi.

Participants who live outside of the Lilongwe District or are less than 18 years old will be excluded.

b. Sources of Materials

All data will be gathered specifically for the purpose of the study. For Aim 1, women will undergo a screening and enrollment visit (baseline), up to six counseling sessions, and will have outcomes assessed at 6 months.

Screening and Enrollment HIV-infected women who are initiating, re-initiating, or continuing ART during pregnancy under the Option B+ will be informed about the study by their provider and invited to participate. Screening and enrollment procedures will take place on the same day as a woman's ANC visit. Women who consent to participate (Appendix 1) will be given an initial screening for perinatal depression or anxiety using the Patient Health Questionnaire (PHQ)-2 and/or the Generalized Anxiety Disorder (GAD)-2 as a part of routine antenatal care. Women who show symptoms perinatal depression or anxiety will be asked to complete the Edinburgh Postnatal Depression Scale (EPDS) and/or the Self-Reporting Questionnaire (SRQ)-20 with a trained psycho-social counselor to confirm symptoms (Appendix 2). Women who screen positively on either the PHQ-2/GAD-2, the EPDS (≥10), or SRQ-20 (≥8) will be invited to participate. Women screening positive for depression who choose not to participate will be referred to a mental health provider for care.

Study Visits (n=2 for participants in all arms)

Baseline Visit: At the baseline visit, women will be asked to fill out a questionnaire about their mental health, HIV, and reproductive health history. In addition to assessing depression with the EPDS, we will assess the prevalence of common mental disorders using the Self-Reporting Questionnaire (SRQ-20). The SRQ-20 was designed by the World Health Organization as a screening tool for common mental health disorders (CMD). The SRQ-20 has 20 questions exploring symptoms of depression, anxiety and somatic complaints, rather than a specific diagnosis of depression or anxiety. The SRQ-20 was validated in Malawi and is available in Chichewa.[50,51] [50,51] [50,51] [50,51] [50,51] [50,51] [50,51] [50,51] [50,51] [50,51] [50,51] [48-51] A cut-point of 8 or above has been previously used in Malawi to identify probable CMD. The baseline interview will also assess socio-demographics, self-reported health, and key structural and psychosocial factors including trauma history, intimate partner violence (IPV), other violence in the home, socioeconomic measures, coping, social support, self-efficacy, and experiences of stigma related to HIV and mental health (Appendix 2). Measures of trauma, IPV, and other violence will be important for understanding participants' experience of depression in their broader socioecological context. We have used these measures previously in similar settings.

6-month Postpartum Visit: At 6 months postpartum, HIV-infected women will be asked to complete the EPDS and SRQ-20, either in person or by phone. Viral load measures for all HIV-infected women will be collected by study personnel at 6 months postpartum. Information on HIV appointment attendance, infant birthweight, and infant HIV testing during the first 6 months postpartum will be collected from a participant's medical record, as we are doing in our ongoing USAID project. Information on infant anthropometry (length, weight, head circumference), infant physical health (presence of respiratory illness, diarrhea, and immunization records) and infant development, assessed using the Observation of Mother-Child Interaction guide, the PAMANED Study Family Care Indicators Questionnaire in Chichewa, and the WHO Indicators of Infant and Young Child Development (IYCD) Item guide, which have been validated for use in children as young as 4 months of age, will also be collected (Appendix 2). HIV-infected women, counselors and supervisors will be asked to complete a brief exit interview, either in person or by phone, to assess the feasibility and acceptability of the intervention.

Counseling Sessions (EFB n= up to 7; ESC, n=0):
Women will be followed from ART initiation through 6 months postpartum. Women in the EFB arm will receive approximately 4 prenatal individual counseling sessions and approximately 2 optional, but recommended postnatal group counseling sessions (n=up to 6 counseling session). Women in the EFB arm will receive an additional social support session described in section F6 (n=up to 7 counseling sessions). Women in the ESC arm will not receive counseling sessions, but will receive psychoeducation from a trained research assistant, referrals as needed, and follow-up calls to assess whether referrals were acted on and whether any further unmet mental health needs remain (n=0 counseling sessions). Counseling sessions will take place every 1-2 weeks at the antenatal care clinic, or via phone, during the prenatal period and approximately monthly during the postnatal period to coincide with routine ART refill visits.

Data Collection: At each counseling session (prenatal and postnatal) women will be asked to complete the

EPDS and SRQ-20 to assess their mental health status [50,51]

All data will be collected by trained research assistants and stored in a database on the secure UNC Project Server, which only the PI will have access to. For each aim, participants will be assigned a study identification number. This study identification number will be linked to their name and clinic site through a separate log book. The log book will be kept at UNC Project's offices in a locked cabinet. At the conclusion of the study the link between the participant's name and study number will be destroyed. The principal investigator will be the only person with access to the subject identities.

c. Potential Risks – Including for Pregnant Women

Potential risks to the study population include loss of confidentiality and social harms to participants. Loss of confidentiality could include disclosure of HIV status. Social harms include emotional harm, economic or financial harm to the participant related to a woman's HIV or PND status being disclosed. While study participants will be pregnant at baseline, we do not anticipate any additional risks to women or their fetuses by being involved in the study. Procedures to protect against these risks are described below.

2. Adequacy of Protection against Risks

a. Recruitment and Informed Consent

The research study will be described briefly to all women initiating, reinitiating, or continuing ART at Lumbadzi, Mitundu, Nathenje, Area 18, and Bwaila healthcare centers in Lilongwe while they wait in the reception area. Once a participant is determined to be eligible for the study and following the standard post-test counseling, a trained interviewer will complete an informed consent process with each participant in their native language, Chichewa. During the informed consent process, the counselor will describe the procedures to be followed, the risks and benefits of participation, the duration of participation, and the steps taken to protect participant's confidentiality, particularly with respect to keeping all personal and private information (such as HIV and PND status) private. Illiterate participants may sign the consent form via thumbprint, in the presence of an impartial witness (Appendix 1). Any questions or concerns about privacy will be answered by the counselor or referred to the PI, who will address them. HIV-infected women initiating, reinitiating, or continuing ART prenatally who screen positive for perinatal depression or anxiety on the PHQ-2, GA-2, EPDS (≥10) or SRQ-20 (≥8) measure, and who consent to participate will be enrolled. All women who screen positive for PND will be referred to outpatient psychiatry services that are currently available and staffed by master's level nursing staff that can prescribe antidepressant medications.

Written informed consent will be obtained from each participant and participants will be provided with a copy of their informed consent forms if they are willing to receive it (Appendix 1). Study staff will document the informed consent process.

b. Protection against Risk

Risks of loss of confidentiality or social harms to participants will be minimized by: 1) training of study staff in the ethical conduct of research; 2) strict protection of confidentiality and personal information; 3) close monitoring of social harms with appropriate IRB reporting.

Discussing personal information – Data collection will include asking women about their mental health, social support, alcohol use and intimate partnerships. All data associates will be trained to keep all information confidential. Research assistants will be trained, and participants informed, that they can pause or discontinue a research interview at any time if they find the topic upsetting.

Data security - All study data, including interview guides, audio recordings of interviews, interview transcribes, and logbooks will be kept in a locked cabinet at the UNC Project data center, where they will be maintained in a locked office at UNC Project accessible only to the principal investigator. Interviews that are transcribed and computerized will be stored on the secure central server at UNC Project. For analysis purposes, data will be de-identified before coding and analysis. Only the principal investigator, data entry personnel, and assigned data analysts will have access to the de-identified electronic study database. Video recordings will be

transferred onto the OneDrive secure server with access restricted to study personnel, where they will be reviewed to verify the accuracy of the interviewer rating.

Home visits for women - For women who receive home visits as part of the EFB, information on the participant's HIV status or the nature of the home visitor's interest in visiting the participant will not be disclosed. All women presenting to HIV clinic sites and accepting the services are considered fully protected by the policies and guidelines outlined in the Government of Malawi's 'National HIV/AIDS Policy, October 2003', 'HIV/AIDS Counseling and Testing, Guidelines for Malawi, Second Edition, 2004'. No participants will be identified in any report or publication about this study.

3. Potential Benefits of the Proposed Research to the Subjects and Others

This study has some minimal risks associated with participation and we anticipate that few participants will experience negative events as a result of taking part in the study. This research will improve our understanding of how an adapted and enhanced counseling intervention may improve PND and engagement in HIV care. Long-term, supporting HIV-infected women with PND through a counseling intervention carried out by counselors is expected to reduce PND, improve engagement in HIV-care, and ultimately improve women's health and HIV outcomes. Therefore, the risk to individual participants in the study is small and the potential benefit to society is substantial.

Individuals participating in study research interview visits will receive a transport reimbursement of 7,000 Malawian kwacha (about US$10) at the completion of the baseline and 6-month interviews. Individuals participating in counseling sessions will receive a transport reimbursement of 3,500 Malawian kwacha (about US$5) at the completion of each counseling session.

4. Importance of the Knowledge to be Gained

This project will provide important information about whether an adapted and enhanced counseling intervention is a feasible and acceptable strategy to improve PND and engagement in HIV care among HIV-infected women. Disengagement from HIV care is a critical issue among women taking ART under the Option B+ program. In the general HIV-infected population, depression has been identified as an important detriment to retention in HIV care. Rates of PND are high among HIV-infected women in Malawi. However, the importance of addressing PND in the context of retention in care support has received little attention. The proposed project builds on formative research on women and healthcare providers' experiences with and preferences for treating PND among HIV-infected women through qualitative interviews, and uses that information to launch a pilot study testing culturally-adapted and enhanced forms of an existing, evidence-based counseling intervention to treat PND and support engagement in HIV care among HIV-infected women.

5. Data Safety and Monitoring Plan

This project involves a pilot randomized controlled trial compared the Adapted Friendship Bench and Enhanced Friendship Bench interventions, to enhanced standard care, to address PND and engagement in HIV care in HIV-infected women. Participation in the study involves sharing possibly personal or sensitive information, such as HIV-status and experiences related to PND. In order to keep participant's private information and identity safe, we will store all data on a secure server at UNC Project in Malawi, which only the PI will have access to. In addition, to prevent any unforeseen risk we will also provide all participants with study contact information and ask that they contact us immediately if they experience any social harm or other adverse event, such as disruption of families, acts of discrimination or physical harm. If a social harm is reported, a short questionnaire will be administered to characterize the social harm and describe its impact. All reported social harms will be documented and communicated to the Malawi Health Science Research Committee (HSRC) and the UNC Institutional Review Board within 7 days.

H. Budget

Line Item	Cost per unit (USD)	# and type units	Total Cost
1. Study Staff			
Counselors	$200	4 x 12 months	$ 9,600
Research assistants*	$200	3 x 12 months	$7,200
Sub-total			$ 16,800
2. Compensation for study participants			
Study visit travel reimbursement	$10	105 participants x 2 study visits (baseline and 6-month follow-up visit	$2,100
Counseling session travel reimbursement	$5	35 AFB participants x 6 counseling sessions; 35 EFB participants x 7 counseling sessions	$2,275
Sub-total			$4,375
3. Other Research Costs			
Paper, toner, and printing costs			$1,000
Fuel for study activities			$500
Airtime for study staff			$525
Tablets for data collection			$500
Translation Fees			$200
Malawi IRB Fee			$150
Sub-total			$2,875
Total			**$24,050**
10% NHSRC fee			**$2,405**

***Research assistants will float between clinics as needed to meet project needs.**

I. BUDGET JUSTIFICATION

PERSONNEL

Counselors in Malawi ($9,600 - 100% effort for 12.0 months) – Four counselors (2 per intervention clinic) will be hired to conduct pre- and post-natal counseling sessions and home visits for HIV-infected women over a 12 month period. $200 salary/month x 4 counselors x 12 months = $9,600.

Research Assistants in Malawi ($7,200 -100% effort for 12.0 months)- Three research assistants will be hired to conduct mental health screening with the Edinburgh Postnatal Depression Scale and Self-Report Questionnaire-20 and to complete data collection for study visits over a 12 month period. $200 salary/month x 3 RAs x 12 months = $7,200.

Total Personnel Costs $16,800

COMPENSATION FOR STUDY PARTICIPANTS

Study Interview Travel Reimbursement ($2,100) – A total of 105 participants will be included in our proposed aim. Each participant will receive 7,000 Malawi Kwacha (~$10/person) as an incentive to participate in the study for each study visit. $10 x 105 participants x 2 visits (baseline and 6 months) = $2,100.

Counseling Session Travel Reimbursement ($2,275) - Participants in the EFB arm (n=up to 6 counseling sessions) and the AFB (n=up to 7 counseling sessions) will also receive travel reimbursement as an incentive to attend intervention counseling sessions. 35 x 5 x 6 = $1050 + 35 x 5 x7 = $1,225, for a total of $2,275.

Total Compensation for Study Participants Costs $4,375

OTHER RESEARCH COSTS

Paper, toner and printing costs ($1,000) – We have budged $1000 to cover the costs of paper, toner, and printing costs for all study material, including informed consent forms, screening and enrollment logs, and logs for counselling sessions.

Fuel for study activities ($500) – We have budged $500 to cover the costs of fuel for study-related activities, including getting staff to and from study sites and for home visits.

Airtime for study staff ($525) – We have budged $500 to cover the costs of airtime for study staff so they can be in contact with one another as needed and with the project coordinator.

Tablets for data collection ($500) – We have budged $500 to purchase 3 tablets ($167 x 3 tablets) to support data collection activities.

Translation and Transcription Fees ($200) – All study materials including informed consent forms, in-depth interview guides, and the Edinburgh Postnatal Depression Scale will be translated into Chichewa, the local language in Lilongwe, Malawi. Translation fees $200.

Malawi IRB Fee ($150) – All research in Malawi must receive ethical approval from the National Health Science Research Committee, which charges a $150 fee to review all applications for ethical approval.

Total Other Research Costs $2,875

TOTAL COSTS: $24,050
10% NHSRC Fee: $2,405

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