A Pilot Trial of Perinatal Depression Treatment in HIV infected Women

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ABBREVIATION LIST

AE	Adverse event
ADM	Antidepressant medication
ANC	Antenatal care
AOR	Adjusted odds ratio
ARR	Adjusted relative risk
ART	Antiretroviral therapy
ARVs	Antiretrovirals
CGI	Clinical Global Impression
CI	Confidence interval
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EPDS	Edinburgh Postnatal Depression Scale
FWA	Federal Wide Assurance
HIV	Human immunodeficiency virus
LTFU	Loss to follow up
IPT	Interpersonal therapy
KHC	Kamwala Health Centre
OHRP	Office for Human Research Protections
PND	Perinatal depression
RCT	Randomized controlled trial
RR	Risk ratio
SAE	Severe adverse event
SSI	Semi-structured interview
SSRI	Selective serotonin uptake inhibitor
UNC	University of North Carolina
UTH	University Teaching Hospital
WHO	World Health Organization

PROTOCOL SUMMARY

Background: Depression is the single largest contributor to global disability. Perinatal depression (PND) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) as an episode of moderate or severe depression that either begins during pregnancy or within 4 weeks of delivery. The severity of PND symptoms typically peaks at 2-4 months postpartum corresponding to the riskiest time for breastfeeding HIV transmission and is thus a critical time for optimal adherence to antiretroviral therapy (ART). Multiple studies suggest that rates of PND are high in HIV infected women in sub-Saharan Africa and that depression is a risk factor for suboptimal medication adherence among HIV infected individuals. The standard of care for treating postpartum depression in the US is antidepressants, psychotherapy or both. Little data exist on the best method for treating PND in Sub-Saharan Africa.

Objectives: In preparation for a possible full-scale efficacy trial, this pilot study will evaluate, through quantitative and qualitative methods, whether different treatments for postpartum depression are feasible and acceptable in postpartum HIV infected women on antiretrovirals. Our study hopes to contribute to reducing barriers to medication adherence with an ultimate public health goal of decreasing intergenerational HIV transmission in low-resource regions.

Design: Mixed method study including a pilot randomized controlled trial (RCT) of antidepressant medication (ADM) versus interpersonal psychotherapy (IPT) and qualitative semi-structured interviews (SSIs)

Study Arms: Daily self-administered selective serotonin reuptake inhibitor (SSRI) *Sertraline* 25 mg tablet versus IPT in a 1:1 ratio commenced between six and 8 weeks postpartum and continued through 30 weeks postpartum.

Population: 150 pregnant HIV infected women over the age of 18 seeking postnatal care and continuing antiretroviral therapy in pregnancy will be enrolled in the pilot RCT; an additional 20+ eligible women who decline to participate in the RCT will be invited to participate in semi-structured interviews (SSIs) and 20 women enrolled in the RCT will be invited to participate in SSIs.

Study Sites: Kamwala Health Centre (KHC) and University Teaching Hospital (UTH), Lusaka, Zambia

Duration and Follow up: Women will be screened and enrolled over a period of 5-12 months. Each participant will be followed for 24 weeks. Total duration of the study is 24 months.

Endpoints: The pilot RCT will measure feasibility including: screening uptake with EPDS, the prevalence of perinatal depression, study uptake, and study retention, as well as preliminary efficacy of the study intervention as a secondary outcome. Semi-structured interviews will evaluate acceptability of a study of treating PND to improve adherence to ART and identify barriers and facilitators to study enrollment, study adherence to study interventions and study retention.

Relevance: More than 1.5 million HIV-infected women become pregnant each year. Approximately half have access to ART, but all are at increased risk of PND. Identifying and treating PND is a potentially promising intervention to improve maternal adherence to ART and improve maternal and infant outcomes in the postnatal period. This pilot study will provide critical insight into the feasibility of a phase III trial by determining whether women are willing to participate, to adhere to study drug, and to complete follow-up.

Statement of Problem: Perinatal depression is a significant and unrecognized problem in many parts of the world. HIV infected women are known to be less adherent to ART in the postnatal period increasing their risk for drug failure and potentially exposing their infants to HIV through breastfeeding. Determining the best treatment of depression in the postnatal period among HIV-infected women is a health care priority.

1.0 INTRODUCTION

Depression is the leading cause of disability worldwide[1,2]. In Lusaka, Zambia, where our group has worked since 2001, as many as 1 in 5 pregnant and recently postpartum women meet criteria for perinatal depression (PND)[3]. This staggering rate coincides with another, equally staggering one: HIV prevalence among pregnant women in Lusaka exceeds 20%.[4]. As combination antiretroviral therapy (ART) has become available to an ever-growing number of pregnant women around the world, perinatal HIV transmission rates have plummeted[5]. To capitalize on both the maternal and neonatal gains that have been made with the widespread scale up of antiretrovirals, mothers must adhere to their prescribed antiretroviral therapy.[6] Many of the hallmark features of depression, such as sadness, fatigue, and withdrawal, work frustratingly against a woman's ability to adhere to her prescribed medication and keep her appointments.[7]

This study will use a formative mixed-methods approach to assess feasibility, acceptability, and preliminary efficacy for treating depression in postpartum clinics in Lusaka. We have chosen a formative mixed-methods approach that involves both the implementation of a pilot trial and a qualitative assessment of participation in it. The pilot will precisely quantify key indices of trial feasibility while also providing estimates of the baseline PND prevalence and preliminary efficacy and safety of treatment. A set of concurrent, qualitative activities will seek a more nuanced understanding of the personal, social, psychosocial, behavioral and structural barriers to trial participation that will be used to design the larger study.

2.0 STATEMENT OF THE PROBLEM

Treatment of depression in non-pregnant adults has been found in randomized trials to improve HIV outcomes[8,9,10] . We hypothesize that treatment of PND in recently postpartum women will improve maternal health and protect the infant from breastfeeding HIV transmission. However, we are concerned about the feasibility of a full-scale efficacy trial, given the lack of knowledge in sub-Saharan Africa concerning depression and its treatment.

3.0 RATIONALE

While treatment of depression has been studied in HIV-infected individuals in industrialized countries[9], interventional data from low resource countries are lacking. This study focuses on exploring the diagnosis and treatment of PND as a potential way to improve not only the health of a new mother, but also the health of her child. This pilot study is setting the stage for an innovative phase III trial where depression screening and treatment will be undertaken to improve maternal and child outcomes among HIV infected women. The primary outcome in the future study will focus on "program failure" – defined as the proportion of women who have died, are lost to follow-up, have been switched to second-line antiretroviral therapy (ART), or who have a plasma viral load > 50 copies / mL at 12 months postpartum. Additional outcomes will be rates of mother-to-child HIV transmission, infant morbidity, infant anthropometry, breastfeeding practices, measures of maternal-infant bonding and infant neurodevelopment. We anticipate that the feasibility study will provide information on choice of treatment design details.

4.0 LITERATURE REVIEW

Major depressive disorder is among the most common ailments faced by women during pregnancy and the postpartum period.[11] Postpartum depression is defined in the DSM-V[12] as an episode of moderate or severe depression that either begins during pregnancy or within 4 weeks of delivery.[12]

The severity of symptoms, however, usually peaks at 2-4 months postpartum[13],corresponding to the riskiest time for breastfeeding HIV transmission[14] and thus a critical time for optimal ART adherence. While the prevalence of postpartum depression in the United States is estimated to be 15%,[15] numerous recent studies suggest that the prevalence in sub-Saharan Africa is much higher. Bangsberg and colleagues report that 39% of HIV infected women in Uganda screened positive for depressive symptoms, a proportion that seemed to remain constant throughout non-pregnancy, pregnancy, and postpartum periods.[16] A systematic review of 21 studies in 8 countries across the African continent reported a prevalence of 18.3% (95% CI: 17.6, 19.1%), and suggested a marked geographic disparity, where the prevalence was considerably higher in southern African countries, compared to West Africa.[1] In Zambia, 229 postnatal women at the University of Zambia Teaching Hospital were screened with the Edinburgh Postnatal Depression Scale (EPDS) between 2 and 6 weeks postpartum and 28% met criteria for PND (defined in this study as EPDS>12). The prevalence did not differ by HIV infection status.[3] In a study of 210 HIV infected and uninfected postnatal women in nearby Zimbabwe, 64 (33%) met criteria for depression (defined by the authors as EPDS>10).[17] (Note: as detailed below, we will use EPDS > 10 as a cut off to offer further diagnostic testing for PND in our study.)

Depression is a known risk factor for suboptimal adherence to ART in many different studies, including those in low resource countries.[18-21] Byakika-Tusiime et al. found that depression (defined as a Beck Depression Inventory score $\geq$ 14) was a risk factor for < 95% adherence using a 30-day visual analog scale in their "MTCT Plus" cohort in Uganda (AOR 0.32; 95%CI: 0.11-0.93). Two systematic reviews also show that depression has a negative impact on ART adherence. Mayston and colleagues conducted a review of all articles addressing mental health, HIV, and low resource countries.[22] Of the six prospective studies that assessed a relationship between depression and adherence, five showed a relationship between depression and poor ART adherence.[18,21,23] Nakimulu-Mpungu performed a similar review of the literature, including over 10,000 adults, to examine the relationship between depression and ART adherence and found that depressed individuals had a 55% (95% CI 0.31-0.66) lower odds of achieving optimal ART adherence.[24] In an analysis of the Nutrition for Healthy Living Study (a US cohort), 22% of participants developed incident depression over the course of up to 2.5 years of follow-up; of these, 45% had concurrent poor adherence (defined as missing $\geq$5% of ART doses in the prior 7 days) compared to 26% among those who did not become depressed (p=<0.01). Further, among those with optimal baseline adherence, those with incident depression were nearly twice as likely to develop suboptimal adherence during follow-up (ARR: 1.8; 95% CI: 1.1, 3.0).[25]

The science behind the recent policy and program shift to lifelong antiretroviral therapy for HIV-infected pregnant women (Option B+) offers – for the first time since the beginning of the HIV epidemic – a pathway to an AIDS-free generation.[26] Currently available antiretrovirals (ARVs) are so potent and well tolerated as to extend an essentially normal lifespan to those who are able to adhere[27], and if the medicine is started early in pregnancy and continued uninterrupted through breastfeeding, the risk of mother-to-child HIV transmission approaches zero.[28,29] Yet, in most developing world settings, the promise of universal lifelong maternal ART has not been fully realized. Health systems are over-stretched and under-resourced. Providers are over-worked. Patients have a variety of competing issues (including mood disorders, as we detail below) that prevent them from remaining in care and adhering consistently to their prescribed ARVs.

Our group has argued in a variety of contexts that **poor ART medication adherence** and **loss to follow-up (LTFU)** are by far the two largest threats to prevention of mother-to-child HIV

transmission (PMTCT) and ART program effectiveness.[30] Adherence rates below 95% correlate strongly with detectable viral load,[31] and almost every published estimate for postpartum ART adherence falls far short of this.[32] In a meta-analysis of 49 studies that examined ART adherence during and after pregnancy in low, middle, and high income countries, only 74% of women overall achieved >80% adherence during pregnancy, and rates during the postnatal period were even lower (53%; 95% CI: 33%-73%).[32] Consistently reported barriers to adherence in the postpartum period include postpartum depression , emotional stress, physical distance from pharmacy, economic hardship, and excessive pill burden.[33,34]

LTFU (completely dropping out of care) presents an equally serious problem. In Lusaka, where our proposed trial will take place, of 6,572 women starting ART in pregnancy or shortly thereafter, 23% (95%CI: 22%, 23%) had dropped out of care by 12 months and 37% (95%CI: 36%, 38%) were lost by 24 months. Similarly, in Malawi, where Option B+ was adopted well before the 2012 WHO recommendations, retention among 1757 women who started ART either antenatally or during breastfeeding was 70% at 6 months (95% CI: 67%-72%) and 67% at 12 months (95% CI: 65%-70%).[33] These proportions are consistent with reports from the US.[35]

Multiple instruments exist to screen women for perinatal depression; some have been studied more than others in developing world settings. The EPDS is the most widely studied perinatal depression screening instrument worldwide, and arguably the gold standard.[7,36,37] It was specifically developed to assess postpartum depression and minimize confounding of the somatic symptoms of the disorder associated with parenting an infant (e.g. insomnia), but has now been validated in pregnancy as well.[37] A 10-item questionnaire with each response 0 to 3 on a Likert scale, EPDS scores > 10 are consistent with PND.[38] It can be self-administered or read to the patient by a clinic worker. The EPDS has been validated in a number of low resource settings, including Zambia. In 1998, Lawrie and colleagues in South Africa validated the EDPS against the DSM-IV. Using a cut-point EPDS score of 12, 100% of postpartum women with major depressive disorder and 70% of women with a minor depressive disorder were identified.[39] In 2013, Chibanda and colleagues validated the EPDS among HIV-infected and uninfected pregnant women in Zimbabwe and found that a cut-off of 12 had 88% sensitivity and 74% positive predictive value compared to structured clinical interviews.[40] Most experts suggest screening at 4-6 weeks postpartum because of the onset of depressive symptoms and worldwide women typically present for a six-week postpartum visit.

Postpartum depression is responsive to the same therapies that are used to treat major depressive disorder in the general population.[8] Pharmacologic therapy is a mainstay of postpartum treatment in industrialized countries and is potentially a more scalable approach to postpartum treatment in low-resource settings than individual psychotherapy.[9,10] The most commonly used antidepressant medications (ADMs) are selective serotonin uptake inhibitors (SSRIs) because of their tolerability and favorable safety profiles. SSRI side effects are usually minor and will manifest in the first few weeks of initiation allowing for dosing changes or termination as indicated.[41] Standard protocols exist on how to titrate these medications when determining a patient's optimal dose. SSRIs have proven to be safe in breastfeeding because only small amounts of the drug transfer into breast milk.[42] Most experts agree that current evidence does not support significant medication interactions between ARVs and most antidepressants and that the benefits of giving an ADM for depression outweighs the potential interaction risks.[43,44]

Psychotherapy is effective for the treatment of major depressive disorder, and different types of psychotherapy seem equally effective.[45] A meta-analysis comparing interpersonal therapy (IPT), cognitive behavioral therapy, and non-directive counseling for PND showed no differences in

success.[46] IPT is a time limited, problem focused therapy that frames depression as a medical illness occurring within a social context. IPT is evidence based, typically lasts 12-20 weeks, and can be administered individually or in a group.[45,47] IPT has been used successfully and adapted in low-income countries in Africa.[48]

Horberg and colleagues examined the effects of SSRIs for depression on ART adherence and clinical outcomes. Patients who took their SSRIs had improved ART adherence and improved viral load suppression that was comparable to patients who were not depressed.[49] Yun also found similar results showing that depressed HIV infected patients who were adherent to their antidepressant therapy were more likely to be adherent to their ART.[50]

5.0 SPECIFIC OBJECTIVES

5.1 Primary objective

- To determine the feasibility of treating PND in HIV infected women on ART by measuring (1) screening uptake with EPDS; (2) the prevalence of perinatal depression; (3) study uptake; (4) and study retention.

5.2 Secondary objectives

- To assess and compare response to therapy at 24 weeks after enrollment in each arm of the study
- To assess acceptability of a randomized clinical trial of depression treatment among women agreeing to trial participation and among those who choose not to participate.
- To describe antenatal PND characteristics in this population of women

5.3 Tertiary objectives

- To evaluate clinical outcomes in study participants including maternal viral load at study completion, medication toxicity, medication adherence, adherence to IPT sessions; and worsening depression.

6.0 STUDY OUTCOMES

6.1 Primary outcomes

Study feasibility as measured by

1) **Screening uptake** at six weeks postpartum– the proportion of women who agree to be screened for depression when offered
2) **PND prevalence** – the proportion of screened women who are EPDS and MINI + at 6 weeks postpartum
3) **Study uptake** – the proportion of trial eligible women who agree to be randomized
4) **Study retention** – the proportion of randomized women who complete follow-up through week 24

6.2 Secondary/tertiary outcomes

- Depression treatment response – defined as the mean decline in the 10-item EPDS at 30 weeks postpartum. We will also investigate the proportion of patients in each treatment arm in whom the Clinical Global Impression (CGI) improves by at least 1 point.

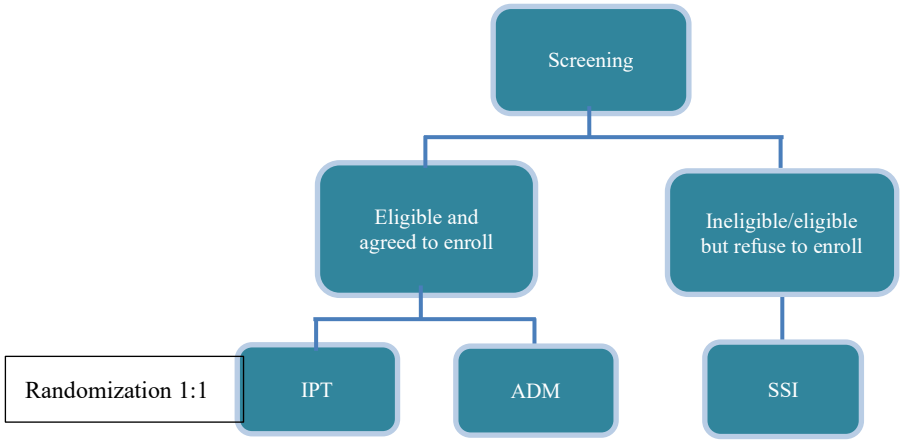
- Reported knowledge, attitudes, and practices related to HIV, ART, postnatal depression, and participation in RCTs, as well as attitudes about medications and counseling for the treatment of PND
- Antenatal PND characteristics: (1) the PND screening rate in pregnancy, (2) the screen positive rate in pregnancy, (3) the proportion of women who screen EPDS+ in pregnancy that are MINI+ at postpartum week 6 (4) the proportion of women who are EPDS negative in pregnancy who are MINI+ at postpartum week 6
- Maternal viral load at study initiation and completion,
- ADM medication toxicity (ADM arm only)
- ADM medication adherence, assessed by pharmacy pill count and patient report
- Adherence to IPT sessions
- Worsening depression as assessed by CGI and/or hospital admission.

7.0 METHODOLOGY

7.1 Study design

This will be a mixed method study to evaluate the feasibility and acceptability of a trial of depression treatment among postpartum HIV-infected Zambian women. To assess the *feasibility* of a full-scale clinical trial, we will implement a pilot two-arm, trial of ADM vs IPT among HIV-infected women seeking postnatal care in Lusaka, Zambia. Participants will be randomly assigned to either a daily self-administered SSRI or IPT starting at their six-week postpartum visit. In this pilot study, we will be able to estimate screening uptake, prevalence of PND, study uptake, adherence to study medication, IPT, and protocol, and study retention. To assess the *acceptability* of a trial to test treatment of depression among HIV-infected postpartum women in Zambia, we will employ a qualitative approach of longitudinal semi-structured interviews among women agreeing to trial participation and one-time SSIs among those who decline to participate.

Schema of the study design:



7.2 Study sites and study population

Participants will be recruited from two antenatal clinics in Lusaka, Zambia: The Women's and New Born Hospital, University Teaching Hospitals (UTH) clinic and the Kamwala District Health Clinic (KHC).

Inclusion criteria:

1. 18 years of age or older
2. Documentation of confirmed HIV-1 infection
3. Six to eight weeks postpartum
4. Currently taking ART treatment
5. Able and willing to provide written informed consent
6. Willing to adhere to study visit schedule
7. PND diagnosis confirmed by Mini-International Neuropsychiatric Interview

Exclusion criteria:

1. Taking an ADM in the prior 12 months prior to enrollment
2. Actively suicidal
3. Known or suspected allergy or contraindication to first line Sertraline
4. any other condition (social or medical) which, in the opinion of the study staff, would make trial participation unsafe or complicate data interpretation.

Two groups of participants will be eligible for participation in the qualitative activities of this study. Women who decline enrollment into the randomized trial will be invited to participate in a one-time face-to-face SSI, while women enrolled and randomized into the placebo-controlled trial will be randomly selected to be followed longitudinally with three serial SSIs.

7.3 Study intervention

Participants will be randomized 1:1 to one of two arms in the pilot randomized controlled trial. The first arm will a self-administered daily SSRI (Sertraline 25mg) while the other arm will be IPT. SSRIs will be administered at enrolment per an evidence-based treatment algorithm based on the Massachusetts Child Psychiatry Access Project (MCPAP)[51] that is currently used at UNC. The Sertraline dose will be titrated up to receive treatment effect. The study nurses administering the ADMs will be overseen by study psychiatrists. The IPT arm will be treated according to an evidence-based IPT structured manual. Patients will have up to 11 planned sessions over a 24-week period beginning the day of randomization. Any patient who needs to be seen for crisis intervention regardless of randomization arm will be seen and referred to the teaching hospital.

7.3.1 Study drug pharmacological information

First line drug: Sertraline

Pharmacologic Category: Selective serotonin reuptake inhibitor

Chemistry: Sertraline hydrochloride is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. It is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol

Mechanism of Action: The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. In humans, following oral once-daily dosing over the range of 25mg to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used. Thus, sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment.

Clinical indication for use: Sertraline has been used to treat Major Depressive Disorder, Obsessive Compulsive Disorder, Panic Disorder, Post traumatic stress disorder, and Social Anxiety Disorder

Formulation: Oral tablet

Strength: The standard dose range is 25mg to 150 or 200 mg once per day. The dose will be titrated up in increments of 25 or 50 mg per day, every one to four weeks to achieve treatment response.

The accountability procedures for the investigational products are outline in the pharmacy SOP number 11.

7.4 Pilot randomized trial procedures

7.4.1 Recruitment

Recruitment activities will begin with community sensitization including education for health staff at the recruiting clinics and other community stakeholders in consultation with community advisory board (CAB) members. Study staff will sensitize the general community though various methods for example; door-to-door education, drama performances, and one to one discussions at health centers to promote messages about HIV testing, mental health, what postpartum depression is, and the purpose of the study. Drama performances at public markets, infant growth monitoring points, and water pumps/collection sites within the community will be held to raise awareness and encourage women to learn more about the study.

Trained study staff will also conduct health talks each morning at antenatal clinics and the mother's shelter. Health talks will focus on the importance of antenatal care, mental health, and overall wellbeing.

7.4.2 Postnatal EPDS and study screening

Trained staff will conduct EPDS screening as part of standard of care at two to seven weeks postnatally and record aggregate numbers of decliners, screen positives, and screen negatives. Those who screen positive for depression (i.e. EPDS >6) will be referred to the study site to learn more about the study and complete the informed consent process if interested prior to the completion of any study specific screening or enrollment activities. Postpartum women may also be referred for study screening from other ongoing studies in which the EPDS is conducted. No identifiable information about individual women will be recorded for study purposes until after

study informed consent has been provided. Once participants sign the informed consent, we will obtain a copy of their ANC card and record the EPDS score from ante and/or postnatal care if available.

Those who meet preliminary eligibility criteria who are interested in participating will complete an informed consent process in English, Nyanja, or Bemba, depending on their language preference. Trial participation will be offered to all HIV-infected women who are determined to meet the listed inclusion and exclusion criteria.

After consenting for participation, study staff will document the EPDS score and confirm the clinical diagnosis of major depression with the Mini-International Neuropsychiatric Interview (MINI).[52,53] The MINI has several modules. We will use the following mood modules to diagnose depression and coexisting morbidities: (a) major depression past and present, (b) PTSD, and (c) anxiety. We will also administer a standardized assessment of domestic violence/gender-based violence. Study staff will then verify antenatal and HIV history data from participants' postnatal cards and HIV clinic charts and collect a blood sample for baseline Viral Load testing.

7.4.3 Study randomization

Women who have been confirmed to be eligible for the study will undergo randomization into one of two study arms between six and eight weeks postpartum. The trial will use REDCAP for randomization with a paper-based system of sealed envelopes as a backup when the electricity is out to assign women 1:1 to either the ADM arm or the IPT arm. A statistician from the UNC Center for AIDS Research Biostatistics Core not otherwise associated with the study will design the scheme using random permuted blocks.

Study medication will be obtained locally. Participants will be instructed to begin daily self-administration of study medication from the day of randomization. Women will be instructed on the importance of adherence at the enrollment visit and at additional study visits, as needed. Study medication will initially be dispensed at 1- week intervals which will then be spaced out to coincide with study visits that will be spaced out over time. Sertraline will be titrated up to achieve treatment effect. (SEE SCHEDULE OF EVALUATIONS) At each visit, medication will be given and an additional 7 to 14-day buffer to be replenished as needed at subsequent study visits. Each participant will be asked to return any leftover medications at follow-up visits.

Participants randomized to the IPT arm will receive weekly IPT for the first month and then biweekly for the next two months and then monthly until the exit visit. All participants will have the same number of face to face visits with clinic staff regardless of study arm. We plan to adapt existing IPT modules to the local context. We have been consulting with a team of researchers who have adapted IPT to improve medication adherence and reduce depression in patients with HIV in South Africa, which they have disseminated to community health clinics across the country, including both rural and urban settings. Their protocol, Mental Health Integration Programme (MhiNT), includes sessions explicitly focused on medication adherence, poverty, social isolation, experienced stigma/discrimination and rejection, and internalized and perceived stigma as they relate to depression. We have spoken to their team about adapting their model for Zambia, and they have agreed to continue consulting on the project to help tailor all elements to the women in our clinics.

7.4.4 Study follow-up

Women will be screened and enrolled over a period of 5-12 months. Each participant will be

	Scr	Enr	Follow-up									Final	
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Weeks postnatal	**6**	**6**	**7**	**8**	**9**	**10**	**12**	**14**	**16**	**18**	**22**	**26**	**30**
Administrative/Regulatory Procedures													
Informed consent	•	•											
Locator information		•											
Eligibility confirmation		•											
Randomization		•											
Qualitative Procedures													
Decliner interview	•												
Longitudinal interviews	•												•
Study Assessments/Interventions													
EPDS	•		•	•	•	•	•	•	•	•	•	•	•
MINI		•											
GBV assessment		•											
CGI		•	•	•	•	•	•	•	•	•	•	•	•
ADM administration		•	•	•	•	•	•	•	•		•	•	
IPT session		•	•	•	•	•	•	•	•	•	•	•	
Adherence assessment		•	•	•	•	•	•	•	•	•	•	•	•
Collection of medical and behavioral data	•	•						•			•		•
Exit survey													•
Viral load		•											•

followed for 24 weeks. Total duration of the study is 24 months. Routine postnatal and HIV care will be provided to all participants following Zambian standard of care guidelines at KHC and UTH. Study staff will conduct follow-up clinical visits at approximately 8 and 16 weeks after enrollment which will occur in addition to the scheduled IPT visits and visits to collect ADM. At these visits, the medical history will be updated by the clinic staff and an EPDS as well as appropriate MINI modules will be completed. Our study staff will work with participants to ensure follow-up visits coincide with scheduled infant visits which occur at 6, 10 and 14 weeks of life to reduce burden on participants with regards to time and travel.

Finally, all participants presenting to the final study visit will have an EPDS, a MINI evaluation as well as an exit survey performed. The study nurse will collect a blood sample at the final visit for Viral Load testing. Visit procedures are summarized in the Table 1 below.

Table 1: Schedule of Evaluations

7.4.5 Retention

Once a participant is enrolled in the trial, the study team will make reasonable efforts to retain her in follow-up to minimize bias associated with loss to follow-up. The study team will track retention rates and address any issues related to retention. Strategies may include:

- Thorough explanation of the study visit schedule and procedures during informed consent, and re-emphasis at each study visit.
- Encouragement of participants to discuss potential study participation with their husbands/partners and other influential family members before agreeing to enrol in the study.
- Collection of detailed locator information at screening, and review and updating of this information at each study visit.
- Use of appropriate and timely visit reminder mechanisms (including phone calls and text messages, if participants specifically agree).
- Follow-up on missed visits, including home or other off-site visits if agreed upon.
- Mobilization of trained outreach workers to complete in-person contact with participants at their homes and/or other locations.

Procedures for when and how to withdraw participants are specified in our Retention and Assessing Suicidality and Need for Discontinuation from the study SOPs.

7.5 Qualitative activities

Women who decline enrollment into the randomized trial will be invited to participate in a one-time, face-to-face SSI to assess the following subject areas: (1) perceptions of depression; (2) health beliefs about and attitudes towards HIV, ART, and depression and towards treatment for depression; (3) acceptability of a daily medicine for treatment of depression as well as acceptability of IPT; and (4) attitudes towards participation in a randomized trial for treatment of depression. We aim to sequentially interview at least 20 women who decline enrollment, with the goal of thematic saturation of data. Prior to the qualitative interviews, a series of five qualitative interviews will be conducted to inform the questions that will be asked in the official pilot.

Additionally, women who are enrolled into the RCT will be randomly selected to be followed longitudinally with two serial SSIs, to be held at enrollment, and at the final study visit. We aim to conduct interviews with women enrolled in the study to address the same domains outlined above, in addition to barriers and facilitators to: (1) adherence to an antidepressant or IPT sessions; (2) returning unused pills– i.e. protocol adherence; and (3) retention in the study. If our random sample does not include women from the full range of adherence levels, we will apply purposeful sampling to capture women of underrepresented adherence levels for a single interview mid-study. Our expected sample size for this group will be 20 women (10 from each arm of the study), based on expectations regarding saturation of qualitative themes.

All interview sessions will be facilitated by a staff member trained in qualitative data collection techniques, in a private location on-site and are expected to last 30 minutes each. Sessions will be audio-recorded and transcribed, with approval provided by participants via informed consent. Where translations are needed, we will have independent reviewers review to ensure accuracy.

Women participating in interviews for the qualitative analysis will also complete a consent process prior to completion of any study activities.

7.6 Biological specimen collection and testing

All samples will be obtained from study participants by trained study staff according to approved standard operating procedures. All samples will be processed for viral load testing according to the assay manufacturers' specifications. With participant consent, leftover specimens will be primarily housed at the University Teaching Hospital, Department of Obstetrics and Gynecology. Use of stored specimens for testing that is not specifically designated in this protocol will require additional regulatory approval.

7.7 Data security and management

Data collected on each participant will include sociodemographic information, relevant HIV and obstetrical history, recent pregnancy outcome, adherence to ART, and side effects of any medications. We will also collect data on adherence to ADM and IPT throughout the study, and qualitative data from semi-structured interviews. If data is missing, we will document why the data is missing.

Study data management (e.g. data transmission, query resolution, storage and security, etc.) will follow site Data Management SOPs. Study identification numbers will be used on all forms, returned ADMs, and communications related to the study.

A separate confidential register will link study identification numbers and participants' names. All data instruments and registers will be securely stored. Data will be entered into a custom-built database and will be validated. Computers will be password protected and their access restricted to authorized study personnel. Backups of the data will be made on a weekly basis. Data may be transmitted electronically to the study investigators through secure cloud-based servers. Study information will not be released without written permission of the participant, except when necessary for monitoring by the relevant ethical committees or their designees.

Data will be disposed of after completion of the study following sponsor guidelines as per Data Management SOPs. At that time, electronic records, including linkage codes and identifiers, will be permanently deleted.

If a participant is withdrawn from study product, all the data except data for intervention (ADM and IPT), will be collected until the study termination. If the participant is withdrawn from the study then no further data will be collected from the participant.

7.8 Statistical considerations

7.8.1 Pilot randomized controlled trial sample size and analysis

The primary objective of this research is to determine whether a phase III efficacy trial would be feasible by measuring four key indices of feasibility including screening uptake with EPDS, the prevalence of perinatal depression, study uptake, and study retention. Given concerns around increased the stigmatization of depression, non-adherence to ART in the postpartum period as well as suspected high rates of postpartum depression among HIV infected women, we have chosen feasibility as our primary outcome. As this is a feasibility study, our sample size is not based on a comparison,[54,55] but rather on the minimum desired precision around our four quantitative measures of feasibility. Since study retention is at the end of the screening and evaluation cascade, it will have the fewest numbers available and thus the least precision. Also, we expect the primary outcome of the planned phase III trial to be a composite measure that we have previously defined as *program failure*[56,57] (detectable maternal viral load, death, or loss-to-

follow-up). Retention is likely to be the driving factor in this composite metric. Thus, we have chosen study **retention as the primary outcome** for our pilot study. Based upon prior experience and the published PND literature, which suggests loss-to-follow-up is a major issue in PND trials,[58] we estimate that 30% of randomized women will be lost to follow-up over the 6-month study period (i.e., retention will be 70%).

We used the normal approximation confidence limit approach to choose the sample size, with the exact binomial confidence interval (CI) as a sensitivity analysis. Using a 95% CI for the proportion of randomized patients retained in the study, n=150 provides a lower confidence limit above 60%. TABLE 2 presents the precision achieved for outcomes with an observed proportion of 50-95% given a total sample size of 150.

Table 2: Anticipated precision with n=150 participants

	Observed proportion (study retention)					
	0.5	**0.6**	**0.7**	**0.8**	**0.9**	**0.95**
Precision	± 0.083	± 0.081	**± 0.075**	± 0.066	± 0.050	± 0.036
Exact binomial CI	0.41, 0.59	0.51, 0.68	**0.63, 0.76**	0.72, 0.86	0.84, 0.94	0.90, 0.98

With a randomization sample size set at 150, we then calculated the number of women to whom we would need to offer enrollment into the study, by applying best estimates for attrition along the screening and follow-up cascade. Based on these estimates, we will need to screen 1130 women, of whom 10% will decline screening (estimate from ongoing prematurity cohort), leaving 1017 evaluated by EPDS. Of these, we expect 70% to be EPDS negative[3,17] and proceed to MINI screening. The specificity of EPDS to screen for clinically confirmed PND (i.e., MINI+) varies widely by study, but we have conservatively assumed 12% of EPDS positive women will be MINI positive for either major depression or anxiety, yielding 268 MINI positives. Of these, we estimate 4% will report suicidal tendencies or otherwise be too ill to randomize and that 10% will be ineligible after applying exclusion criteria, leaving 231 to whom we will offer enrollment. Finally, we estimate from prior trial experience, that 35% of eligible women will decline participation in the study, leaving 150 who are consented and randomized.

For our **primary analyses**, we will measure the quantitative feasibility outcomes in the entire trial cohort – (i.e., without accounting for randomization arm). This will involve screening uptake with EPDS, the prevalence of perinatal depression, study uptake, and study retention. All statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CIs).

In a **secondary analysis**, we will investigate response to therapy at 24 weeks in each arm of the study. Depression treatment response – defined as the mean decline in the 10-item EPDS at 24 weeks postpartum. Since this will be analyzed as a continuous variable, our study will have 80% power to detect a difference of 3 points in the EPDS between each of the intervention arms (alpha = 0.05; EPDS sd ± 5 points). We will also investigate the proportion of patients in each treatment arm in whom the CGI improves by at least 1 point.

In other **secondary analyses**, we will quantify the following antenatal PND characteristics: (1) the PND screening rate in pregnancy; (2) the screen positive rate in pregnancy (3) the proportion of women who screen EPDS+ in pregnancy that are MINI+ at postpartum week 6 (4) the proportion of women who are EPDS negative in pregnancy who are MINI+ at postpartum week 6. In **tertiary analyses** of clinical outcomes, we will evaluate: (1) maternal viral load at study completion, (2)

ADM medication toxicity (ADM arm only); (3) ADM medication adherence, assessed by pharmacy pill count and patient report; (4) adherence to IPT sessions (5) worsening depression as assessed by CGI and/or hospital admission.

We will define uptake strictly as the proportion of women meeting initial (screening) eligibility criteria who are randomized in the trial. If uptake in the pilot is very low, enrollment of a large trial might not be feasible. Low uptake might also make us worry about external validity and whether the trial would be representative enough to be of real policy value.

To quantify study retention, we will calculate the proportion of women randomized in the trial who complete the final visit. For the present study, we will require a clinic visit to define retention success.

Univariate analyses will be performed to identify maternal demographic and health characteristics associated with adherence, uptake and retention; and adjusted associations will be analyzed with a multivariable log-binomial model as appropriate (for outcomes with a sufficient number of events).

Other outcomes will include: (a) maternal viral load at study completion; (b) ADM medication toxicity; (c) ADM medication adherence, assessed by pharmacy pill count and patient report; (d) adherence to IPT sessions; (e) requirement of up titration of ADM; (f) worsening depression; (g) other maternal or neonatal adverse events. We will attempt to trace all participants who are lost to follow-up to determine obstetrical and neonatal outcomes. In an exploratory analysis of these outcomes, we will conduct descriptive statistics of participant demographic and clinical features, and of the proportion of patients experiencing the secondary outcomes of poor maternal and neonatal outcomes. Although our study is not powered for efficacy, we will perform univariate analyses to determine if a numerical difference in risk of these secondary efficacy and safety outcomes exists between women who were randomized to ADM compared to those randomized to the IPT arm. Sensitivity analyses will be used to investigate how limiting the analysis to high adherers impacts the estimated RR. The effect of participant demographic variables (and any additional potential measured confounders) will be explored in multivariable analyses using a log-binomial model. Exploratory analyses will be stated as such and presented as pilot effect estimates with a 95% CI; such analyses will provide useful results for planning a full-scale trial. All hypothesis tests that are observed to be not statistically significant will be reported as being inconclusive.

In sum, we expect this feasibility study to allow us to estimate the proportion of women who (a) are eligible to participate, (b) will agree to participate, (c) are able to comply with the visit schedule, (d) will adhere to prescribed study drug and therapy sessions, and (f) will remain in the study once enrolled. We will gain insight into the (g) baseline event rate, (h) preliminary effect size, and (i) rates of adverse events. Finally, the study will allow us to develop and test study-specific SOPs and gain experience with randomization.

We will report the proportion of missing baseline data as well as missing data for the primary outcome. Our main analysis will be intent to treat. We will perform a sensitivity analysis to quantify the effect of missing outcome data on study results.

7.8.2 Qualitative analysis

Our primary objective is to identify common facilitators and barriers to screening and treatment of depression in a clinical trial. We will first analyze data from women who decline enrollment

independently from data among those who enroll. Then, findings from common baseline domains evaluated in both assessment groups will be compared to identify commonalities or discrepancies between decliners and enrollees. The longitudinal data assessed from interviews with enrolled participants will be compared across time and between those randomized to ADM vs IPT. After translations and transcription, a team of coders with qualitative data analysis experience will use qualitative analysis software to organize the transcribed data. Transcript data will initially be organized based on the questions in the semi-structured guides. Coders will read and "memo" each transcript and compare memos to create a preliminary codebook. They will apply the codes to significant utterances, comparing their results periodically (such as every 4-5 interviews) to assess consistency between coders in order to refine a final codebook. They will examine codes and utterances for clusters of meaning to construct themes and maps reflecting categories and relationships among codes. They will then examine the themes identified from each dataset for contrasts and overlaps between them, which may lead to reconstructions of the existing themes or the emergence of new subthemes. A summary report of the analyzed SSI data will be created which will inform the development of the following materials for the planned full-scale efficacy and safety trial: study protocol, consent forms, adherence monitoring and counseling guide, and provider training materials.

7.9 Dissemination of Findings

Study findings will be disseminated through appropriate local channels, including academic and public health research symposia. One or more publications will also be submitted to a peer-reviewed journal. Our study team will plan to publish results whether positive or negative. The study participants' privacy and confidentiality will be strictly maintained in all results dissemination or publication activities.

8.0 ETHICAL CONSIDERATIONS

The study protocol, informed consent, and all participant materials will be reviewed by relevant ethics committees maintaining Federal Wide Assurances (FWA) with Office for Human Research Protections (OHRP) approval. All staff who have contact with participants will receive training on the protection of human research participants prior to conducting any study activities and routinely thereafter.

8.1 Informed consent

Discussions with prospective participants and informed consent procedures will be conducted in private to protect patient confidentiality. Where possible, a private room will be used to discuss the study and potential participant's eligibility. If a private room is not available, a designated area far enough away from other patients such that they cannot hear the conversation will be used. The study nurse will obtain written informed consent from all participants. The study procedures, risks, and benefits will be discussed and the study nurse will answer all questions prior to obtaining consent. The consent forms will be translated into local languages (Nyanja and Bemba) and back-translated into English to assure accurate translation. All versions of the consent forms will be approved by the relevant ethics committees prior to study initiation. For illiterate participants, a literate impartial witness will be present during the entire consent process to ensure that all of the relevant information has been provided and the participant voluntarily gives consent.

Eligible women who do not wish to participate in this study will continue to receive postnatal care and treatment according to local clinical standards.

8.2 Potential risks to participants

We expect participant risk to be minimal. We will exclude any woman with an initial EPDS >25 and treat her accordingly. Any participant found to have active thoughts of suicide will be referred for immediate psychiatric care She will be accompanied to the referral by a study staff member. As the study will be conducted while the patient is at the clinic, she will have the opportunity to disclose any issues or concerns to the provider immediately during her participation in the study participation. In addition, investigators will be available to discuss acute psychiatric concerns by study staff as needed and to liaison with the psychiatric team in Zambia.

A small number of women in the antidepressant medication arm may develop side effects or potential interactions with their ART, so we will closely monitor adverse events and document all concomitant medication use. We are not aware of any contraindications to potential treatment combinations but will maintain a laminated notebook with commonly prescribed medications and potential interactions with Sertraline. The book will be color coded and easily interpreted. All of the enrolled participants will be diagnosed with clinical depression. There is a possibility that these women will not respond to the therapies in our study and will need additional treatment. Any woman who experiences worsening depression based on an EPDS or a MINI or who has suicidal or homicidal ideations, will be withdrawn from the study and referred to UTH for further individualized management.

We do not expect to uncover any incidental findings given that study assessments will be relatively limited. In the event this does occur, we will make assisted referrals by completing a referral form with all relevant information available and escorting the participant to the appropriate care provider. We will then follow up with both the participant and the provider routinely to ensure that she has received proper care

Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions, particularly when discussing HIV infection or mental health. At each step in the study, we will protect participant privacy and confidentiality to reduce these risks, such as not revealing all study inclusion criteria to participants or the community, consenting participants in a private setting, screening for risk factors that may increase the risk for social harm, carefully collecting locator information with details about how to communicate with participants, not including names on case report forms, and storing all research records securely. Although investigators make every effort to protect participant privacy and confidentiality, it is possible that participant involvement in the study could become known to others, and that social harms may result (i.e. as participants could become known as HIV infected). Should that occur, study staff will work with the participant and his/her family as appropriate to resolve the situation in whatever manner is preferred including additional counseling or referrals for community services for the participant and her partner/family.

Risks to the participant will be minimized by thorough training and supervision of all staff. The confidentiality of all study records will be safeguarded to the extent legally possible. All study data, reports, laboratory specimens, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All databases will be secured with password-protected access systems, and computer entries will be identified by coded number only. Forms, lists, logbooks, appointment books, audio-recordings, and any other listings or data forms that link participant ID numbers to other identifying information will be stored in a separate, locked cabinet. All data analysis will be done on datasets which have only the study number as a unique identifier.

Clinical information with individual identifiers will not be released without the written permission of the participant. We expect these procedures to adequately protect participant confidentiality.

The Victim Support Unit in the Zambia Police provides support to women who report domestic violence, and a number of non-governmental organizations work with women who are victims of gender based violence (GBV). All women who are screened for our study will be provided with pamphlets printed in local language outlining where women can receive care for gender-based violence, which will also be available in the clinic waiting room at all times. A few of the local organizations that support GBV are: World Vision, WILSA, ZCCP, and Lifeline-Childline Gender Based Violence Call Centre. We will also directly facilitate contact with any of these organizations.

8.3 Potential benefits to participants and others

Individual participants in both arms of the study may benefit from treatment of depression if the intervention is found to be effective, but it is also possible that there will be no effect. We believe that equipoise exists between the study arms since neither treatment has been previously studied in HIV infected women receiving antiretroviral therapy in sub-Saharan Africa, and the exact risk for untreated PND unclear. All participants may benefit from close clinical monitoring. Knowledge generated from this study has the potential to inform future clinical trials on the best way to treat depression among HIV-infected women, which may enable policymakers worldwide to make informed decisions regarding effective interventions for treating PND among HIV infected individuals taking ART.

At the clinic level, all staff involved in the study will receive refresher training on the diagnosis and treatment of PND[59]. Increased awareness about screening and treatment for PND may help to improve care overall at KHC and UTH. Additionally, our community sensitization activities may help to encourage more women to come for screening for PND earlier in pregnancy which is a known risk factor for depression in the postpartum period.

In summary, we expect participant risk to be minimal. The knowledge generated from this study regarding the feasibility of diagnosing and treating PND among HIV-infected women is expected to outweigh the risks of participation.

8.4 Participant follow up once the study is completed

Treatment for perinatal depression is typically offered for 6-12 months. Our study will follow up women for 24 weeks after enrollment. At the end of the 24 weeks, women will be assessed for depression. Women who are no longer depressed at the end of the study will be offered to discontinue the SSRI or to continue the SSRI for another 6 months, per patient preference. Women who desire to continue for another six months will follow up at UTH. Sertraline, the SSRI antidepressant medication we have chosen for our study, is on the Ministry of Health Essential Medicine list and is available to patients free of charge. Women who choose to discontinue their antidepressant will be followed up with a phone call 2-4 weeks after discontinuing the medication to ensure that they do not need a referral to UTH. Women in the IPT arm who remain depressed at the end of the study will be referred to UTH to start an antidepressant.

Participants will be followed up until the end of trial if they are withdrawn from the investigational products. If the reason for withdrawal requires more follow up after the close of the study, the participant will continue to be seen and cared for by Dr. Ravi Paul in UTH Psychiatry department.

9.0 SAFETY MONITORING

At each study visit, study staff will evaluate participants for social harms and adverse events (AEs). A social harm will be defined as a non-medical untoward consequence of study participation, including: difficulties in personal relationships, stigma, or discrimination from family or community. An AE will be defined as any untoward medical occurrence in a study participant including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the individual's participation in the research, whether or not considered related to participation in the research. In addition to events related to study procedures and ADM treatment, we can expect that this population of HIV-infected postpartum women to experience adverse events unrelated to study procedures, including opportunistic infections, side effects from ART or other medications, hospitalization, and death.

The severity of study-related adverse events and social harms will be graded using the National Institute of Health's Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. We will also record information on all serious adverse events (SAEs) occurring in participants whether or not they are related to study participation or the study drug, including AEs that:

1. Result in hospital admission (unless hospitalization is preplanned, i.e. for delivery) or prolongation of existing hospitalization
2. Are immediately life-threatening, including drug reactions that necessitate discontinuation of study participation,
3. Cause significant, persistent, or permanent harm or disability, either physical or psychological,
4. Result in death to mother or infant

9.1 Data Safety Monitoring Board (DSMB)

We will constitute a 5-member Data Safety and Monitoring Board (DSMB) through NC TraCS, the North Carolina Translation and Clinical Sciences Institute, to review the safety of the interventions, but its purpose would only be to monitor safety because there will be no stopping rules as this is not a comparative study. The three main outcomes that will be monitored are 1) interactions between antiretrovirals and antidepressants 2) side effects of antidepressants among participants requiring them to either switch antidepressant medication or discontinue the medication 3) worsening depression symptoms in either arm despite treatment. The DSMB will meet twice per year and additionally as needed, either in person or via conference call. The committee will discuss the project, review its progress, and assess unanticipated problems and adverse events. The DSMB members do not have any direct involvement in the study or conflict of interest with the study team.

9.2 Trial safety reporting

For all enrolled participants, study staff will collect information on adverse events, adverse drug reactions/side effects, perceived social harms, and suicidal and homicidal ideations at each follow up visit. All events will be documented, assessed for seriousness / severity and relatedness, carefully monitored, and managed by the onsite investigators. Our trial will adhere to the NIMH reportable events reporting guidelines and will assess AEs following the current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

We can expect that this population of postpartum HIV infected women may experience adverse events unrelated to study procedures including new diagnoses of opportunistic infections, side effects from ART medications, hospitalization, and possibly death. Participant records will be carefully monitored internally by the Study Coordinator and investigators to ensure that no adverse events or social harms are missed. We will record relevant information about AEs, SAEs, social harms, and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) in the study records.

Participants in the ADM arm of the study may experience common side effects associated with this medication. We do not expect any participants to have major side effects, but if any do occur, we will evaluate the participant and potentially discontinue her use of the study drug. Any participants who develop active suicidal or homicidal ideation will be referred to the study psychiatrist for immediate care and may also be discontinued from their assigned intervention as needed.

The site investigators and/or Study Coordinator will report all related serious adverse events, social harms, protocol violations, and UPIRSOs to the PI immediately within 24 hours of site awareness. The DSMB will be notified of any serious adverse events (related or unrelated) within 24 hours of site awareness. If the investigators determine that study-related adverse events are occurring at an unexpected rate, the PI will facilitate re-training for study staff on clinical procedures or in protection of patient confidentiality as applicable and notify the DSMB and study sponsor as needed. AEs/SAEs, UPIRSOs, serious or continuing non-compliance, and protocol violations will be reported to all regulatory bodies and the NIMH following their requirements as outline in the Communication with Ethics and Regulatory Authorities SOP.

If terminating the study trial, a DSMB will be convened. Recommendations to terminate the trial can be found in the DSMB charter. We will plan one interim test of SAEs or Adverse Drug Reactions after one half or 75 patients have been enrolled. The following SAEs or severe drug reactions will be assessed across both treatment arms: nausea, diarrhea, insomnia, agitation, mania, and active suicidal ideations. If after 75 participants are enrolled, there is a two-fold increase in SAEs or severe adverse drug reactions among women randomized to the ADM arm (20%) vs the IPT arm (10%), then the study should be suspended until further review.

10.0 BUDGET (1 USD = 11.5 ZMW)

	Year 1 USD	Year 1 ZMW	Year 2 USD	Year 2 ZMW	Total USD	Total ZMW
Personnel	**$60,511**	**695,877**	**$60,510**	**695,865**	**$121,021**	**1,391,742**
Investigator	$5,000	57,500	$6,000	69,000	$11,000	126,500
Study Coordinator	$15,500	178,250	$14,500	166,750	$30,000	345,000
Research Nurse	$10,500	120,750	$11,050	127,075	$21,550	247,825
Counselors	$12,500	143,750	$13,200	151,800	$25,700	295,550
Data Staff	$8,585	98,728	$7,340	84,410	$15,925	183,138
Support Staff	$8,426	96,899	$8,420	96,830	$16,846	193,729
Travel	**$4,010**	**46,115**	**$4,010**	**46,115**	**$8,020**	**92,230**
Supplies & materials	**$6,364**	**73,186**	**$3,505**	**40,308**	**$9,869**	**113,494**
Office Supplies	$2,855	32,833	$955	10,983	$3,810	43,815

Clinic Supplies	$1,200	13,800	$1,200	13,800	$2,400	27,600
Study Drug	$2,309	26,554	$1,350	15,525	$3,659	42,079
Participant Reimbursement	**$2,753**	**31,660**	**$2,692**	**30,958**	**$5,445**	**62,618**
Full study visit - 50 ZMW	$1,586	18,239	$1,640	18,860	$3,226	37,099
Intervention only visit - 25 ZMW	$1,167	13,421	$1,052	12,098	$2,219	25,519
Other	**$8,200**	94,300	**$2,520**	28,980	**$10,720**	**123,280**
Admin costs (talk time, printing, shipping, utilities, etc)	$2,200	25,300	$2,000	23,000	$4,200	48,300
Regulatory/Translation costs	$4,000	46,000	$250	2,875	$4,250	48,875
Training/Community Outreach	$2,000	23,000	$270	3,105	$2,270	26,105
TOTAL	**$81,838**	**941,137**	**$73,237**	**842,226**	**$155,075**	**1,783,363**

11.0 TIMELINE

Participants will be followed from enrollment through 30 weeks postpartum. We have allocated 6 months to start-up activities and 3 months to wind-down activities.

PHASE	**Year 1**				**Year 2**			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Pre-implementation								
Regulatory approvals	X							
Site preparation and training	X	X						
Implementation								
Enrollment		X	X	X	X			
Follow-up			X	X	X	X	X	X
Data management, analysis & reporting								
Transcription and coding of interviews			X	X	X	X		
Data entry and management		X	X	X	X	X	X	X
Statistical analysis					X	X	X	X
Publication and dissemination								X

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