PROBABLE PERINATAL DEPRESSION, ENGAGEMENT IN HIV CARE, AND VIRAL SUPPRESSION AMONG MALAWIAN WOMEN

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ABSTRACT

Bryna J. Harrington: Probable Perinatal Depression, Engagement in HIV Care, and Viral Suppression among Malawian Women
(Under the direction of Brian W. Pence)

With broadened antiretroviral treatment (ART) eligibility, long-term HIV care engagement has been sub-optimal. Care engagement may be hindered by antenatal depression, yet depression screening is not routine in most African countries. We estimated factors associated with antenatal depression, the prevalence and incidence of perinatal depression, and the relationship of antenatal depression with HIV care engagement among a cohort study of pregnant women living with HIV (n=725) recruited from a government antenatal clinic in Malawi in 2015-2016. Depression was assessed at enrollment and four times postpartum with the Edinburgh Postnatal Depression Scale (EPDS) and Patient Health Questionnaire-9 (PHQ-9).

Participants' median age was 29 years, and at enrollment had a median 22 weeks gestation. Most were married (90%) and their current pregnancy was unintended (68%). Many women reported a history of depression or anxiety: 46% had a personal history and 20% had a family history; 17% reported experiencing intimate partner violence (IPV). Women were more likely to have probable antenatal depression if they reported a history of depression (adjusted prevalence ratio 2.42; 95%CI 1.48-3.95), IPV (1.77; 1.11-2.81), had an unintended current pregnancy (1.78; 0.99-3.21), were unmarried (1.66; 0.97-2.84), or were employed (1.56; 1.00-2.44).

Among women initiating ART (n=299), 10% had probable antenatal depression, yet only 2-5% postpartum. Sensitivity analyses to account for loss to follow up suggested that postpartum depression prevalence could have ranged from 2-11%. EPDS and PHQ-9 scores were concordant for 95% of assessments.

Most women were engaged in care through 12 months post-ART initiation: 85% attended all scheduled visits, and 81% were in care and virally suppressed. For both care engagement outcomes, there were no differences by antenatal depression status (visit attendance risk difference: -0.02; 95%CI -0.16-0.12; adjusted: -0.04; 95%CI -0.18-0.10) (viral suppression prevalence difference: -0.02; 95%CI -0.17-0.13; adjusted: -0.01; 95%CI -0.17-0.15).

Probable perinatal depression was more common antenatally than postpartum among women with HIV in Malawi. Factors associated with probable antenatal depression represented heightened psychosocial stress. Women with and without antenatal depression were equally likely to remain engaged in care postpartum. Programs should consider screening and support services for psychosocial factors to facilitate women's sustained HIV care engagement.

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AIDS	Autoimmune deficiency syndrome
aPD	Adjusted prevalence difference
aRD	Adjusted risk difference
ART	Antiretroviral therapy
CI	Confidence interval
DAG	Directed acyclic graph
DRC	Democratic Republic of the Congo
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EPDS	Edinburgh Postnatal Depression Scale
HIV	Human immunodeficiency Virus
IPV	Intimate partner violence
IQR	Interquartile range
LTFU	Lost to follow up
PD	Prevalence difference
PHQ-9	Patient Health Questionnaire-9
PMTCT	Prevention of maternal to child transmission of HIV
PrEP	Pre-Exposure Prophylaxis
RD	Risk difference
S4	Safety, Suppression, Second-Line, Survival Study
SMR	Standardized Mortality Ratio
UNAIDS	Joint United Nations Programme on HIV/AIDS

UNC	University of North Carolina
VL	Viral Load
WHO	World Health Organization

CHAPTER I: INTRODUCTION

Women of reproductive age in Malawi have one of the highest HIV prevalence rates in the world, with 12% of adult women infected.[1] Moreover, 16,000 infants are infected each year in Malawi during pregnancy or breastfeeding.[2] Access to antiretroviral treatment (ART) for adult women is a priority to maintain women's health and to reduce HIV transmission to their infants and partners. ART drastically reduces the likelihood of HIV transmission via suppressing viral load and rendering the person effectively noninfectious.[3–6]

To realize the full health and prevention potential of ART, people living with HIV must know their HIV status, initiate HIV care, and remain engaged in care long-term with high ART adherence and sustained viral suppression.[7] Antenatal care provides an inherent opportunity to identify women living with HIV during pregnancy due to routine opt-out testing. Until recently, in Malawi as in most African countries, women were eligible for ART only during pregnancy and breastfeeding unless their HIV disease progression was advanced. In 2011, in order to increase ART coverage among women overall, the Malawian Ministry of Health implemented the Option B+ program: pregnant women living with HIV became eligible for *lifelong* ART regardless of their CD4 count or HIV disease stage. While the Option B+ program has increased the number of women initiating ART antenatally,[8] long-term engagement in HIV care and sustained viral suppression postpartum have emerged as major challenges for the program: 25% of women starting ART in Option B+ are lost to follow up within six months, yet the United Nations Programme on HIV and AIDS (UNAIDS) target to eliminate the AIDS epidemic is to have 90% of those living with HIV on ART.[9–11]

Engagement in HIV care, ART adherence, and viral suppression may be influenced by perinatal depression. Perinatal depression includes depression that begins during pregnancy (antenatal

depression) or within 12 months after delivery (postpartum depression).[12] In studies from the United States, depression is more common in persons living with HIV than in the general population,[13,14] and predicts poor engagement in HIV care, lower ART adherence,[15–17] poorer HIV viral suppression,[18] and higher mortality rates.[19,20] Among women living with HIV in sub-Saharan Africa, perinatal depression prevalence estimates are as high as 43%.[21] However, there is little information on the timing and predictors of perinatal depression, or on how perinatal depression affects engagement in HIV care and viral suppression during the postpartum period.

To address these gaps, we leveraged data from a longitudinal cohort study on the safety and efficacy of the Option B+ program in Malawi among pregnant women with HIV who sought antenatal care at a public clinic in the capital city. Specifically, we addressed the following three aims:

Aim 1: Identify factors associated with probable antenatal depression

Rationale: Identifying demographic, clinical, and psychosocial items that are associated with probable antenatal depression will be useful in focusing depression screening and treatment efforts.

Hypothesis 1: We anticipate that variables indicative of stressors will be more prevalent among women with probable antenatal depression.

For this aim, we assessed factors that may be associated with probable antenatal depression among 299 pregnant women initiating ART and 426 pregnant women who had been on ART for at least 6 months (total n=725). We described the prevalence of and factors associated with probable antenatal depression among pregnant women enrolled in Option B+ HIV care in Malawi.

Aim 2: Estimate the prevalence and incidence of probable perinatal depression through 12 months postpartum

Rationale: Estimates of the proportion of women in Option B+ who suffer from probable perinatal depression and characterizing when during the perinatal period they are affected can inform efforts to identify and treat perinatal depression.

Hypothesis 2: Malawian women enrolled in Option B+ will have a prevalence and incidence of perinatal depression comparable to that of other perinatal women living with in sub-Saharan Africa.

For this aim, we followed women in the cohort study who were initiating ART for the first time during their pregnancies and up to 12 months postpartum. Women's depressive symptoms were assessed at four time points (enrollment, postpartum week 6, and postpartum months 3, 6, and 12). Both the Edinburgh Postnatal Depression Scale (EPDS), a 10 question instrument that is validated for both antenatal and postpartum depression screening, and the Patient Health Questionnaire-9 (PHQ-9), a 9 question depression screening instrument, were used to assess depression. A total of 299 women who initiated ART through Option B+ in 2015 and 2016 were included. We calculated point prevalence and incidence of probable perinatal depression, concordance between EPDS and PHQ-9 scores, and identified the most frequently endorsed depressive symptoms.

Aim 3: Estimate the association of probable antenatal depression with postpartum engagement in care and viral suppression

Rationale: Antenatal depression is a modifiable condition, and properly managing antenatal depression may improve postpartum engagement in care and viral suppression.

Hypothesis 3a: Women with probable antenatal depression will be less likely to have attended all expected visits through 12 months post-ART initiation than women without probable antenatal depression.

Hypothesis 3b: Women with probable antenatal depression will be less likely to have a suppressed viral load at 12 months post-ART initiation than women without probable antenatal depression.

In this aim, all women (n=299) were initiating ART during their pregnancies, as in aim 2. We estimated the difference in probability of being engaged in care as defined by visit attendance, and as viral suppression (<1000 copies/mL) at 12 months post-ART initiation, comparing women who screened positive for probable antenatal depression on the EPDS and those who screened negative on the EPDS.

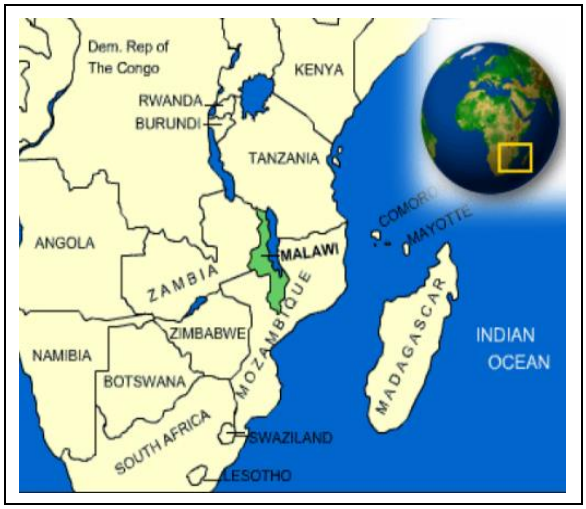
We conducted two sensitivity analyses to address potential outcome measurement error and the influence of including women who may have already been on ART at baseline. In secondary analyses, we extended the estimate of visit attendance through 12 months postpartum, and excluded women who may have already been on ART prior to joining the study.

CHAPTER II: BACKGROUND

Sub-Saharan Africa bears a large proportion of the global burden of HIV. Of the 37 million people living with HIV globally, over 25 million live in sub-Saharan Africa; 58% of the individuals living with HIV in sub-Saharan Africa are women.[22] Within the goal of helping all people living with HIV manage their disease to stay healthy, women are particularly important in strategies to reduce HIV incidence because they can transmit to both their sexual partners and their infants. While recent prevention of maternal to child transmission (PMTCT) of HIV efforts have been successful – the number of new HIV infections among children declined by 24% between 2009 and 2011 in sub-Saharan Africa – there are still approximately 1,000 infants infected with HIV per day.[23]

Malawi, a country in southern Africa of 16 million inhabitants (Figure 1), is a leader in implementing a public health approach to PMTCT. Malawi has a notable HIV epidemic with 12% of adult women infected with HIV.[1] Along with its neighboring countries, Malawi has recognized the importance of providing HIV care in the context of antenatal visits as a way to reach both women and their infants. Despite the improvements and expanded HIV programs, over 16,000 infants were infected during their gestation, birth, or breastfeeding in Malawi each year as of 2010.[2] In this setting of an undesirably high number of infant HIV infections and high HIV prevalence, Malawi was the first country to opt for an expanded ART program, called "Option B+" in 2011.

Figure 1. Map of Malawi in sub-Saharan Africa [24]



Option B+ has dramatically expanded the number of pregnant women with HIV eligible for antiretroviral treatment (ART). Option B+ is an innovative strategy that expanded national HIV treatment coverage, and provides *lifelong* ART to pregnant or breastfeeding women living with HIV *regardless of their immune status*. Option B+ is a public health approach to reduce maternal to child transmission of HIV and to improve long-term maternal outcomes. The rationale stemmed from high HIV prevalence in reproductive age women, high fertility rates, prolonged breastfeeding, programmatic simplification, and scientific evidence supporting the preventive benefit of earlier ART initiation.[2,3,5,8] The number of pregnant women starting ART increased by 748% during Option B+'s first year, a major success for Malawi.[8] Moreover, in 2013, the WHO formally recommended Option B+ for PMTCT guidelines, and multiple countries in sub-Saharan Africa have since implemented Option B+.[25]

Despite the rapid expansion of the Option B+ program, sustained engagement in care has been sub-optimal, and has fallen short of the UNAIDS 90-90-90 goals.[11] In Malawi's first year of Option B+, only 37% of facilities had >90% of clients engaged in care 6 months post-ART initiation.[10] Compared to women starting ART due to advanced disease stage, women who initiated ART through Option B+ had 5 times the odds of never returning for follow up.[10] Some women may not feel ready to initiate ART on the same day as their HIV diagnosis.[26–29] The drop off in care engagement tends to occur within the first few months of ART initiation: 15% of women may not return after the initial ART visit; 20% have stopped seeking HIV care by 3 months after ART initiation, and 25% by 6 or 12 months.[10,30–34] Estimates of sustained engagement in care in neighboring countries that have implemented Option B+ vary depending on the definition used and the maturity of the Option B+ program, but best case scenario estimates still show one in five women are not engaged in care. At 12 months post-ART initiation, engagement was 81% in Cameroon, 79% in Zimbabwe, 73% in Uganda, and 42% in Mozambique, with a pooled regional estimate of 76% in a recent systematic review.[32,35–38]

Engagement among women in Option B+ is generally lower than among non-pregnant or non-postpartum adults on ART in sub-Saharan Africa, which ranges from 80-93%.[35,39] Some of the women who appear to be 'lost to follow up' may have actually transferred their HIV care to another clinic without notifying their original health facility. However, tracing efforts found that only one in three women who had missed their scheduled HIV visits were still obtaining ART from another source.[40] Long-term engagement in care and viral suppression are keys to the success of Option B+, but currently the program is not adequately engaging one-fifth of women.

Engagement in care and viral suppression are necessary for reducing mortality and transmission of HIV. A higher fraction of deaths occurred in patients who were lost to follow up compared to those who remained in care in a study of multiple HIV care settings in east Africa.[41] Sustained viral suppression dramatically reduces the risk of heterosexual [4] and of mother to child transmission.[3] Grounded in the evidence supporting sustained viral suppression, the UNAIDS developed the '90-90-90' goals to reduce the number of new infections and to curb the AIDS epidemic.[11] The goals are to have 90% of persons living with HIV know their status, to have 90% of those who test positive for HIV to be on ART, and to have 90% of those on ART have a low viral load. In the antenatal setting in Malawi, HIV testing is opt-out, and coverage is reasonable but has room for improvement.[42,43] The focus of the current research is on care engagement through Option B+ once women know their HIV status. For ART, about 75-80% of women remain in care 12 months after initiation.[31,44] For viral suppression in Option B+, the single available estimate is 84% among women in care.[45] There is clear room for progress toward reaching 90% of those living with HIV on ART, and 90% of those on ART to be virally suppressed. Moreover, the first-line ART regimen for Option B+ has a relatively low barrier to resistance, so poor adherence or treatment interruptions raise the risk of developing resistant virus and needing to switch to more costly and less tolerable second-line regimens.[46]

Engagement in care consists of linking to HIV care, initiating ART, and continuing to take ART.[47] A practical goal of engagement in HIV care is to achieve viral suppression to reduce the likelihood of transmitting HIV to infants or partners. Facilitators to engaging in care include a desire to prevent transmission of HIV to the infant, motivation to help one's own health, a desire to prevent visible symptoms of HIV, and knowledge about ART.[48–50] Barriers include initiating ART at a younger age (<25), on the same day as receiving an HIV diagnosis, or late in pregnancy, having a lack of social support, HIV-related stigma, denial of HIV status, lack of understanding about Option B+ and ART, financial concerns, and clinic-level factors such as poor treatment from health care workers or long wait times at clinics.[38,40,51–55]

Engagement in care may be hindered by antenatal depression, but evidence is sparse from sub-Saharan Africa. In higher-resource settings, depression reduces HIV care engagement, ART adherence, and viral suppression in non-pregnant adults.[13–20,56–58] Among adults in sub-Saharan Africa, depression has a negative or null effect on engagement in HIV care.[56,59–61] However, the general adult population have historically been sick patients with advanced HIV, due to ART eligibility guidelines; consequently, generalization to relatively healthy perinatal women is unclear. In a study among women in Option B+ engaged in a cash transfer randomized controlled trial, antenatal depression did not appear to be associated with postpartum visit attendance, but women were followed only for 6 weeks.[62]

What has been established specific to the perinatal time period typically consists of studies citing depression as an actual or theoretical barrier to care engagement, but without a quantification of the effect of depression on engagement in care.[51,63–66] For example, among Kenyan women diagnosed with HIV at their first antenatal visit, those with sub-optimal engagement in care were disproportionately affected by postpartum depression, but the temporality of depression and care engagement was not well-delineated.[64] In a small study in the US, women with a history of depression and who had perinatally acquired HIV had lower ART adherence and higher viral loads at delivery than

those without a history of depression.[67] To our knowledge, only one study in the Option B+ population has explicitly examined the effect of antenatal depression on postpartum retention in HIV care; it had null results.[62] In Ethiopia, women with antenatal depressive symptoms had similar attendance at scheduled antenatal care visits, yet had more non-scheduled antenatal or urgent care visits compared to their non-depressed counterparts; HIV status was not incorporated into their analysis.[68] In a recent systematic review of barriers and facilitators to retention in Option B+ care in sub-Saharan Africa, none of the featured studies examined perinatal depression as a distinct contributor.[38] Given the lack of substantial data from sub-Saharan Africa, results from other countries supporting a null or negative relationship between depression and HIV care engagement, qualitative evidence suggesting a link between depression and HIV in Malawi,[69,70] and the documented challenges with sustained engagement in care in Option B+, we sought to characterize the burden and predictors of perinatal depression, and estimate the association between probable antenatal depression and engagement in HIV care.

Quantifying the burden and timing of perinatal depression is needed to best direct mental health treatment efforts. Considering perinatal depression in its own right aside from HIV, estimating the prevalence among a group of women who are already interfacing with the health care system due to being pregnant provides information that clinicians and policy makers need to improve mental health care, as currently systematic screening in antenatal care for perinatal depression has not been widely implemented in sub-Saharan Africa.[42] Good coverage for antenatal depression screening could be feasible given that ≥95% of women attend at least one antenatal care visit in Malawi.[1] We focus on antenatal rather than postpartum depression with regards to engagement in HIV care for multiple reasons: antenatal depression predicts postpartum depression, and could be treated in the context of antenatal care[71]; most all women have an antenatal visit; women with antenatal depression may not continue HIV care postpartum; and in routine care postpartum, the focus is typically on the infant's

rather than the mother's health. Thus, identifying the magnitude of perinatal depression provides information relevant to discussions around improving mental health screening and treatment services.

Estimates of the prevalence of perinatal depression vary, yet the condition is considered to be one of the most common during pregnancy.[12] In Western populations, estimates are 10-15%,[12,72,73] and from sub-Saharan Africa, estimates are generally higher with a wider range: among the general perinatal population, the estimated prevalence is 11% antenatally and 18% postpartum, and among women living with HIV in the region, a pooled study estimated that approximately 23% suffer from depression in the antenatal and in the postpartum periods.[21,74] However, prevalence estimates range from 8.3%[75] to 48.7% among perinatal African women,[76] and from 7.7%[77] to 55.0%[78] among pregnant African women living with HIV. The significant spread of prevalence estimates could be due to heterogeneity of depression assessment methods used (screening tool versus diagnostic, self-report versus clinician interview, major versus major or minor depression), variability in timing of depression assessment during pregnancy, variations in the populations studied, and cultural differences in depressive symptom expression. Some studies note similar a prevalence of depression among participants with and without HIV,[66,79,80] whereas others estimate a higher burden among women living with HIV.[12–14,81,82] Overall, perinatal depression is not rare, and additional information on the magnitude, timing, and associated factors would guide care improvements and further research.

Little is known about the risk factors for antenatal depression among women living with HIV in sub-Saharan Africa. From other countries, predictors of antenatal depression that have been identified include history of depression, history of trauma, poor social support, food insecurity, recent stressful life events, past-year intimate partner violence, and unplanned pregnancy.[75,80,83–86] A recent systematic review of perinatal mental health research in Africa demonstrated that lack of support and family/marital conflict are associated with poorer mental health, but that evidence regarding sociodemographic and obstetrical or medical variables is inconclusive.[74] Notably, this review did not

focus on factors that may be unique to or more prominent among women living with HIV, such as disclosure of HIV status, infant HIV status, or intimate partner violence.[87] Identifying predictors that are readily available to clinicians would expand the toolset to customize comprehensive HIV care.

Early recognition of perinatal depression among women living with HIV is imperative given that untreated perinatal depression can lead to adverse outcomes for mothers and infants. For mothers, consequences include impaired functioning, poor quality of life, or death.[79] Infants born to mothers with untreated perinatal depression have increased risk of low birth weight,[88] preterm birth,[89,90] behavioral difficulties,[89] malnutrition,[91] and social interaction difficulties.[92,93] Mothers with perinatal depression can be less responsive and less sensitive to their infants,[94,95] which can lead to infants with insecure attachment and colic.[96] Children of mothers with perinatal depression may be at higher risk for depression themselves.[97–99]

Taken together, we know that engagement in Option B+ is sub-optimal, that depression is at least as common among people living with HIV as among those uninfected, that untreated perinatal depression carries adverse outcomes for mothers and infants, and that depression may negatively affect engagement in HIV care. Despite over 6 years passing since Malawi implemented Option B+, perinatal depression has not been well characterized among participants. Thus, the motivation for this research is to shed light on the magnitude of perinatal depression, and to evaluate to what degree antenatal depression contributes to sub-optimal engagement in care.

Significance

The prevalence of HIV in Malawi among women is high, long-term engagement in Option B+ is sub-optimal, and perinatal depression is understudied but may impede the success of Option B+. This research addresses questions of real-world clinical significance, namely, what is the burden of perinatal depression, what predicts antenatal depression, and how does antenatal depression influence women's engagement with the Option B+ ART program? The answers to these questions will help inform both HIV

and mental health services. The study focuses on Malawi, but could be useful to other sub-Saharan African countries that have implemented Option B+ as part of their prevention of maternal to child transmission of HIV program. The contribution from this research include estimates and characterization of probable antenatal depression, and the effect of these symptoms on postpartum engagement in care among women living with HIV enrolled in Option B+.

Innovation

In 2011, Malawi became the first sub-Saharan African country to implement Option B+, which went on to become the WHO-recommended PMTCT approach. As such, Malawi has the most mature Option B+ program, and results from Malawi may be informative for neighboring countries who have subsequently adopted the Option B+ program. Our research leverages the data from an established cohort study that collected thorough covariate data on clinical, demographic, and psychosocial factors. We provide the first estimates of the magnitude of perinatal depression and factors associated with antenatal depression among Malawian women enrolled in Option B+.

The current research follows women through 12 months postpartum, which is notable because in the setting of Option B+, which aims to provide *lifelong* ART to women, the longer term follow up will provide timely and relevant information for optimizing the Option B+ efforts. The Ministry of Health is keenly interested in how well their program is able to achieve one of its main goals: maintain women with HIV engaged in HIV care beyond and between their pregnancies. To maximize the full potential benefits of Option B+, we need to identify ways to help women remain engaged in HIV care with viral suppression. Ours is the first longitudinal study to prospectively assess the relationship between antenatal depression and two important HIV care outcomes (viral suppression and visit attendance) in Malawi's Option B+ population. Most studies to date have been cross-sectional, or had limited follow up postpartum. Our study highlights the effect of antenatal depression on viral suppression and engagement in care through at least 12 months post-ART initiation, with a sensitivity analysis extending

engagement through 12 months postpartum. Follow up through the first year postpartum expands our understanding of perinatal depression in the Option B+ population, which may inform longer term care engagement efforts.

CHAPTER III: METHODS

Overview

The overarching questions that drove this research were: 1) Who in Option B+ has probable perinatal depression?; 2) When in the perinatal period does probable perinatal depression occur among women enrolled in Option B+?; and, 3) Does the presence of probable antenatal depression contribute to the sub-optimal engagement in Option B+ HIV care during the postpartum period? Thus, the goals of this research were to identify factors associated with probable antenatal depression, characterize the prevalence and incidence of probable perinatal depression, and examine the relationship between probable antenatal depression and HIV care outcomes. The data come from a cohort study of pregnant women living with HIV in Lilongwe, Malawi called the Safety, Suppression, Second Line, Survival (S4) study. We used the available perinatal depression scores to estimate the prevalence, incidence, and associated factors using a dichotomous threshold for probable perinatal depression. Participant follow up data provided information on who remained engaged in care through 12 months post-ART initiation and 12 months postpartum.

Study Description and Design

The current research aims were an ancillary component of the ongoing Safety, Suppression, Second-Line, Survival ("S4") study at The UNC Project – Malawi (see Table 1; ClinicalTrials.gov identifier: NCT02249962). Malawi is a land-locked country in south eastern Africa of 16 million inhabitants, with 12% of adult women infected with HIV.[1]

Table 1. S4 study: safety, suppression, second-line, survival in Lilongwe, Malawi

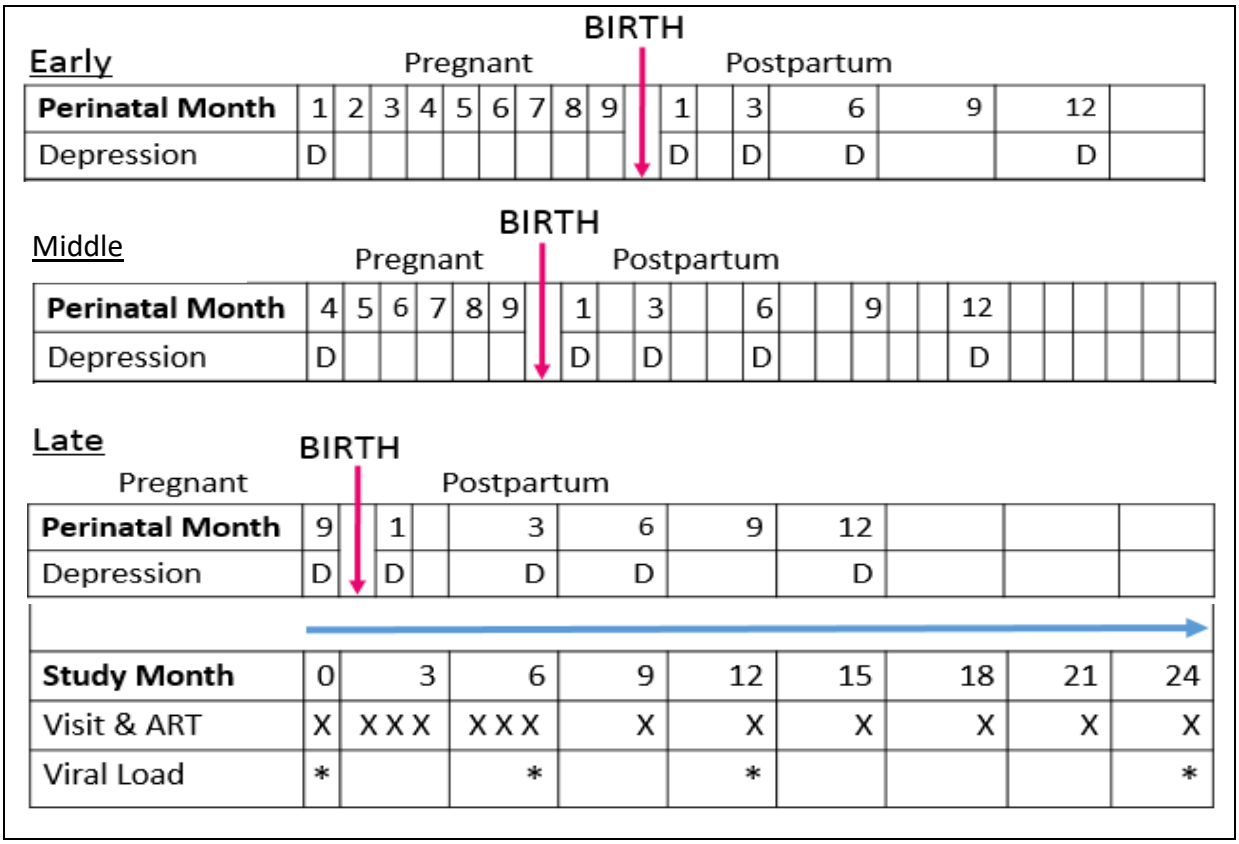
Objective	Characterize the safety, durability, ART resistance, and clinical outcomes for mothers and infants enrolled in Option B+ for prevention of mother to child transmission and HIV treatment in Malawi
Study design	Longitudinal observational cohort, following until ≥12 months postpartum (S4 duration: 2015-2020)
Study population	600 women living with HIV in Lilongwe city, recruited at their 1st antenatal care visit
Inclusion criteria	• Female age ≥18 years (or 16-17 and married), pregnant; plan to birth in Lilongwe • HIV positive by 2 rapid tests approved by the Malawi Ministry of Health (Alere Determine™ and Unigold™) • Willing and able to provide informed consent
Exclusion criteria	• Female age <18 years (or 16-17 but unmarried); not pregnant; plan to give birth outside Lilongwe • HIV negative • Incapable or unwilling to provide informed consent

For this dissertation's study population, the S4 study enrolled women at their first antenatal care visit at a governmental antenatal health center in Lilongwe between May 2015 and July 2016. Women living with HIV were enrolled at any point during pregnancy if they met eligibility criteria for one of two sub-cohorts: newly HIV-diagnosed pregnant women initiating first-line ART (cohort A); or established HIV-positive women on ART during a subsequent pregnancy requiring second-line ART (cohort B). Women living with HIV who defaulted from ART care (either for their own health or for a previous pregnancy) but return for subsequent pregnancy management, were enrolled into S4 but are not featured in this dissertation. In the current research, cohort A (women initiating ART) are the study population for aims 1 and 3, and both cohorts A and women screened for cohort B (women who had been on ART ≥6 months) constitute the population for aim 2. S4 participants returned to the S4 clinic for their antenatal and postpartum care, which includes ART medicine dispensing. All S4 study visits were in-person at a clinic adjacent to the governmental health facility.

We examined probable perinatal depression and the effect of probable antenatal depression on HIV care outcomes over 12-months postpartum using S4 study data. In S4, viral load was measured at enrollment, delivery, and months 6, 12, and 24 post-ART initiation. Given that women were enrolled in

the study at any month of gestation, the alignment of the study month and pregnancy/postpartum time scales varies. Perinatal depression was assessed at study entry and four times postpartum (months 1.5, 3, 6, and 12). Figure 2 features example timelines for a study participant based on whether she enrolled in S4 in the early, middle, or late in her pregnancy.

Figure 2. S4 exposure & outcome assessment timeline



Study Population

During the period when participants featured in the current research were enrolled (May 2015 – June 2016), n=18,116 women registered for antenatal care at Bwaila hospital. Of those, n=952 (5.2%) were newly diagnosed with HIV, and n=964 (5.3%) had previously tested positive for HIV, for an overall HIV prevalence of 10.6% among women who sought antenatal care at Bwaila. During the same time period in the overall Lilongwe district, n=97,154 women registered for antenatal care, and n=5,504

(5.8%) were living with HIV. Thus, Bwaila served 19% of women seeking antenatal care, and had a population with a higher HIV prevalence compared to the overall Lilongwe district.

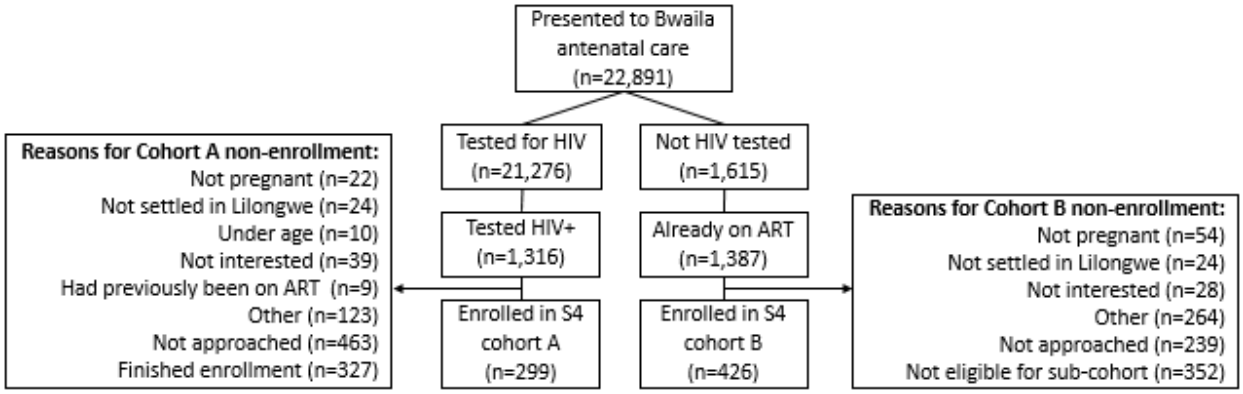
S4 study nurses recruited from women who tested positive or were known positive for HIV at their first antenatal visit. More women were available for recruitment than S4 could enroll, so nurses approached as many women with an HIV diagnosis as possible each day to describe what participation in S4 would entail, and referred interested women who could not be seen on the same day to return on a subsequent day. Women who chose not to participate or were ineligible received routine antenatal and HIV care through the government clinic. Aim 1 (chapter 4) required baseline data from women initiating ART (cohort A) and women who had been on ART at least 6 months (cohort B; see Table 2). Aims 2 and 3 (chapters 5 and 6) required follow up data through 12 months postpartum from women newly initiating ART (cohort A).

Women in S4 who were newly initiating ART (n=299, cohort A) represented 31% of the women who had a new HIV diagnosis at Bwaila from May 2015 – June 2016. Women who participated in S4 who had been on ART at least 6 months (n=426, cohort B) represented 43% of those at Bwaila on ART for at least 6 months between May 2015 – December 2016. Overall, of the women S4 nurses were able to approach, 59% of new initiators and 57% of women with at least 6 months on ART enrolled in the S4 study (see Figure 3).

Table 2. Dissertation aims and contributing data

Aim	*Data source*
Aim 1: factors associated with probable antenatal depression	Baseline data from cohorts A & B Total sample size: 725 (A=299; B=426)
Aim 2: prevalence & incidence of probable perinatal depression	Baseline & postpartum follow up data from cohort A (n=299)
Aim 3: association of probable antenatal depression with engagement in HIV care (visit attendance, and viral suppression)	Baseline & postpartum follow up data from cohort A (n=299)

Figure 3. Enrollment diagram for S4 cohorts A and B at Bwaila antenatal clinic, May 2015 – December 2016



Data Collection & Variable Descriptions

All S4 study visits were in-person interviews at the study site conducted at enrollment, monthly for 6 months, and quarterly thereafter including visits coinciding with postpartum months 1.5, 3, 6, 9 and 12 (see Figure 2 above). The interviews were conducted in Chichewa (the predominant language in Lilongwe) by an S4 study nurse in a quiet, private room at the antenatal care clinic. The S4 nurses received training directly on the questionnaires used in S4 to assess the psychosocial aspects of interest. All S4 study nurses and physicians were veteran researchers with ample experience interviewing participants in a non-judgmental manner and providing HIV and perinatal care. Specifics of the exposure, outcomes, and covariates as obtained from S4 are included below.

S4 visit schedule & interviews

The baseline antenatal interview addressed demographics (age, education, socioeconomic measures), relationship status, HIV testing and treatment history, pregnancy history, and antenatal depression. Follow up interviews at postpartum months 1.5, 3, 6, and 12 addressed HIV status disclosure, postpartum depression, social support, and stressful life events. At all follow up visits, S4 collected self-reported ART adherence and treatment side effects.

Perinatal depression assessment

Perinatal depression was assessed at the first antenatal care visit (S4 study enrollment), and at postpartum months 1.5, 3, 6, and 12 with the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire-9 (PHQ-9). The EPDS contains 10 questions about depressive symptoms in the past 7 days, and was designed to detect depression while women are pregnant or postpartum.[100] The EPDS omits the physical symptom items featured on other depression screening tools including the PHQ-9 because pregnant women may experience increased fatigue and appetite or sleep changes due to pregnancy or having a young infant and not necessarily due to any depression.[101] Anxiety symptoms may be more prominent in perinatal depression compared to major depression that occurs at other times in life,[102] and 3 of the 10 EPDS questions focus on about anxiety symptoms. Each item on the EPDS is scored from 0 to 3, giving an overall score range of 0 to 30. A previous study validated the EPDS in Chichewa,[103] and recommended a score threshold of 6 rather than the typical 13 for a dichotomous cut-point to indicate probable major perinatal depression (sensitivity: 76.3%, specificity: 74.1%). Thus, in our analyses, women who scored ≥6 on the EPDS screened positive for probable perinatal depression. In a review of EPDS validation studies in Africa, the EPDS performed well as a screening tool for major depression among perinatal populations.[104]

The PHQ-9 is a 9-question instrument that assesses depressive symptoms in adults, and asks about how often each symptom has occurred in the past 2 weeks. Responses to each item range from 0

(symptom occurred zero days in the past two weeks) to 3 (nearly every day), for an overall score range of 0 to 27. A score of 10 or more is traditionally used as indicative of major depression, with a score of 5-9 suggestive of mild depression.[105,106] In the current analyses, a score of 5 or greater on the PHQ-9 was considered a positive screen for probable perinatal depression. The PHQ-9 was translated and back-translated in Chichewa and has been used in multiple neighboring countries, however there has not yet been a validation of the PHQ-9 published in Malawi.[107–109]

For either the PHQ-9 or EPDS, prevalent probable depression is defined as screening positive on the EPDS or PHQ-9 at any given time point during study participation, whereas incident probable postpartum depression is defined as a positive EPDS or PHQ-9 screen during the postpartum period among women who were previously classified as not meeting depression criteria. A new postpartum depression episode in women with a history of depression prior to S4 enrollment will be considered incident. Continuous EPDS or PHQ-9 scores were not used due to the low overall prevalence of probable perinatal depression and the heavily skewed distribution of the scores. Any woman scoring ≥6 on the EPDS, ≥5 on the PHQ-9, or who endorsed suicidal ideation was referred to a study clinician and offered a referral to local mental health services as indicated.

Outcome assessments

In Aim 3, the outcomes of interest center on engagement in care in the postpartum period. Engagement in HIV care for those who test positive for HIV includes initiating and continuing to take ART, which requires returning to the clinic regularly to pick up ART medicines. There is not a gold standard definition, and context-specific definitions are both reasonable and most meaningful.[110] For the purposes of the Option B+ program, we focus on engagement as defined in two ways that are meaningful for mothers and infants in the first year after ART initiation: visit attendance through 12 months, and being in care with viral suppression at 12 months post-ART initiation. Twelve months after initiating ART while pregnant captures whether women remained engaged in HIV care through their

pregnancies and the early postpartum period. We focus on 12 months post-ART initiation because it contained the same amount of follow up time for all participants. We examined 12 months postpartum in a sensitivity analysis because it provides information on whether women had ART coverage during pregnancy and the majority of the breastfeeding period, and programmatically is the middle of 3 time points when HIV-exposed infants are tested for the virus and aligns with WHO breastfeeding recommendations.[111,112]

Engagement is operationalized in the current analyses as HIV care visit attendance because the visits are when women received their monthly or quarterly supply of ART medicines. The *primary* outcome definitions are:

- Visit attendance: participant attended all 8 scheduled visits in the first 12 months post-ART initiation within 30 days of the appointment date
- HIV viral suppression: in care and <1000 viral copies/mL at 12 months post-ART initiation

Visit attendance is assessed by reviewing the S4 database and whether each scheduled visit was attended or not according to the above definition. For patients initiating ART in Malawi, standard of care involves monthly visits through 6 months and visits every 3 months thereafter. Patients receive their next month(s) supply of ART during these visits. Similarly, pregnant clients are encouraged to attend monthly antenatal, and then well-child visits at week 6 and months 3 and 9 postpartum. Regular attendance is important for medication refills and infant care, so returning to clinic within 30 days of the next scheduled visit was be the primary measure of engagement in care. All participants will have a result for this outcome (0 = did not attend all 8 visits within 30 days of schedule; 1 = attended all 8 scheduled visits within 30 days of the expected date). Per Malawi National ART Guidelines, if a patient returns to HIV care after missing scheduled visit(s), she can resume ART[113]; the above retention definition still holds.

In a sensitivity analysis, we examined engagement in care through 12 months postpartum, and used the same "engaged in care" definition of attended all scheduled visits from ART initiation through the first 12 months postpartum. Women who missed any of their scheduled visits were considered to be inadequately engaged in care. Scheduled visits were counted as those when a woman was due to pick up her next supply of ART medicines.

HIV viral suppression at 12 months post-ART initiation was defined as <1000 copies/mL per Malawi Ministry of Health HIV ART Management Guidelines.[113] Women were considered unsuppressed if they did not attend their 12 month visit within the 30 day window, or if they attended but had a viral load ≥1000 copies/mL. The local standard of care treatment algorithm is based in part on this 1000 copies/mL cut-point. Viral load is an objective measure of ART adherence. Adequate ART adherence generally results in viral suppression, yet measuring adherence itself is prone to error with methods such as patient self-report, pill counts, dispensary information, or serum drug levels.[114–119]

HIV viral load was assessed in the UNC Project-Malawi laboratory from standard venipuncture at enrollment, delivery, and at months 6 and 12 post-ART initiation with the Abbott m2000rt using the Abbott HIV-1 Real Time Quantitative Viral Load Assay, with standard protocol. The laboratory is certified by the ACTG and HPTN network laboratory leadership. Laboratory values were exported to the main S4 study database and linked via the participant's unique study identification number. All participants who were virally unsuppressed (≥1000 copies/mL, per Malawi Ministry of Health guidelines)[113] were notified by a study clinician and clinical management followed standard of care. Venipuncture specimens also permitted CD4 count measurement.

Covariates

Factors potentially associated with current probable antenatal depression were broadly grouped into demographic, clinical, and psychosocial variables. Demographic variables included age, education attained, and employment status; clinical variables included death of a previous child, ART history, and

WHO HIV clinical stage; psychosocial variables included current relationship status, whether the current pregnancy was intended, HIV status disclosure to partner (among women who had been on ART ≥6 months), history of verbal or physical intimate partner violence (IPV), and self-reported personal or family history of depression or anxiety. The self-reported personal history was asked as "Do you have any past history of depression or anxiety?", and an analogous question was asked about first-degree family history. No information was available on clinical diagnoses of psychiatric conditions for participants or their family.

All potential factors were dichotomized due to sample size and response distribution: age above versus below the median (29 years); education as finished at least primary school (through Standard 8, approximately equivalent to 8th grade) versus less; unemployed versus any employment; relationship status as currently married versus not; pregnancy intendedness as wanted to become pregnant at that time versus not; HIV status disclosure as already disclosed to partner versus not; personal and family history of depression or anxiety as ever versus never; history of previous child death and of IPV as ever versus never; ART history as ART-naïve versus currently on ART; and WHO HIV clinical stage as 1 versus stages 2-4.

Data Analyses for the Specific Aims

Aim 1: Identify factors associated with probable antenatal depression

Statistical analysis. We used bivariable log binomial regression models to estimate unadjusted prevalence ratios (PRs) to identify items associated with current probable antenatal depression (EPDS ≥6). All items that had a bivariable *p*-value <0.25 were included in a multivariable model; a higher p-value threshold was used to retain potentially important variables that may have had confounding.[120] We excluded variables that would have caused extremely sparse cells (n≤5) in the multivariable model regardless of *p*-value. We evaluated whether any pairs of variables had notable collinearity (OR ≥ 3.0) and retained the variable with a larger bivariable beta coefficient estimate in any such cases. We

evaluated collinearity prior to simplifying the full model via manual backward elimination. To estimate PRs while addressing convergence issues, we used a previously described 2-step modeling process that first uses a modified Poisson model to generate starting estimates for the second-stage log binomial model.[121–124] For backward elimination, we omitted the variable that had the highest *p*-value, then re-ran the simplified model. Variables were eliminated one at a time until each remaining variable had a *p*-value of <0.10. As in bivariable models, a higher p-value threshold was chosen to retain variables with potentially meaningful relationships with probable antenatal depression. A variable indicating whether the woman was newly initiating ART or had been on ART for ≥6 months (referent) was retained in the multivariable model for theoretical differences between the two groups of women. We present adjusted PRs (aPR) and 95% confidence intervals (CI) for each variable retained in the final model.

The binary outcome (probable antenatal depression) was modeled as follows: $(\Pr(\text{antenatal depression}_i)) = \beta_{0i} + \beta_1 X_{1i} + \cdots + \beta_n X_{ni} + \varepsilon_i$ with predictor variables $X_1 \ldots X_n$, coefficients $\beta_0 \ldots \beta_n$, and binomially distributed error term ε. We only included 6 independent variables given our sample size and the prevalence of depression so to not over stratify our data.

Handling missing data. We had minimal missing data in the baseline dataset. The following variables were missing values for participants: WHO clinical stage (n=1 missing); family history of depression or anxiety (n=2); personal history of depression or anxiety (n=2); previous child died (n=3); and disclosed HIV status to partner (n=10). A total of 723 women of the 725 were included in the final multivariable model. Thus, with the small proportion of missing data, we did not use multiple imputation to address those missing values.

Aim 2: Estimate the prevalence and incidence of perinatal depression through 12 months postpartum

Statistical analyses. Using S4 perinatal depression scores from each available time point, we quantified probable antenatal and postpartum depression. We estimated the prevalence and incidence of probable depression using descriptive statistics with an exact 95% confidence intervals (CI). Perinatal

depression coding was binary (0 = EPDS score <6; 1 = EPDS ≥6; and 0 = PHQ-9 <5; 1 = PHQ-9 ≥5). We compared participants' PHQ-9 and EPDS scores to determine how often scores were concordant positive (PHQ-9 ≥5 and EPDS ≥6), concordant negative (PHQ-9 <5 and EPDS <6), or discordant (PHQ-9 ≥5/EPDS <6, or EPDS ≥6/PHQ-9 <5). We calculated Cohen's kappa statistic, proportions of negative and positive agreement, and the prevalence and bias adjusted kappa given that the prevalence of positive probable perinatal depression was very low.[125,126] We further categorized each EPDS and PHQ-9 score into no, mild, moderate, or severe symptoms based on score categories from previous studies[106,127] and compared concordance of EPDS and PHQ-9 scores at a given clinic visit to understand how the symptom severity endorsed for each instrument aligned. From this comparison, we calculated a kappa statistic and weighted kappa.[128] The most and least commonly endorsed items on the EPDS and PHQ-9 are noted as proportions of people who scored >0 on that item. Three women died during postpartum follow-up and five women withdrew from the study; their completed EPDS and PHQ-9 scores are included, but they are not in the analysis for the postpartum time points after their deaths or study withdrawal.

Handling missing data. Not all women attended all follow up visits when the depression questions were asked. Although loss to follow-up was in the expected range, in order to gain a fuller understanding of the potential bias introduced by missing data on prevalence estimates, we completed a sensitivity analysis to estimate the prevalence of probable depression we would have observed with complete data. There were two broad reasons for missing data: 1) the participant did not come to the clinic for that visit, or 2) the participant attended the visit but was not asked the PHQ-9 or EPDS questions due to an error on the part of the study staff. One reason for the PHQ-9 or EDPS questions not being asked at an attended visit was an adverse birth outcome (miscarriage, stillbirth, or neonatal death). All women, regardless of pregnancy outcome, were supposed to be asked the EPDS and PHQ-9 questions at the same time points. However, operationally the administration of the EPDS and PHQ-9

was linked to the infant's week 6 and month 3, 6 and 12 visits; thus, when no infant was present the depression questions were not asked.

In the sensitivity analysis, we estimated a plausible range of the prevalence of probable depression we would have observed with complete data. For all scenarios, we assumed that women who attended clinic with a live infant but were not asked the EPDS/PHQ-9 had a prevalence of probable perinatal depression comparable to that of women who completed the EPDS/PHQ-9. To account for the other two groups of missing data (women who attended clinic without a live infant, and women who did not attend clinic), we considered the following three scenarios of low, intermediate, and high depression: 1) In the lowest prevalence scenario, we estimated that women who did not attend clinic had a prevalence of probable depression half that of women who answered the EPDS/PHQ-9 but women with non-live infants who attended clinic had a prevalence equal to that of women who did have scores at that visit; 2) In the intermediate prevalence scenario, women who did not attend clinic or attended but had a non-live infant had a prevalence of probable depression twice as high as women who answered the EPDS/PHQ-9; and 3) In the highest prevalence scenario, women who did not attend clinic or attended but had a non-live infant had a prevalence of probable depression five times as high as women who answered the EPDS/PHQ-9. In our "lowest prevalence" scenario 1, we did not assign a lower probable depression prevalence to the women who had non-live infants based on previous literature that suggests pregnancy losses and infant deaths may be associated with increased maternal depression.[129–132]

Power, sample size & precision. Precision is important for calculating a clinically meaningful estimate of prevalence and of incidence for this Aim. With a sample size of 300, there was 80% power for our estimates to be precise within ±2.5-5.7 percentage points with a prevalence and incidence range from 5-50%.[133]

Aim 3: Estimate the association of probable antenatal depression with engagement in care and with viral suppression

Statistical analyses. In the primary analyses, two separate models were run. The exposure was defined as an EPDS score ≥6 on the day of ART initiation, and the two engagement in care outcomes of interest – visit attendance through 12 months post-ART initiation, and viral suppression – were defined as dichotomous variables at 12 months post ART-initiation (attended all ART-dispensing visits within 30 days of scheduled date in the first 12 months, and viral load <1000 copies/mL). We used linear binomial regression models to estimate crude and adjusted risk differences (RD) for visit attendance and prevalence differences (PD) for viral suppression, each with 95%CI at 12 months by probable antenatal depression status.

Our literature review informed the development of directed acyclic graphs (DAGs) representing each of the exposure-outcome relationships. The DAGs identified the following potential confounders: depression history, IPV history, marital status, and social support. We used standardized mortality ratio (SMR) weights with robust variance estimation for the 95% confidence interval to control for the minimally sufficient set of potential confounders, but did not have a measure of social support. We did not include any mediators in the models for theoretical reasons.[134] SMR adjustment reweights the unexposed population to resemble the exposed to remove confounding, and produces estimates of the difference in HIV care engagement outcomes if antenatal depression could be removed from those who screened positive for the condition.[135–138] Our models yielded estimates of the risk or prevalence difference of engagement in care defined as visit attendance (RD) and as engaged in care with viral suppression at 12 months post-ART initiation (PD), while adjusting for potential confounders.

We undertook two secondary analyses using comparable binomial regression models to the main analysis. In one, we relaxed the definition of visit attendance through 12 months post-ART initiation to allow women to miss 1 visit out of the 8 scheduled visits (attended ≥7 visits) and still qualify as having adequate attendance. In another, we estimated the relationship of probable antenatal depression with

100% visit attendance through 12 months postpartum, a time interval that coincides with the WHO breastfeeding recommendation.[112]

We performed two sensitivity analyses to address potential bias from inappropriate selection into the study and from outcome misclassification. Inappropriate selection into the study sample could have arisen because some women may have reported being ART-naïve at enrollment when in fact they were already taking ART. In our sample, 28 women had viral loads ≤400 copies/mL on the date of ART initiation. While it is possible to have a low viral load in the absence of ART, a recent study from Malawi showed that over half of participants who said they had not been on ART but had viral loads ≤400 copies/mL at enrollment were found to have detectable plasma ART drug levels.[139] In this first sensitivity analysis, we repeated our models after excluding these 28 women.

Outcome misclassification may have arisen because we defined all women lost to study care as out of care and unsuppressed, whereas in fact some of them may have transferred care to another HIV clinic and remained on ART and suppressed without the study's knowledge. A study in Malawi found that 36% of women "lost to follow up" were accessing ART from other clinics not documented in the available electronic medical record.[40] Thus, to account for potential imperfect sensitivity in our outcome assessment, we calculated the crude risk difference of visit attendance and of viral suppression with lower sensitivity. For visit attendance, sensitivity was 36% lower per the previous study, and for viral suppression, sensitivity was 32% lower. We chose 32% lower sensitivity as plausible for viral suppression if 36% of women who were lost to follow up in our sample were in care elsewhere, and 90% of those in care were virally suppressed (36%*90%=32%), as was found among our observed participants. We assumed 100% specificity, meaning no false positives in our outcome assessments. We conducted all analyses in SAS 9.4.

Handling missing data. In primary analyses, those who were lost to follow up and had neither evidence of ART refills in the electronic medical record system nor documented transfer of care to another clinic were considered to be virally unsuppressed. We conducted a sensitivity analysis guided by literature that found 36% of women "lost to follow up" were accessing ART from other clinics not documented in the available electronic medical record.[40] Thus, a notable proportion of women lost to follow up could have still been on ART and some virally suppressed. We accounted for potential bias in the sensitivity analysis described above.

Power, sample size & precision. For these calculations, visit attendance is used as the outcome. We will test the null hypothesis that there is no difference in visit attendance between those with versus without antenatal depression symptoms. Calculations are based on two-sided hypothesis tests, an alpha level of 0.05 and a power of 80% (beta=0.20). We present power estimates based on a sample of 300 participants.

Literature from our study sites show that 75% of women will remain in care by 12 months post-ART initiation.[140] A clinically meaningful difference in engagement in care is 20%. We expect attendance to be lower among women with probable depression. We have between 80-98% power to detect a RD of 0.20 comparing non-depressed to depressed, depending on the prevalence of antenatal depression (range: 10-33%). Thus, the study is powered to detect moderate effects, which are plausible based on prior literature.[60]

Overall Limitations

Our research results should be interpreted in light of some limitations. The perinatal depression assessments are screening tools, not diagnostic instruments, which may introduce measurement error. The EPDS and PHQ-9 were read aloud to participants by study nurses to ensure consistency in administration in a setting of low literacy among participants. However, some women may have under reported their symptoms because they did not want to admit them to the nurse. For all chapters,

variables included in analyses were self-reported, and there could be misclassification on items such as history of depression or anxiety, history of IPV, pregnancy intendedness, or HIV status disclosure to partner. With our cross-sectional dataset in the first aim (chapter 4), we report the prevalence of probable antenatal depression at study enrollment, but cannot make causal inferences about how any of the considered variables affect incidence and duration of probable antenatal depression. Our sample size is modest for the second and third aims (chapters 5 and 6) (n=299). While there are additional potential confounders of the probable antenatal depression-engagement in care relationship that ideally would have been accounted for (such as social support), data on all potential confounders were not collected. Given the sample size, including additional covariates in the model in the third aim (chapter 6) would have potentially introduced extrapolation beyond our data. We conducted sensitivity analyses as described above where possible to evaluate the degree of potential bias in our main effect estimates that may have been introduced by mismeasurement, misclassification, or inappropriate selection into the study.

Figure 4. Directed acyclic graph (DAG) of probable antenatal depression and visit attendance at HIV care appointments (AIM 3)

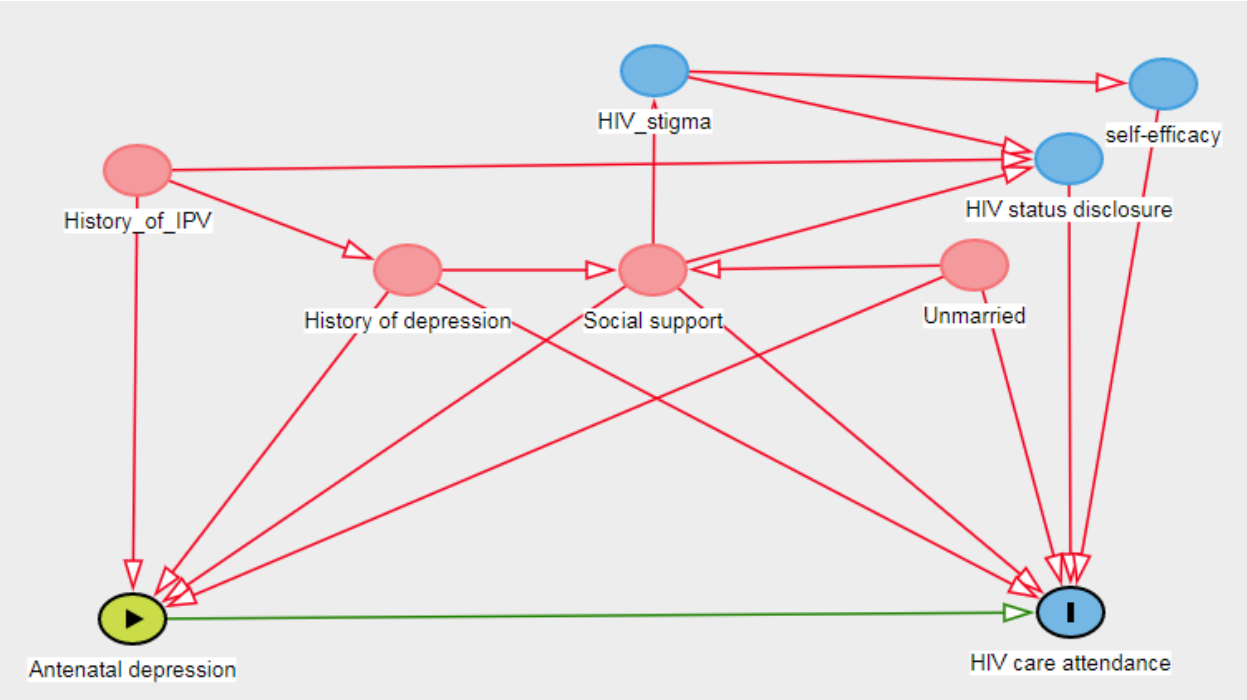
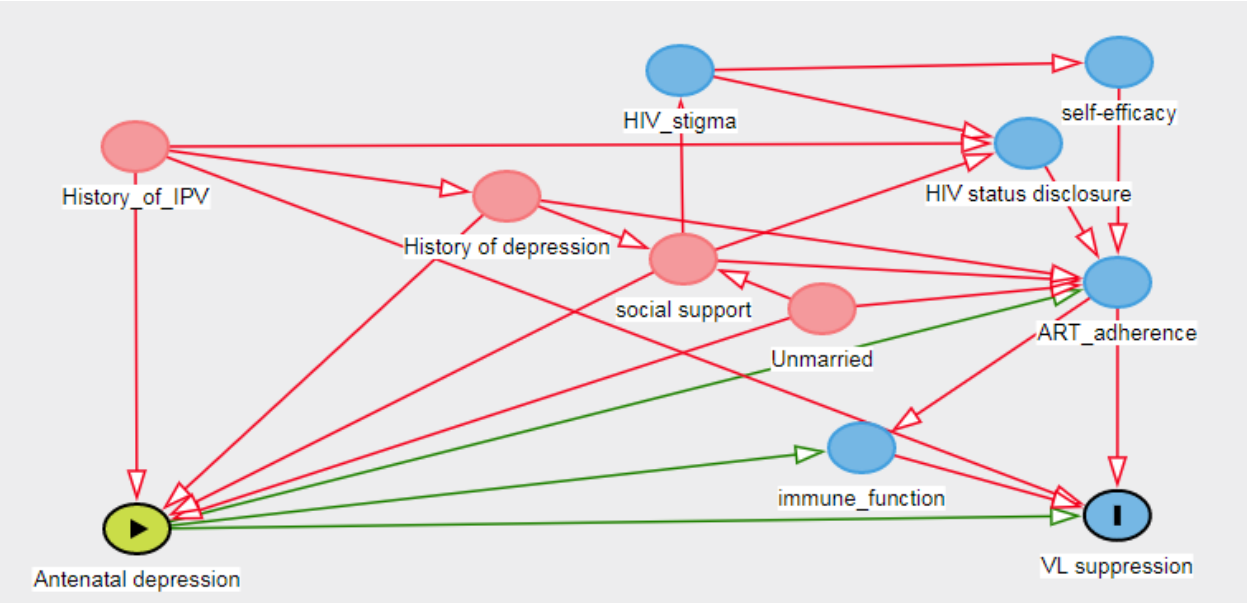


Figure 5. Directed acyclic graph (DAG) of probable antenatal depression and viral suppression (AIM 3)



CHAPTER IV: PREVALENCE AND FACTORS ASSOCIATED WITH PROBABLE ANTENATAL DEPRESSION AMONG WOMEN ENROLLED IN OPTION B+ IN MALAWI

Introduction

Antenatal depression is common worldwide, affecting over one in ten pregnant women.[12] Antenatal depression strongly predicts postpartum depression,[71] and if untreated, is associated with poor outcomes for both mothers and infants. For mothers, consequences include impaired functioning, poor quality of life, or death due to suicide.[79] Infants born to mothers with untreated antenatal depression have increased risk of low birth weight,[88] preterm birth,[89,90] and behavioral difficulties.[89]

Predictors of antenatal depression include history of depression or trauma, poor social support, food insecurity, recent stressful life events, intimate partner violence, and unplanned pregnancy.[75,80,83–86] In Africa, lack of support and family/marital conflict are associated with poorer mental health, but evidence regarding sociodemographic and obstetric or medical variables is inconclusive.[74] Notably, factors that are unique to or more prominent among HIV positive women, such as disclosure of HIV status or intimate partner violence, have not been thoroughly addressed.[87] Overall, depression may be more common among persons with HIV than the general population and depression negatively affects engagement in care, including retention in care, antiretroviral therapy (ART) adherence, and viral suppression.[13–20,56,57] The risk factors for antenatal depression among women living with HIV in sub-Saharan Africa have been underexplored.

Despite the prevalence and consequences of antenatal depression, screening is not routine in many countries regardless of HIV status, including Malawi. Located in south eastern Africa, Malawi has a high prevalence of HIV: 12% of women are infected.[1] Malawi was the first country to implement the "Option B+" prevention of maternal to child transmission (PMTCT) of HIV program in efforts to reduce

the number of perinatal HIV infections. Option B+ is novel because it provides lifelong eligibility for ART to pregnant and breastfeeding women regardless of their immune status – there are no CD4 count or AIDS-defining condition criteria for ART eligibility. While Option B+ has increased the number of women who initiated ART,[8] retention in HIV care has been suboptimal: approximately 25-30% of women stopped returning to HIV care within 12 months of initiating ART.[10,44,141] Antenatal depression may affect retention in HIV care, yet the prevalence of antenatal depression or its associated factors among women enrolled in Option B+ is unclear. We describe here the prevalence of and factors associated with probable antenatal depression among pregnant women enrolled in Option B+ HIV care in Malawi.

Materials and Methods

Study setting and population

Data are cross-sectional from baseline interviews conducted in 2015-2016 for an observational cohort study ("Safety, Suppression, Second-line, Survival - S4", ClinicalTrials.gov identifier: NCT02249962) at the Bwaila Family Health Unit, the busiest government antenatal clinic in Lilongwe, Malawi, with over 15,000 deliveries annually. S4's primary objectives are to evaluate the long-term safety and efficacy of Option B+. All women presenting for antenatal care were offered HIV testing with two rapid tests (Alere Determine™ and Unigold™) per the Malawi standard of care for opt-out HIV testing. Women who tested positive or were known to be HIV positive at their first antenatal care visit were approached to enroll in the S4 study. More women were available for recruitment than S4 could enroll, so nurses approached as many women with an HIV diagnosis as possible each day to describe what participation in S4 would entail, and referred interested women who could not be seen on the same day to return on a subsequent day. Women who chose not to participate or were ineligible received routine antenatal and HIV care through the government clinic.

Women considered eligible for the study were pregnant, at least age 18 years (or 16-17 years and married), planned to give birth in Lilongwe, and able to provide informed consent. S4 study nurses

interviewed participants on the day of their first antenatal care visit in rooms adjacent to the antenatal clinic; all interviews were conducted in Chichewa, the predominant local language, with interview guides that had been translated and back-translated by certified professional Chichewa and English speakers. Most women initiating ART (tenofovir/lamivudine/efavirenz) were newly diagnosed, but a small portion had a previous positive HIV test but had not yet started ART. Our analyses include women who at the time of study enrollment, were initiating ART through Malawi's Option B+ program, and those who had been on tenofovir/lamivudine/efavirenz ART for at least 6 months. While an important group, women who had been on ART less than 6 months were not invited to enroll because the parent study was evaluating women for potential need to switch to second line ART, which is only done among women with at least 6 months on ART.

Measures

Outcome. Current probable antenatal depression was evaluated with the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a 10-question instrument designed to identify symptoms of depression among women who are pregnant or postpartum.[100] The EPDS omits physical symptom items featured on other depression screening tools because pregnant women may experience increased fatigue and appetite changes due to pregnancy and not necessarily their depression.[101] Additionally, the EPDS features three items about anxiety symptoms, which can be particularly prominent during the perinatal period.[102] Scores range from 0 to 30. The EPDS has been translated, back translated, and validated in Chichewa.[103] Although typically a threshold of 13 on the EPDS is used to indicate likely major depression, the Malawian validation study recommended a threshold of 6, which had a sensitivity of 76.3% and specificity of 74.1%.[103] Thus, we considered women who scored ≥6 on the EPDS to screen positive for current probable antenatal depression.

Potential predictors. We evaluated demographic, clinical, and psychosocial factors potentially associated with current probable antenatal depression. Demographic variables included age, education

attained, and employment status; clinical variables included death of a previous child, ART history, and WHO HIV clinical stage; psychosocial variables included current relationship status, whether the current pregnancy was intended, HIV status disclosure to partner (among women who had been on ART ≥6 months), history of verbal or physical intimate partner violence (IPV), and either self-reported personal or family history of depression or anxiety. The self-reported personal history was asked as "Do you have any past history of depression or anxiety?", and an analogous question was asked about first-degree family history. No information was available on clinical diagnoses of psychiatric conditions for participants or their family.

All potential factors were dichotomized: age above versus below the median (29 years); education as finished at least primary school (through Standard 8) versus less; unemployed versus any employment; relationship status as currently married versus not; pregnancy intendedness as wanted to become pregnant at that time versus not; HIV status disclosure as already disclosed to partner versus not; personal and family history of depression or anxiety as ever versus never; history of previous child death and of IPV as ever versus never; ART history as ART-naïve versus currently on ART; and WHO HIV clinical stage as 1 versus stages 2-4.

Statistical analysis

We used bivariable log binomial regression models to estimate unadjusted prevalence ratios (PRs) to identify items associated with current probable antenatal depression (EPDS ≥6). All items that had a bivariable *p*-value <0.25 were included in a multivariable model; a higher p-value threshold was used to retain potentially important variables that may have had confounding.[120] We excluded variables that would have caused extremely sparse cells (n≤5) in the multivariable model regardless of *p*-value. We evaluated whether any pairs of variables had notable collinearity (OR ≥ 3.0) and retained the variable with a larger bivariable beta coefficient estimate in any such cases. We evaluated collinearity prior to simplifying the full model via manual backward elimination. To estimate PRs while addressing

convergence issues, we used a previously described 2-step modeling process that first uses a modified Poisson model to generate starting estimates for the second-stage log binomial model.[121–123] For backward elimination, we omitted the variable that had the highest *p*-value, then re-ran the simplified model. Variables were eliminated one at a time until each remaining variable had a *p*-value of <0.10. As in bivariable models, a higher p-value threshold was chosen to retain variables with potentially meaningful relationships with probable antenatal depression. A variable indicating whether the woman was newly initiating ART or had been on ART for ≥6 months (referent) was retained in the multivariable model for theoretical differences between the two groups of women that may not have been captured in other variables in our dataset. We present adjusted PRs (aPR) and 95% confidence intervals (CI) for each variable retained in the final model.

All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethical approval: Both the University of North Carolina at Chapel Hill institutional review board and the Malawi National Health Sciences Research Committee approved the S4 study. Any woman scoring ≥6 on the EPDS or who endorsed suicidal ideation was counseled by a study clinician and offered a referral to local mental health services.

Results

Between May 2015 and December 2016, 22,415 women presented to the Bwaila antenatal clinic for an initial visit; most women (93%, n=20,838) received an HIV test through the standard of care opt-out testing, with 6.2% (n=1,294) testing positive, and another 6.1% (n=1,347) already known to have HIV and on ART. If approached by an S4 study nurse, 59% of women newly initiating ART and 57% of women who had been on ART for ≥6 months enrolled in the study. Overall, a total of 725 pregnant women with HIV enrolled in the S4 study during the time period; n=299 women initiated ART through Option B+ and n=426 women had been on ART for ≥6 months.

Participants' median age was 29 years (interquartile range (IQR) 24-33), and women presented at a median 22 weeks gestation (IQR 18-26) (Table 3). Most women were married (90%), unemployed (62%), and reported that their current pregnancy was unintended (68%). Half had completed primary school or more (53%), 17% reported ever experiencing IPV, and 12% had a WHO HIV clinical stage ≥2. Many participants self-reported a history of depression or anxiety: 46% had a personal history and 20% had a family history.

Overall, 9.5% (95%CI 7.5-11.9%) (n=69) of women screened positive for depression, with EPDS scores distributed as shown in Figure 6 (mean score 1.5 (SD 2.8)). By pregnancy trimester, 12.8% (5/39), 8.7% (46/528), and 11.4% (18/158) screened positive in the first, second, and third trimester of pregnancy, respectively. The prevalence of probable antenatal depression among women newly initiating ART (10.0%) and those who had been on ART ≥6 months (9.1%) was similar in bivariable analyses. Unmarried women had the highest prevalence of probable antenatal depression (18.3%), whereas women without a personal history of depression or anxiety had the lowest prevalence (5.6%).

In bivariable analyses, the prevalence of probable antenatal depression was higher among women who were employed (PR 1.67; 95% CI 1.03-2.52), unmarried (2.14; CI 1.23-3.71), had a personal history of depression or anxiety (2.56; CI 1.58-4.15), had a family history of depression or anxiety (2.06; CI 1.30-3.29), had ever experienced IPV (2.08; CI 1.29-3.35), had not intended the current pregnancy (2.00; CI 1.12-3.58), and had an advanced WHO HIV clinical stage (1.50; CI 0.84-2.69) (p <0.25). The initial multivariable model contained a variable for ART status (newly initiating versus been on ART for ≥6 months), plus each variable from the bivariable models with p <0.25 except for family history of depression or anxiety due to collinearity with participant history of depression or anxiety. In the final multivariable model (p<0.10), women who had a personal history of depression or anxiety (adjusted PR [aPR] 2.42; CI 1.48-3.95) or had ever experienced IPV (1.77; CI 1.11-2.81) were more likely to screen positive for current depression. Being employed (1.56; CI 1.00-2.44), unmarried (1.66; CI 0.97-2.84), or

having not intended their current pregnancy (1.78; CI 0.99-3.21) were associated with probable antenatal depression but had confidence intervals that included the null. While a less precise estimate, women newly initiating ART were more likely to have probable antenatal depression than women who had been on ART for ≥6 months (1.39; CI 0.88-2.18).

Discussion and Conclusions

In this study of pregnant women living with HIV enrolled in Malawi's Option B+ ART program, we estimated the prevalence of and identified factors associated with probable antenatal depression. About 10% of participants screened positive for current probable depression during the antenatal period. Compared to other maternal morbidity conditions during pregnancy, only anemia and HIV infection are more prevalent in Malawi.[142]

In other sub-Saharan African countries, antenatal depression prevalence estimates range from 8.3% [75] to 48.7%,[76] with an estimated 10.7% among antenatal Malawian women.[143] Among pregnant women with HIV, estimates range from 7.7% [77] to 55.0%,[78] with a weighted mean prevalence of over 20%.[21] The significant range of prevalence estimates could be due to heterogeneity of depression assessment methods used (screening tool versus diagnostic, self-report versus clinician interview), variability in timing of depression assessment during pregnancy, and cultural differences in depressive symptom expression. Our estimate that nearly 1 in 10 pregnant women with HIV suffer from probable antenatal depression approximates the weighted average of 11.3% (95%CI 9.5-13.1%) estimated in a systematic review of studies in Africa that did not stratify by participants' HIV status.[74] Some studies have found that persons living with HIV have higher prevalence of depression,[13,14,57,144] whereas others have shown a comparable burden of depression among those living with and without HIV.[80,143,145]

Our participants, pregnant women with HIV enrolled in Malawi's Option B+ program, exhibited similar factors associated with current probable antenatal depression as those documented in previous studies: history of depression or anxiety,[71,85,146] history of IPV,[71,76,84,85,143,147,148] unintended

pregnancy,[71,76,84,146–149] and being unmarried.[74,75,84,149] About half of participants self-reported a history of depression or anxiety. While the reported depression or anxiety was not necessarily clinically diagnosed, the information serves as a marker of notable past stress, though participants with current depression may have had recall bias that led to over-reporting a history of depression or anxiety. Women in low resource settings appear to be at increased risk of depression given structural challenges such as food insecurity, unemployment, and gender-based violence, yet evidence has been inconsistent.[150] Age and having had a previous child die were not significantly associated with current probable antenatal depression among participants.

The psychosocial factors that were significantly associated with probable antenatal depression in our sample – IPV, unintended pregnancy, and being unmarried – could be indicators of a less stable social situation or having lower social support. IPV has been linked with depression in both resource-rich and resource-poor settings,[151,152] and especially in the context of the perinatal period.[153] Unintended pregnancy could be an acute stressor that contributes to depression.[84] Only one-third of our participants intended their current pregnancy compared to 60% of respondents in the 2015 Malawi Demographic Health Survey.[1] Becoming pregnant while unmarried is not socially desirable in Malawian culture. However, similar proportions of married and unmarried participants endorsed having an unintended pregnancy, which suggests that marital status has an association with probable depression that goes beyond pregnancy intent. Low social support has been associated with antenatal depression in Malawi; our data lacked a social support measure at baseline, which could have shed light on social support directly.[154] While we cannot determine the directionality between psychosocial factors and probable depression, our data highlight that some pregnant Malawian women with HIV experience probable antenatal depression in conjunction with potentially stressful social situations indicative of instability or low social support.

We considered HIV status disclosure to the participant's sexual partner among women who had been on ART ≥6 months. Women who had not disclosed their status had a prevalence of probable antenatal depression about twice that among women who had disclosed, but did not reach statistical significance. The positive association between HIV status non-disclosure and probable antenatal depression could also be a marker of relationship instability and lack of social support from the partner.[155]

For theoretical reasons, we retained the variable for ART initiation status in our multivariable model to distinguish women who had been on ART from those who were initiating ART that day. Most women who were initiating ART on the day of their first antenatal visit (study enrollment) were newly diagnosed with HIV. As such, newly diagnosed women had not yet had the opportunity to fully process their HIV diagnosis or disclose their status to anyone because it is uncommon for male partners or other family members to accompany women to their antenatal visits. Newly diagnosed women may have had slightly higher EPDS scores in part due to the diagnosis. In the multivariable model, initiating ART was positively associated with probable antenatal depression, although the confidence interval for the adjusted PR includes the null. It is plausible that women who demonstrated longer-term engagement in HIV care had a lower prevalence of probable antenatal depression because women with probable antenatal depression may be less adherent to their ART.[58] Women who had trouble adhering to ART, due to depression or otherwise, would not have met the study criterion for enrollment to the group of women who had been on ART ≥6 months.

Two indicators of socioeconomic status, education and employment, had dissimilar relationships with probable antenatal depression in bivariable models: education was not associated with depression, yet having any sort of employment was positively associated with depression. In the final multivariable model, women who were employed had an adjusted prevalence for probable antenatal depression that

was 1.5 times as high as for unemployed women. It is possible that being employed was a stressor rather than representative of socioeconomic resources.

Our results have some limitations. With our cross-sectional dataset, we report the prevalence of probable antenatal depression at study enrollment, but cannot make causal inferences about how any of the considered variables affect incidence and duration of probable antenatal depression. Our data do not show whether probable antenatal depression was incident during pregnancy or preceded the pregnancy. The EPDS is a screening tool, and does not diagnose antenatal depression. While our cut-point of ≥6 based on the validation study[103] demonstrated reasonable sensitivity and specificity, it is possible that some participants were falsely categorized as screening positive or negative for probable antenatal depression. Altering the cut-point would result in a different prevalence estimate. Applying the reported range of cut-points in the validation article (≥4 to ≥13) in our sample yields prevalence estimates of 17% and 0.8%, respectively.[103]

All variables included in analyses were self-reported, and there could be misclassification on items such as history of depression or anxiety, history of IPV, pregnancy intendedness, or HIV status disclosure to partner. We had no information about recent stressful life events, validated social support metrics, HIV-related stigma, or food insecurity that may have contributed to probable antenatal depression.[84] The S4 study enrolled as many women as possible, but could not enroll all interested women. Some women refused participation due to lack of time, interest, or permission from their male partner. Women who suffered from severe depressive symptoms may have been less likely to participate in the S4 study.

In Malawi, women are not screened antenatally for depression, regardless of HIV status.[42,111] Early recognition of antenatal depression among women living with HIV is imperative given that some women with antenatal depression may not follow through with optimal ART care,[64] and could benefit from prompt depression treatment. Similarly, screening for psychosocial stressors such as IPV, social

support, and HIV-related stigma could be helpful. Moreover, efavirenz, a drug commonly in first-line ART regimens, has been linked with neuropsychiatric side effects including depression.[156] Thus, ART prescribing practices and symptom monitoring may need revision to avoid potential exacerbation of psychiatric symptoms among women with underlying depression. Good coverage for antenatal depression screening could be feasible given that >95% of Malawian women attend at least one antenatal visit.[1] Quantifying the cost effectiveness of depression screening and treatment would be useful for programmatic planning in Option B+.

In conclusion, our estimate of current probable antenatal depression prevalence among women enrolled in Option B+ provides evidence that Malawian women living with HIV bear a substantial burden of probable antenatal depression, comparable to the prevalence observed in other global regions. Integrating depression screening into routine HIV care such as Option B+ should be considered.

Table 3. Participant characteristics (n=725)

Characteristic at enrollment	Median (IQR)	Total N (%)
Age in years	29 (24-33)	
Weeks gestation	22 (18-26)	
Marital status		
Currently married		654 (90)
Not currently married		71 (10)
Education attained		
None/some primary		340 (47)
Finished at least primary		385 (53)
Employment status		
Unemployed		452 (62)
Employed		273 (38)
Current pregnancy intendedness		
Intended		230 (32)
Not intended		495 (68)
Ever experienced IPV		
No		599 (83)
Yes		126 (17)
Disclosed HIV status to partner*		
No		36 (8)
Yes		389 (92)
Participant history of depression or anxiety		
No		394 (54)
Yes		329 (46)
Family history of depression or anxiety		
No		582 (80)
Yes		141 (20)
Previous child died		
No		543 (75)
Yes		179 (25)
WHO HIV Clinical Stage I		
Stage I		635 (88)
Stage II-IV		89 (12)
ART initiation status		
Newly initiating ART		299 (41)
On ART for ≥6 months		426 (59)

*Disclosure of HIV status to partner only listed among women who had been on ART for ≥6 months because some women who were newly initiating ART were diagnosed with HIV the day of the interview

Figure 6. Histogram of EPDS scores at first antenatal care visit with reference line for positive depression cut-point (EPDS score ≥6)

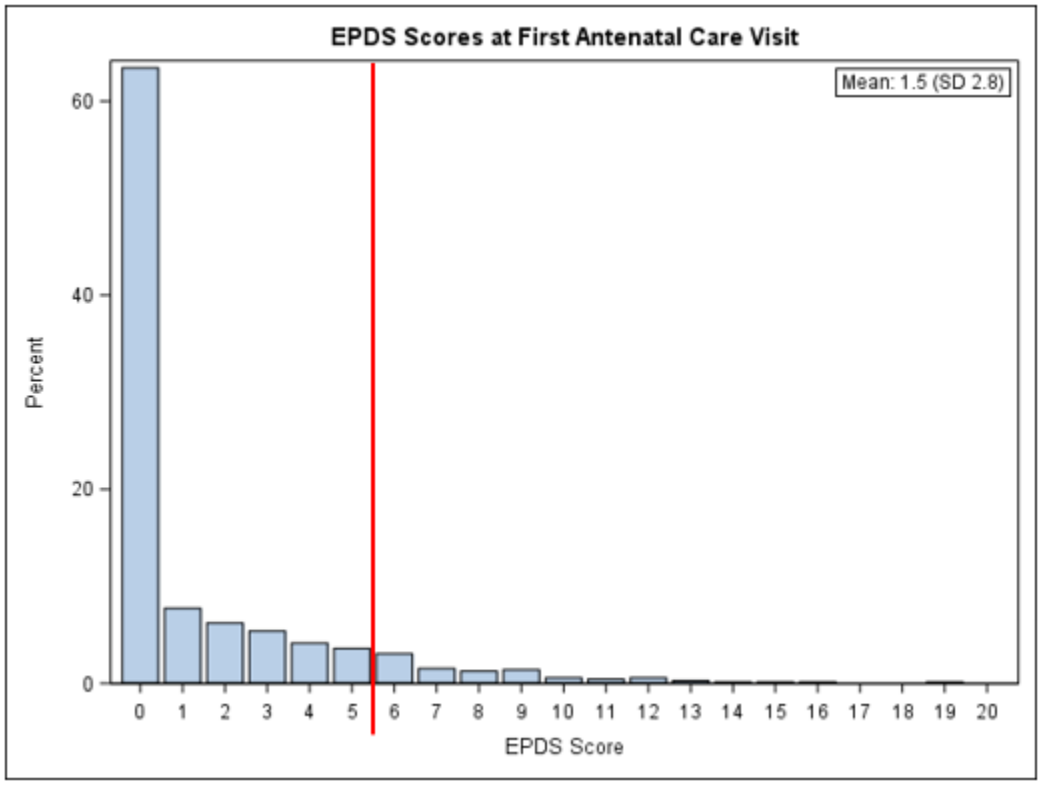


Table 4. Probable antenatal depression prevalence and prevalence ratios (unadjusted, and adjusted (aPR)) according to participant characteristics

Variable	Prevalence (%) EPDS ≥6	PR (95%CI)	aPR (95%CI)
Marital status			
Currently married	8.6	1.00	1.00
Not currently married	18.3	2.14 (1.23-3.71)	1.66 (0.97-2.84)
Education			
None/some primary	9.4	1.00	
Finished at least primary	9.6	1.02 (0.65-1.60)	-
Employment status			
Unemployed	7.7	1.00	1.00
Employed	12.5	1.61 (1.03-2.52)	1.56 (1.00-2.44)
Current pregnancy intendedness			
Intended	5.7	1.00	1.00
Not intended	11.3	2.00 (1.12-3.58)	1.78 (0.99-3.21)
Ever experienced IPV			
No	8.0	1.00	1.00
Yes	16.7	2.08 (1.29-3.35)	1.77 (1.11-2.81)
Disclosed HIV status to partner*			
No	16.7	1.00	
Yes	8.5	0.51 (0.23-1.13)	-
Participant history of depression or anxiety			
No	5.6	1.00	1.00
Yes	14.3	2.56 (1.58-4.15)	2.42 (1.48-3.95)
Family history of depression or anxiety			
No	7.9	1.00	
Yes	16.3	2.06 (1.30-3.29)	-
Previous child died			
No	8.8	1.00	
Yes	10.6	1.20 (0.73-1.99)	-
WHO HIV Clinical Stage			
I	9.0	1.00	
II-IV	13.5	1.50 (0.84-2.69)	-
ART initiation status			
On ART for ≥6 months	9.1	1.00	1.00
Newly initiating ART	10.0	1.10 (0.70-1.72)	1.39 (0.88-2.18)

*Disclosure of HIV status to partner only listed among women who had been on ART for ≥6 months because some women who were newly initiating ART were diagnosed with HIV the day of the interview

CHAPTER V: PREVALENCE AND INCIDENCE OF PROBABLE PERINATAL DEPRESSION AMONG WOMEN ENROLLED IN OPTION B+ ANTENATAL HIV CARE IN MALAWI

Introduction

Perinatal depression, defined as depression which occurs during pregnancy or the first 12 months postpartum, is common, affecting at least one in ten women.[12] When untreated, perinatal depression can lead to poor outcomes for both mothers and infants. Mothers may experience poor quality of life, impaired functioning, less responsivity and sensitivity to their infants, and death due to suicide.[79] Infants of mothers with untreated perinatal depression experience increased risk of low birth weight,[88] preterm birth,[89,90] behavioral difficulties,[89] malnutrition,[91] social interaction difficulties,[92,93] and insecure attachment and colic.[94–96]

Currently, screening for perinatal depression is not conducted systematically during antenatal, postpartum, or well-child care appointments in most countries in sub-Saharan Africa. Prevalence estimates of perinatal depression in sub-Saharan Africa are higher than most global estimates: in the general population, the estimated prevalence is 11% antenatally and 18% postpartum, and among women living with HIV, approximately 23% suffer symptoms in the antenatal and in the postpartum periods.[21,74] Early recognition of perinatal depression among HIV-positive women is imperative given that some women with perinatal depression may not follow through with optimal ART care,[64] and could benefit from mental health treatment.

Malawi, a country in south eastern Africa, has been a leader in the treatment as prevention model of HIV care, particularly through the "Option B+" antiretroviral treatment (ART) program for pregnant and postpartum women.[5,25] The Option B+ model of perinatal HIV care was endorsed as a WHO policy in 2013, and many countries in sub-Saharan Africa have adopted Option B+.[157] Despite the

rapid scale-up of Option B+ for pregnant and postpartum women, perinatal depression has not been assessed longitudinally where Option B+ is active. Implementing systematic screening for perinatal depression in Option B+ HIV care would require data on when during the perinatal period women suffer from the condition.

In the current paper, we estimate the prevalence and incidence of probable perinatal depression through 12 months postpartum among women initiating HIV antiretroviral therapy through the Option B+ program in Malawi. We identify the most commonly reported depression symptoms, consider the influence of missing data on our estimates, and explore factors that might affect measurement of depression severity in this context.

Methods

Study setting and population

Participants were recruited from a government antenatal clinic in Lilongwe, Malawi in 2015-2016. Per the Malawi standard of care for opt-out HIV testing, all women who sought antenatal care were offered HIV testing with two rapid tests (Alere Determine™ and Unigold™). Pregnant women who tested positive for HIV and initiated antiretroviral therapy (tenofovir/lamivudine/efavirenz) through the Option B+ prevention of maternal to child transmission of HIV program were invited to enroll in a cohort study (ClinicalTrials.gov identifier: NCT02249962). All participants were at least age 18 years (or 16-17 years and married), planned to give birth in Lilongwe, and provided informed consent. Study nurses conducted all interviews in Chichewa, the predominant local language. All depression assessments were conducted by study nurses aloud because a significant portion of study participants had limited literacy. Most participants were newly diagnosed with HIV; a small portion had a previous positive HIV test but had not yet started ART. Study interviews assessing probable depression occurred at enrollment (antenatal), and at week 6 and months 3, 6, and 12 postpartum.

Measures

At each time point, participants' depression severity was evaluated with the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire-9 (PHQ-9). The EPDS contains 10 questions about depressive symptoms in the past 7 days, and was designed to detect depression while women are pregnant or postpartum.[100,101] Anxiety symptoms may be more prominent in perinatal depression compared to major depression that occurs at other times in life,[102] and the EPDS contains three questions about anxiety symptoms. Each item on the EPDS is scored from 0 to 3, giving an overall score range of 0 to 30. A previous study validated the EPDS in Chichewa,[103] and recommended a score threshold of 6 rather than the typical 13 for a dichotomous cut-point to indicate probable depression (sensitivity: 76.3%, specificity: 74.1%). Thus, in our analyses, women who scored ≥6 on the EPDS screened positive for probable depression.

The PHQ-9 is a 9-question instrument that assesses depression in adults, and asks about how often each symptom has occurred in the past 2 weeks. Responses to each item range from 0 (symptom occurred zero days in the past two weeks) to 3 (nearly every day), for an overall score range of 0 to 27. A score of 10 or more is traditionally used as indicative of major depression that requires treatment, with a score of 5-9 suggestive of mild depression.[105,106] In the current analyses, a score of 5 or greater on the PHQ-9 was considered a positive screen for probable depression to be consistent with the lower threshold used for the EPDS. The PHQ-9 was translated and back-translated in Chichewa and has been used in multiple neighboring countries, but to date, no validation study of the PHQ-9 has been published in Malawi.[107–109] Prevalent probable depression was defined as screening positive on the EPDS or PHQ-9 at any given time point during study participation, whereas incident postpartum depression was defined as a positive EPDS or PHQ-9 screen during the postpartum period among women who were previously classified as not meeting depression criteria during the antenatal period. Any woman scoring ≥6 on the

EPDS, ≥5 on the PHQ-9, or who endorsed suicidal ideation was counseled by a study provider and offered a referral to local mental health services.

At enrollment, participants were asked whether they had ever experienced verbal or physical intimate partner violence (IPV), or if they or their immediate family members had a history of depression or anxiety. The self-reported personal history of depression or anxiety was asked as "Do you have any past history of depression or anxiety?", and an analogous question was asked about family history. No information was available on actual clinical diagnoses of psychiatric conditions for participants or their family members.

Statistical analysis

We present the raw prevalence and incidence proportions for each time period for the PHQ-9 and EPDS with an exact 95%CI. We compared participants' PHQ-9 and EPDS scores to determine how often scores were concordant positive (PHQ-9 ≥5 and EPDS ≥6), concordant negative (PHQ-9 <5 and EPDS <6), or discordant (PHQ-9 ≥5/EPDS <6, or EPDS ≥6/PHQ-9 <5). We calculated Cohen's kappa statistic, proportions of negative and positive agreement, and the prevalence and bias adjusted kappa given that the prevalence of positive probable depression was very low.[125,126] We further categorized each EPDS and PHQ-9 score into no, mild, moderate, or severe symptoms based on score categories from previous studies,[106,127] and compared concordance of EPDS and PHQ-9 scores at a given clinic visit to understand how the symptom severity endorsed for each instrument aligned. From this comparison, we calculated a kappa statistic and weighted kappa.[128] The most and least commonly endorsed items on the EPDS and PHQ-9 are noted as proportions of people who scored >0 on that item. Three women died during postpartum follow-up and five women withdrew from the study; their completed EPDS and PHQ-9 scores are included, but they are not in the analysis for the postpartum time points after their deaths or study withdrawal.

Sensitivity analysis

Although loss to follow-up was in the expected range, in order to gain a fuller understanding of the potential bias introduced by missing data on prevalence estimates, we completed a sensitivity analysis to estimate the prevalence of probable depression we would have observed with complete data. There were two broad reasons for missing data: 1) the participant did not come to the clinic during that study protocol defined visit window, or 2) the participant attended the visit but was not asked the PHQ-9 or EPDS questions due to an error on the part of the study staff. One common reason for the PHQ-9 or EPDS questions not being asked at an attended visit was an adverse birth outcome (miscarriage, stillbirth, or neonatal death). All women, regardless of pregnancy outcome, were supposed to be asked the EPDS and PHQ-9 questions at the same time points. However, operationally the administration of the EPDS and PHQ-9 was linked to the infant's week 6 and month 3, 6 and 12 visits; thus, when no infant was present the depression questions were not asked.

In the sensitivity analysis, we estimated the plausible range of probable postpartum depression prevalence we would have observed with complete data. For all scenarios, we assumed that the prevalence of probable postpartum depression among women who attended clinic with a live infant but were *not* asked the EPDS/PHQ-9 was the same as the observed prevalence among women who completed the EPDS/PHQ-9. To account for the other two groups of missing data (women who attended clinic without a live infant, and women who did not attend clinic), we considered the following three scenarios of low, intermediate, and high depression: 1) In the lowest prevalence scenario, we estimated that women who did not attend clinic had a prevalence of probable depression half that of women who answered the EPDS/PHQ-9 but women with non-live infants who attended clinic had a prevalence equal to that of women who did have scores at that visit; 2) In the intermediate prevalence scenario, women who did not attend clinic or attended but had a non-live infant had a prevalence of probable depression twice as high as women who answered the EPDS/PHQ-9; and 3) In the highest prevalence scenario,

women who did not attend clinic or attended but had a non-live infant had a prevalence of probable depression five times as high as women who answered the EPDS/PHQ-9. In our "lowest prevalence" scenario 1, we did not assign a lower probable depression prevalence to the women who had non-live infants based on previous literature that suggests pregnancy losses and infant deaths may be associated with increased maternal depression.[129–132] Three women died during postpartum follow-up and five women withdrew from the study; their completed EPDS and PHQ-9 scores are included, but they are not in the analysis for the postpartum time points after their deaths or study withdrawal.

All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethical approval: Both the University of North Carolina at Chapel Hill institutional review board and the Malawi National Health Sciences Research Committee approved the S4 study.

Results

From May 2015 to June 2016, 299 pregnant women living with HIV were enrolled and initiated ART. Participants had a median age of 26 years (IQR 22-30 years) and presented to antenatal care at a median gestational age of 22 weeks (IQR 18-26 weeks) (Table 5). Most women (94%, n=282) enrolled with a WHO clinical stage of HIV of 1, and 6% (n=17) had stage 2 or 3. Many women (38%, n=115) self-reported a history of depression or anxiety, and 16% (n=47) of women reported a family history of depression or anxiety. One-fifth of participants (19%, n=57) reported ever experiencing physical or verbal intimate partner violence.

Prevalence and incidence of probable perinatal depression

The prevalence of probable perinatal depression at each time point was similar between the EPDS and PHQ-9 (Table 6 and Figure 7). At antenatal enrollment, 10% (95%CI 7-14%) (n=30) of women screened positive on the EPDS and 13% (CI 9-17%) (n=38) on the PHQ-9. Postpartum, using the EPDS, the prevalence of probable postpartum depression was 2% (CI 1-6%) (n=4) at 6 weeks, 1% (CI 0-4%) (n=2) at 3 months, 3% (CI 1-7%) (n=7) at 6 months, and 6% (CI 3-10%) (n=12) at 12 months. Postpartum

prevalence using the PHQ-9 was 2% (CI 0-5%) (n=3), 2% (0-4%) (n=3), 2% (CI 1-5%) (n=5), and 3% (CI 1-7%) (n=7) at the same time points. Scores on both the EPDS and PHQ-9 were lower at all postpartum time points than at enrollment (antenatal).

Few women had incident probable postpartum depression (EPDS or PHQ-9 scores above the threshold following scores below the threshold at previous time points). For the EPDS, 16 participants had incident probable postpartum depression: 2.5% (n=4) at week 6, 0% at month 3, 2.6% (n=5) at month 6, and 3.8% (n=7) at month 12 (Figure 8). Estimated incidence was similar with the PHQ-9: 1.3% (n=2) at week 6, 0.6% (n=1) at month 3, 2.2% (n=4) at month 6, and 2.8% (n=5) at month 12.

All participants had EPDS and PHQ-9 scores at enrollment, but only 66% (n=793 of 1196) of expected postpartum EPDS and PHQ-9 scores were collected (range: 58% at postpartum week 6 to 72% at postpartum month 6). At each postpartum time point, approximately one in six participants (17%) was missing depression scores because the woman did not attend clinic. Ten percent of participants attended clinic but were not asked the EPDS or PHQ-9, and 6% attended clinic but were not asked because the infant was not alive due to miscarriage, stillbirth, or neonatal death. In the "lowest prevalence" scenario of our sensitivity analysis, the point prevalence of probable postpartum depression ranged from 1.0% to 5.1% on the EPDS, and 1.4% to 3.0% on the PHQ-9 (Figure 9). In our "intermediate prevalence" scenario, the point prevalence of probable postpartum depression ranged from 1.3% to 7.0% on the EPDS and 1.9% to 4.1% on the PHQ-9 across the postpartum period. Our "highest prevalence" scenario yielded an EPDS prevalence range of 1.9-11.1% and PHQ-9 range of 2.9-6.5% across the postpartum period.

Agreement between the EPDS and PHQ-9

The EPDS and PHQ-9 scores had high concordance when using the dichotomous cut-points: 92.6% had concordant negative scores, and 2.7% had concordant positive scores. Of those with discordant scores, 2.3% of participants had an EPDS score ≥6 but a PHQ-9 score <5, and 2.4% had a PHQ-

9 score ≥5 but an EPDS score <6. The Cohen's kappa statistic was 0.52, and the prevalence and bias adjusted kappa was 0.91. The proportion of negative agreement across assessments was 0.98, whereas the proportion of positive agreement was 0.54. Comparing categories of depressive symptom severity (none, mild, moderate, severe) between the EPDS & PHQ-9, 80% of participants had concordant scores (Table 7). About 10% of participants endorsed no symptoms on the EPDS but endorsed mild symptoms on the PHQ-9, and about 7% of participants endorsed mild symptoms on the EPDS but endorsed no symptoms on the PHQ-9. The Cohen's kappa statistic was 0.45, and the weighted kappa was 0.53.

Commonly endorsed depressive symptoms

The most frequently endorsed items on the EPDS were "things have been getting on top of me," which 9.1% (n=99) of participants cited, and feeling sad or miserable (8.8%, n=96) (Table 8). The least common symptom was thoughts of self-harm (1.3%, n=14). Three items on the EPDS measure anxiety symptoms (items 3, 4, and 5), which were endorsed by 7.0%, 3.5% and 2.5% of participants, respectively. On the PHQ-9, the most commonly endorsed symptom was depressed mood (11.5%, n=126), with the somatic symptoms of fatigue, change in appetite, or sleep disturbances the next most common (10.0%, 9.9%, and 8.2%, respectively). The least frequently endorsed item on the PHQ-9 was psychomotor agitation (1.9%, n=21), and 2.4% (n=26) of participants endorsed thoughts of being better off dead or suicidal ideation.

Discussion

Our study measured probable perinatal depression on the EPDS and PHQ-9 during the antenatal and 12-month postpartum period among women living with HIV in Malawi who enrolled in the Option B+ ART program. We estimated about one in ten women suffered from probable depression antenatally, while only about 1-6% of women met criteria postpartum.

Overall, our antenatal and postpartum prevalence estimates for probable depression were lower than expected based on prior literature. Our estimate of 10-13% probable antenatal depression

prevalence fell at the low end of the range of prior estimates from other sub-Saharan African countries (8.3-48.7%),[75,76] and below a prevalence estimate among women living with HIV in Africa (23.4%).[21] For probable postpartum depression, our prevalence estimates (2-5%) were lower than the estimated 22.5% prevalence among women living with HIV in sub-Saharan Africa,[21] even in a sensitivity analysis with a potentially strong assumption that participants who were lost to follow up or who had an adverse birth outcome had a prevalence of probable depression five times as high as the participants who answered the EPDS and PHQ-9 questions at a postpartum time point. At the time of depression assessment among women living with HIV in prior studies, some were naïve to ART while others had been on ART. Multiple possibilities exist to explain our estimates. Our participants might have been particularly optimistic and resilient, given that they were women who agreed to enroll in a study despite recently receiving an HIV diagnosis and confirmation that they were pregnant – a potentially complicated time for social and health reasons. We do not have attitudinal data to compare the women who agreed to participate in our study and those who refused participation but were eligible.

The low prevalence and incidence of perinatal depression, particularly postpartum, must be interpreted in light of the instruments (both screening tools) and the context. Screening tools have imperfect sensitivity and specificity, even if validated in the local language. The EPDS and the PHQ-9 may not be adequately capturing the burden of probable perinatal depression in our population due to imperfect translation of words or concepts into the Chichewa versions. “Depression” itself may mean something different to women in Malawi, and may manifest in ways outside of the scope of the EPDS or PHQ-9. Not all of our participants were fully literate. All study staff read the EPDS and PHQ-9 questions aloud to the participants and recorded their answers, but the questions and differentiating between answer choices might have been confusing to participants. In a similar setting in Uganda, the performance of a clinician-administered PHQ-9 was high.[158] Cognitive interviews on women’s

comprehension of the questions on the EPDS and PHQ-9, and on the concept of depression would be particularly informative.

In our context, fewer women screened positive for probable depression postpartum than antenatally, yet many women endorsed situations indicative of psychosocial vulnerability, such as personal or family history of depression or anxiety, and history of IPV. The lower postpartum scores could reflect multiple processes. Women may have under-reported their symptoms in part because most health care visits focus on the mother antenatally but on the infant postpartum. Social desirability bias may have also played a role, in which participants may have answered what they thought the interviewer wanted to hear: it is common in Malawi to say that "things are fine" or that "I have managed," which could have led to participants under-reporting depressive symptoms. Additionally, among new mothers, the prevalence of probable perinatal depression was higher postpartum than antenatally, which was in contrast to women with prior children, who had higher antenatal prevalence compared to postpartum. We did not evaluate these differences statistically due to sample size. Further information on the accuracy of the perinatal depression prevalence, the importance of other psychosocial factors, and on cost-effectiveness of depression treatment will be important for discussions about adopting perinatal depression screening in Malawi. In sum, our results suggest the need for data from the local context to determine the optimal process, timing, and setting for implementing screening initiatives.

Both the EPDS and PHQ-9 scores provided similar results regarding probable depression. The EPDS has been validated in Malawi, whereas the PHQ-9 has not but has been used in research and clinical settings, and has been validated in several other sub-Saharan African populations.[103,107–109] On both tools, one of the most frequently endorsed symptoms was that of depressed mood or sadness, and one of the least frequently endorsed symptoms was that of self-harm or suicidal ideation. Many participants endorsed the somatic symptoms present on the PHQ-9 (but absent from the EPDS), which

can be important manifestations of depressive symptoms.[159–162] However, significant physiological and social changes occur during pregnancy and the postpartum period; these changes may influence somatic depressive symptoms of energy level, sleep quality, and appetite. Thus, some women may have endorsed the PHQ-9 somatic symptoms due in part to physiological and social changes related to pregnancy and a new infant.

Thoughts of self-harm or of being better off dead were noted by more participants on the PHQ-9 than when asked about self-harm alone on the EPDS. The wording of the question on the PHQ-9 is broader in that it includes thoughts of self-harm or that the person would be better off dead, rather than only thoughts of self-harm as asked on the EPDS. Additionally, the PHQ-9 asks about a longer time period (past 2 weeks), whereas the EPDS asks about the past 7 days. It is possible that both the different time period and the scope of the question influenced participants' responses to these questions.

The EPDS features three questions about anxiety symptoms that can be used as an anxiety sub-scale.[163,164] The prominence of anxiety symptoms is one way in which perinatal depression may be considered different from non-perinatal major depression.[12,165] Antenatally, the anxiety symptoms were between the 3rd and 9th most commonly endorsed items, and postpartum they were between the 4th and 9th most common. The symptom of "blaming myself unnecessarily when things go wrong" was the leading anxiety symptom noted by the women at any time point. But anxiety symptoms were less frequently endorsed among the women than "things have been getting on top of me" or being sad.

Limitations: Unfortunately, our study did not feature any diagnostic or inter-rater reliability assessments for the depression scores, so we are unable to quantify the extent to which measurement error may have influenced our estimates. Assignment of patients to providers at each time point was essentially random; participants were not triaged to certain providers based on suspected depression status. For capacity building and administration fidelity, future research on depression could consider periodic

refresher training of study staff or clinic providers on how to administer and interpret the EPDS and PHQ-9 as well as nested validation or calibration sub-studies.

In summary, in a sample of women living with HIV and engaged in HIV care through Option B+, we found that one in ten women antenatally and one in twenty postpartum screened positive for probable depression. Although our estimates of perinatal depression were lower than in some comparable populations, a large proportion of the women reported characteristics consistent with heightened mental health vulnerability, including history of depression and anxiety, family history, and IPV. Efforts to scale up Option B+ treatment programs should give careful consideration to the psychosocial supports that patients will need to remain successfully engaged in care for the long term.

Table 5. Participant demographics (n=299)

Characteristic at enrollment	Median (IQR)	Total N (%)
Age in years	26 (22-30)	
Weeks gestation	22 (18-26)	
Marital status		
Currently married		263 (88)
Not currently married		36 (12)
Education attained		
None/some primary		172 (58)
Finished at least primary		122 (42)
Employment status		
Unemployed		190 (64)
Employed		109 (36)
Current pregnancy intendedness		
Intended		132 (44)
Not intended		167 (66)
Ever experienced IPV		
No		242 (81)
Yes		57 (19)
Participant history of depression or anxiety		
No		184 (62)
Yes		115 (38)
Family history of depression or anxiety		
No		252 (84)
Yes		47 (16)
WHO HIV Clinical Stage I		
Stage I		282 (94)
Stage II-IV		17 (6)

Table 6. Prevalence of screening positive for probable perinatal depression on the EPDS or PHQ-9 at enrollment and postpartum time points

Time point	**EPDS ≥6** Prevalence % (95% CI)	**PHQ-9 ≥5** Prevalence % (95% CI)
Enrollment/antenatal (n=299)	10% (7-14%)	13% (9-17%)
Postpartum week 6 (n=174)	2% (1-6%)	2% (0-5%)
Postpartum month 3 (n=193)	1% (0-4%)	2% (0-4%)
Postpartum month 6 (n=215)	3% (1-7%)	2% (1-5%)
Postpartum month 12 (n=211)	6% (3-10%)	3% (1-7%)

Figure 7. Prevalence of probable depression and 95% confidence intervals

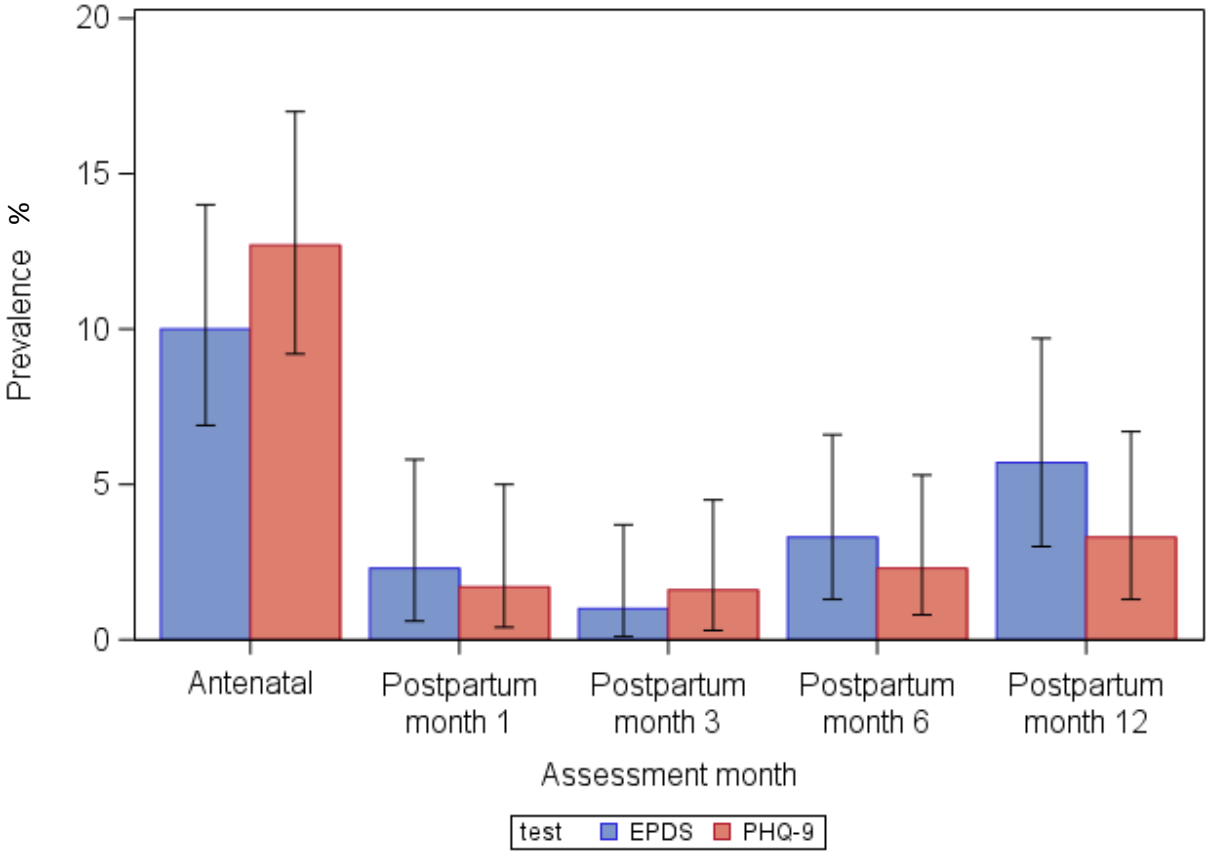


Figure 8. Prevalence and incidence of probable perinatal depression

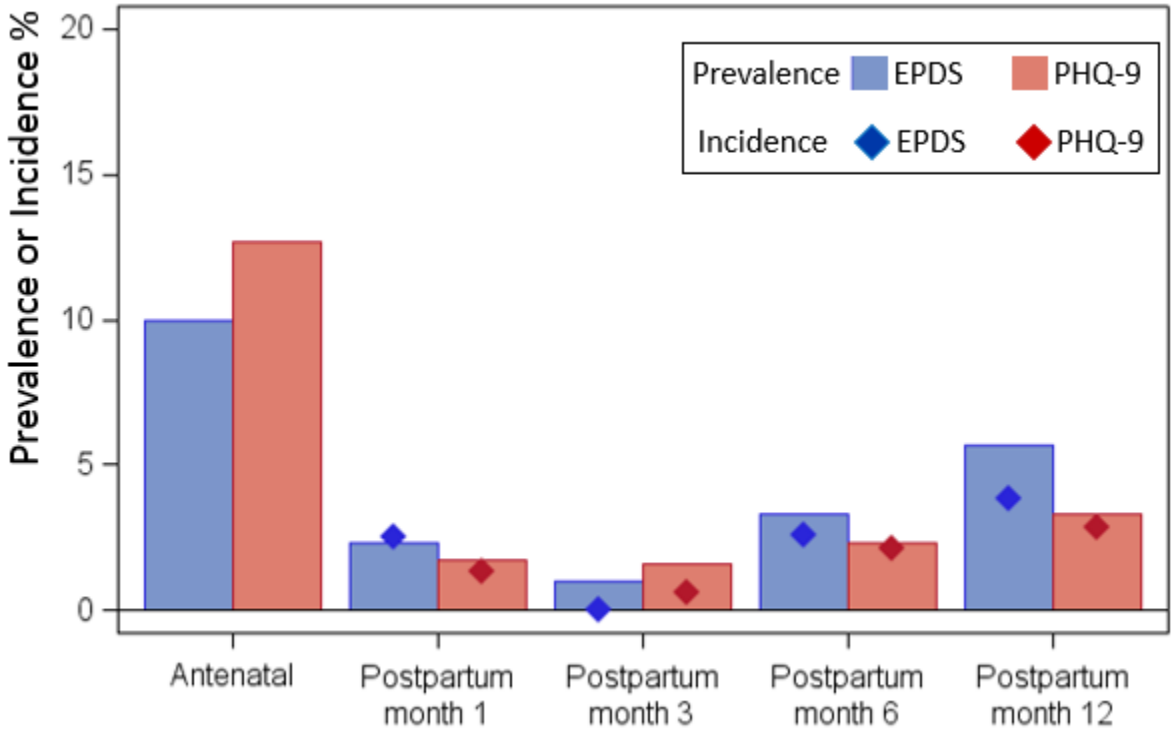
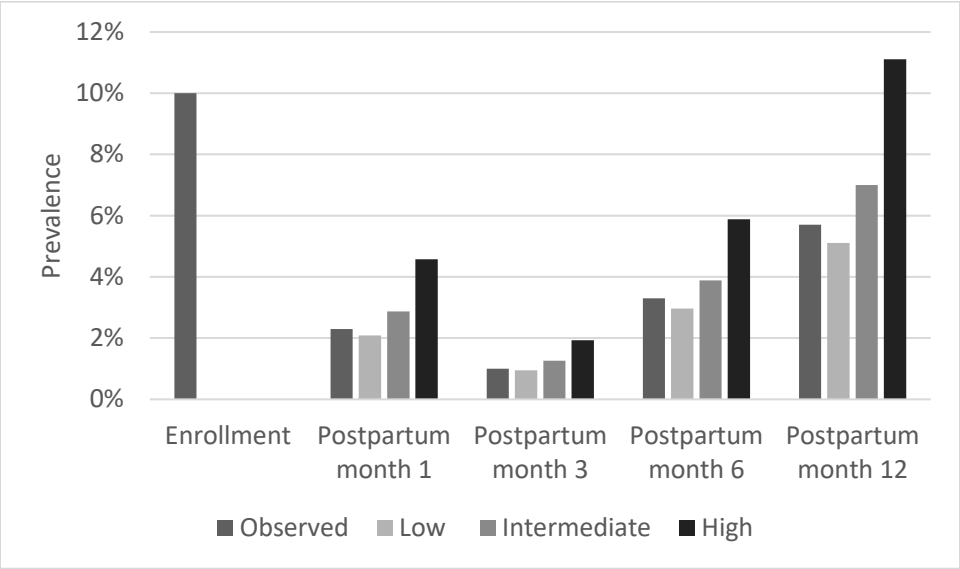


Figure 9. Sensitivity analysis of probable depression prevalence at postpartum time points on the EPDS, accounting for missing data



$N_{observed}$:	299	174	193	215	211

Table 7. Concordance of EPDS & PHQ-9 scores when using categories based on no, mild, moderate, or severe depressive symptoms

Depressive symptom severity	None EPDS: 0	Mild EPDS: 1-5	Moderate EPDS: 6-9	Severe EPDS: 10+	TOTAL
None PHQ-9: 0	69.1%	5.9%	0.7%	0%	75.7%
Mild PHQ-9: 1-4	9.2%	8.3%	1.6%	0%	19.1%
Moderate PHQ-9: 5-9	0.6%	1.6%	1.4%	0.6%	4.2%
Severe PHQ-9: 10+	0%	0.2%	0%	0.7%	0.9%
TOTAL	79.0%	15.9%	3.7%	1.4%	100%

Kappa = 0.45; weighted kappa = 0.53

Table 8. Endorsed items on the EPDS and PHQ-9 – proportion of women who scored >0 on each item on the EPDS and PHQ-9

		Postpartum				
Depressive symptom	Enrollment (n=299)	week 6 (n=174)	month 3 (n=193)	month 6 (n=215)	month 12 (n=211)	Overall (n=1092)
EPDS items	**%**	**%**	**%**	**%**	**%**	**%**
1. Can't laugh/see the funny side of things	9.7	2.9	4.7	6.1	5.2	6.1
2. Haven't looked forward to things	9.7	2.9	1.0	3.7	5.7	5.1
3. Blamed self unnecessarily	16.1	2.3	1.6	2.8	7.1	7.0
4. Anxious or worried for no good reason	7.4	1.7	1.0	0.9	4.3	3.5
5. Felt scared/panicky for no good reason	4.4	1.2	1.6	2.3	1.9	2.5
6. Things have been getting on top of me	21.1	3.5	4.2	5.6	4.7	9.1
7. Unhappiness caused difficulty sleeping	13.0	1.2	2.6	4.2	2.4	5.5
8. Felt sad or miserable	19.7	3.5	3.6	5.6	5.7	8.8
9. Been so unhappy have been crying	9.4	1.7	1.6	3.7	5.2	4.9
10. Thoughts of self-harm	2.7	0.6	0.0	0.9	1.5	1.3
PHQ-9 items	**%**	**%**	**%**	**%**	**%**	**%**
1. Depressed mood	23.1	5.8	5.2	8.4	9.0	11.5
2. Loss of interest	14.4	2.3	2.6	4.7	3.8	6.4
3. Sleep disturbance	22.1	1.2	3.6	4.2	2.4	8.2
4. Low energy, fatigue	26.4	4.0	4.2	2.8	4.3	10.0
5. Loss of appetite or overeating	24.1	6.9	4.2	4.7	2.8	9.9
6. Feel bad about self, that failure	8.7	1.2	0.5	3.3	3.3	3.9
7. Trouble concentrating	6.0	1.2	0.5	1.9	2.8	2.8
8. Psychomotor agitation/retardation	3.7	1.2	0.5	1.9	1.4	1.9
9. Thoughts that better off dead/self-harm	5.4	1.2	0.0	1.9	1.9	2.4

CHAPTER VI: PROBABLE ANTENTATAL DEPRESSION AT ANTIRETROVIRAL INITIATION AND POSTPARTUM VIRAL SUPPRESSION AND ENGAGEMENT IN OPTION B+ HIV CARE IN MALAWI

Introduction

In Malawi, about 12% of adult women are living with HIV.[1] In 2011, Malawi was the first country to adopt the Option B+ program, an innovative strategy that expanded its antiretroviral treatment (ART) eligibility.[2] Consistent with "test and treat" principles, Option B+'s goals are to reduce maternal to child transmission of HIV and to improve long-term maternal health by providing *lifelong* ART to all pregnant or breastfeeding women regardless of how advanced their HIV infection is. Through Malawi's Option B+ program, the number of pregnant women starting ART increased by 748% during the first year.[8]

Despite the rapid expansion of Option B+, sustained patient engagement in HIV care has been challenging and has fallen short of the UNAIDS 90-90-90 goals.[11] The decline in care engagement happens soon after ART initiation: 15% of women may not return after the initial ART visit, and 25% stop seeking HIV care by 6-12 months after ART initiation.[10,30,31,34] Only 37% of facilities in Malawi had >90% retention in care 6 months post-ART initiation.[10] For viral suppression in Option B+, the single available estimate is 84% among women in care.[45] There is clear room for progress toward reaching 90% of those living with HIV on ART, and 90% of those on ART virally suppressed.[11] Long-term engagement in care and viral suppression are necessary for reducing mortality and both heterosexual[4] and vertical[3] transmission of HIV.

Engagement in care may be hindered by antenatal depression, but evidence is sparse from sub-Saharan Africa. In higher-resource settings, depression reduces HIV care engagement in non-pregnant adults.[13–20,56–58] Among adults in sub-Saharan Africa, depression has a negative or null effect on engagement in HIV care.[56,59–61] However, the general adult population have historically been sick

patients with advanced HIV, due to ART eligibility guidelines; consequently, generalization to relatively healthy perinatal women is unclear. In a study among women in Option B+ engaged in a cash transfer randomized controlled trial, antenatal depression did not appear to be associated with postpartum visit attendance, but women were followed only for 6 weeks.[62] In a recent systematic review of barriers and facilitators to retention in Option B+ in sub-Saharan Africa, none of the featured studies examined antenatal or postpartum depression as a distinct contributor.[38]

Antenatal depression is common, associated with adverse maternal and infant outcomes, and treatable.[12,21,89–91,98] But currently, systematic screening has not been widely implemented in sub-Saharan Africa.[42] Understanding how antenatal depression may affect postpartum HIV care engagement is important to improve Option B+. Thus, we quantified the relationship between probable antenatal depression and two important measures of engagement in HIV care (visit attendance and viral suppression) among Malawian women initiating ART through Option B+.

Methods

Study setting and population

In 2015-16, pregnant women living with HIV who sought antenatal care at a government antenatal clinic in the capital city of Lilongwe, Malawi were enrolled into an observational cohort study ("Safety, Suppression, Second-line, Survival - S4", ClinicalTrials.gov identifier: NCT02249962). The objective of the cohort study was to evaluate the long-term safety and efficacy of Option B+. Per Ministry of Health standards, opt-out HIV testing was performed as part of routine antenatal care with two rapid tests (Alere Determine™ and Unigold™). The study staff approached women at their first antenatal visit in any trimester of pregnancy who tested positive for HIV or were already known to be HIV positive to enroll in the S4 study.

Study eligibility included being pregnant, at least 18 years (or 16-17 years and married), planning to give birth in Lilongwe, and able to provide informed consent. The current analyses focus on women

who were initiating ART on the day of their first antenatal visit. Participants were interviewed by study nurses at enrollment, monthly for 6 months, then quarterly for up to 36 months. The cohort study was the source of ART for these women unless they officially transferred care to a non-study clinic. All women initiated ART on Malawi's first line regimen (tenofovir/lamivudine/efavirenz) on the day of study enrollment, and received ART at each study visit. Participants were counseled on Option B+ and encouraged to continue taking ART for life. All interviews were conducted in Chichewa, the predominant local language.

Measures

We evaluated current probable antenatal depression at the first antenatal visit when women enrolled in the study and initiated ART. We used the Edinburgh Postnatal Depression Scale (EPDS consists of 10 questions about symptoms of perinatal depression.[101,102] The EPDS has been validated for use in both the antenatal and postpartum periods, and validated in Malawi in Chichewa.[100,103] EPDS scores range from 0 to 30, and the validated Chichewa version recommends a threshold of 6, which had a sensitivity of 76.3% and specificity of 74.1% for probable major depression.[103] In our analyses, women who scored ≥6 were considered to have current probable antenatal depression. Given that women initiated ART and joined the study during any trimester of pregnancy, the timing of the antenatal EPDS assessments and the postpartum month when women reached 12 months on ART varied.

All women were asked basic demographic and psychosocial questions at their first study visit such as age, marital status, history of verbal or physical intimate partner violence (IPV), and self-reported history of depression or anxiety. The self-reported history was asked as, "Do you have any past history of depression or anxiety?"; no information on clinical diagnoses of psychiatric conditions was available. Marital status, history of IPV, and history of depression or anxiety were included as potential confounders in the multivariable model. Each of the variables was dichotomized: marital status as

currently married versus not, and personal history of IPV and of depression or anxiety as endorsed versus not.

A novel component of the Option B+ program is that it provides lifelong ART, not only during pregnancy and breastfeeding as in prior programs. To maximally reduce the risk of mother to child transmission of HIV, a woman should initiate ART early enough so that she has a low viral load throughout the perinatal period. Both of the featured outcomes of interest capture long-term engagement in care. The two outcomes in the current analyses are: 1) attendance at all scheduled ART-dispensing visits; and 2) in care with viral suppression. Both outcomes were assessed at 12 months post-ART initiation, a time point that captures whether women remained engaged in HIV care through pregnancy and early postpartum.

For the visit attendance outcome, women who attended all of their scheduled visits (n=8) during the first 12 months post-ART initiation were counted as engaged in care. Women who missed any scheduled visit were considered to be insufficiently engaged in care. We chose 100% attendance because women received ART from the study, so missing any visit would indicate an ART lapse. We relaxed the definition in a secondary analysis to allow women to miss 1 out of the 8 scheduled visits in the first 12 months. Additionally, we extended attendance estimates to 12 months postpartum, which was a longer time period than 12 months post-ART initiation, and shows whether women had ART coverage during pregnancy and most of the breastfeeding period.[111] For this time scale, we similarly categorized women as attended all scheduled ART-dispensing visits versus missed any visits since ART initiation.

Viral suppression was defined as <1000 copies/mL, following the Malawian HIV Treatment Guidelines which base treatment change decisions in part on this threshold.[111] Viral loads were assessed at baseline, and at 6 and 12 months after ART initiation. For the outcome of engaged in care with viral suppression, women who attended their 12 month visit within a 30 day window and had a viral load

<1000 copies/mL at that visit were counted as virally suppressed. Women who had a viral load ≥1000 copies/mL or did not attend the visit were considered unsuppressed.

Statistical analysis

Linear binomial regression models estimated crude and adjusted risk differences (RD) for visit attendance and prevalence differences (PD) for viral suppression, each with 95% confidence intervals (CI) at 12 months by probable antenatal depression status. Adjusted estimates controlled for potential confounding via standardized mortality ratio (SMR) weights with robust variance estimation for the 95% confidence interval. SMR adjustment reweights the unexposed population to resemble the exposed to remove confounding, and produces estimates of the difference in HIV care engagement outcomes if antenatal depression could be removed from those who screened positive for the condition.[135–138]

We undertook two secondary analyses for the visit attendance outcome using binomial regression models comparable to the main analysis. One to allow 1 missed visit out of the 8 scheduled in the first 12 months and still qualify as adequate attendance. The other to estimate the relationship of probable antenatal depression with 100% visit attendance through 12 months postpartum, which coincides with the WHO breastfeeding recommendation.[112]

We performed two sensitivity analyses to address potential bias from inappropriate selection into the study and from outcome misclassification. Inappropriate selection into the study could have arisen because some women may have reported being ART-naïve at enrollment when in fact they were already taking ART. In our sample, 28 women had viral loads ≤400 copies/mL on the date of ART initiation. While it is possible to have a low viral load in the absence of ART, a recent study from Malawi showed that over half of participants who said they were ART-naïve but had enrollment viral loads ≤400 copies/mL were found with detectable plasma ART.[139] In this first sensitivity analysis, we repeated our models after excluding these 28 women.

Outcome misclassification may have arisen because we defined all women lost to study follow up as out of care and unsuppressed, yet some may have transferred care to another HIV clinic and remained on ART and virally suppressed without our knowledge. A study found that 36% of Malawian women "lost to follow up" were accessing ART from other clinics not documented in the electronic medical record.[40] To account for potential imperfect outcome sensitivity, we calculated the RD of visit attendance with 36% lower sensitivity, and PD of viral suppression with 32% lower sensitivity. We chose 32% as plausible if 36% of women lost to follow up were in care elsewhere, and 90% of those in care were virally suppressed (36%*90%=32%), as was found among our observed participants.

All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethical approval: Both the University of North Carolina at Chapel Hill institutional review board and the Malawi National Health Sciences Research Committee approved the S4 study.

Results

Between mid-2015 to 2016, 299 pregnant women living with HIV started ART through the Option B+ program and enrolled in the cohort study. Nearly two-fifths of participants self-reported a history of depression or anxiety (38%, n=115), and one-fifth a history of physical or verbal intimate partner violence (19%, n=57) (Table 9). Participants had a median age of 26 years (IQR 22-30) and initiated ART at a median of 22 weeks gestation (IQR 18-26). At 12 months post-ART initiation, women had reached a median of 8.5 months postpartum (range: 4-12). Given the variable timing of delivery relative to ART initiation, at 12 months postpartum, women had reached a median of 16 months since initiating ART (range 12-21). Three women (1%) died before reaching 12 months post-ART initiation, and were excluded from analyses. Five women (2%) withdrew from the study or relocated before reaching 12 months post-ART initiation; we count them as engaged in care and virally suppressed because they officially transferred care to another HIV clinic.

Ten percent of women (n=30) screened positive for current probable antenatal depression on the day of ART initiation. Engagement in care through the first 12 months post-ART initiation was high. Most women (85%) attended the 8 scheduled ART-dispensing visits, including 83% of women with probable antenatal depression and 85% of women without. Six percent of women missed 1 or 2 of the 8 scheduled visits, and 6% of women missed between 3 and 7 visits. A minority (4%) attended no visits after ART initiation.

Participants with and without probable antenatal depression at ART initiation had comparable visit attendance through 12 months (RD: -0.02; 95%CI -0.16-0.12). After adjustment, the point estimate moved slightly further from the null but the confidence interval still contained the null value (aRD: -0.04; 95%CI -0.18-0.10).

Viral loads 12 months after ART initiation were available for 91% (n=269/296) of women, although some had missed prior visits. Of those who presented to care for their 12 month visit, 241 women (90%) had viral loads <1000 copies/mL; thus 81% (241/296) of women both presented to care and were virally suppressed. Proportions of women in care with viral suppression were comparable by probable antenatal depression status at both 6 and 12 months post-ART initiation: 80% each at 6 months, and at 12 months, 80% among women with probable antenatal depression and 82% among women without (Figure 10). In crude and adjusted analyses, the probability of viral suppression at 12 months did not differ whether a woman had probable antenatal depression (PD: -0.02; 95%CI -0.17-0.13; aPD: -0.01; 95%CI -0.17-0.15) (Figure 11).

Our estimates from secondary analyses that relaxed the definition of 100% visit attendance, and extended the time on follow up through 12 months postpartum were similar to those reported in the main analyses. Eighty-eight percent of women attended ≥7 ART-dispensing visits in the first 12 months, and there was no difference in visit attendance by antenatal depression status (RD: -0.02; 95%CI: -0.14-0.11; aRD: -0.02; 95%CI -0.15-0.11). Through 12 months postpartum, fewer women (82%) attended all

visits compared to through 12 months post-ART initiation (85%). One in twelve women (8%) missed 1 or 2 scheduled visits, and 10% missed 3 or more visits. The probability of visit attendance through 12 months postpartum was similar to results from 12 months post-ART initiation, and similar by probable antenatal depression status (RD: -0.06; 95%CI: -0.21-0.10; aRD: -0.08; 95%CI: -0.24-0.08).

We performed two sensitivity analyses. To account for the possibility that women with low enrollment viral loads at enrollment (≤400 copies/mL) were not ART-naïve, we excluded these women (n=28) and recalculated our estimates. Crude and adjusted estimates were comparable to the main analyses for both visit attendance (RD: -0.06; 95%CI -0.24-0.11; aRD: -0.08; 95%CI -0.26-0.09) and viral suppression (PD: -0.07; 95%CI -0.26-0.12; aPD: -0.06; 95%CI -0.25-0.13). To account for potential outcome misclassification (imperfect sensitivity) and found for both visit attendance and viral suppression through 12 months post-ART initiation, point estimates did not differ substantively from the main analyses (RD visit attendance: -0.07; 95%CI: -0.19-0.06) (PD viral suppression: -0.01; 95%CI: -0.15-0.13).

Discussion

In our population of pregnant women initiating ART in Malawi, one in ten women had probable antenatal depression, and engagement in care was high at 12 months post-ART initiation. The presence of probable antenatal depression at the time of ART initiation did not appreciably affect postpartum engagement in care. Our results are analogous to but over a longer period of follow up than a study of women living with HIV in the Democratic Republic of the Congo (DRC), which evaluated visit attendance at 6 weeks postpartum comparing women with and without probable antenatal depression, and found no difference in visit attendance by antenatal depression status.[62] Although depression is widely cited as a barrier to engagement in HIV care,[58,63,166–170] the effect of probable antenatal depression on engagement in care has not been quantified outside of the DRC study and the current study, which also includes viral load data.

Compared to recent studies from Malawi, a similar or higher proportion of our participants were engaged in care at 12 months post-ART initiation.[10,26,31,44] Our participants may have been motivated to remain in the study due to perceived receipt of better care, the study's less crowded clinic space, or transport reimbursement provided to participants. Engagement in care was approximately consistent between 12 months post-ART initiation and the longer 12 months postpartum, suggesting that suboptimal engagement in care occurs in the early months after ART initiation. However, later lapses in visit attendance were noted: more women missed any visits through 12 months postpartum than did in the first 12 months after starting ART.

Once women initiate ART, the individual and public health benefits of ART hinge on women having sustained viral suppression through the end of the breastfeeding period for infants, and long-term for women's sexual partners. Crudely, our participants met all three 90-90-90 targets at 12 months post-ART initiation: 100% knew their HIV status, 91% attended the 12 month visit, and 90% of those who attended the visit were virally suppressed.[11] However, women who were not engaged in care may represent a group with specific needs and are not likely a random sample of ART-eligible women. Engagement in care is complex, and may be influenced by numerous facilitators and barriers.[110,171,172] Facilitators to engaging in care include a desire to prevent transmission of HIV to the infant, motivation to help one's own health, a desire to prevent visible symptoms of HIV, and ART knowledge.[48–50] Barriers include initiating ART at a younger age (<25), on the same day as receiving an HIV diagnosis, or late in pregnancy, having a lack of social support, HIV-related stigma, denial of HIV status, lack of understanding about Option B+ and ART, financial concerns, side effects from ART, food insecurity, traveling away from home without access to medications, and clinic-level factors such as poor treatment from staff or long wait times at clinics.[38,40,51–55] Isolating any single factor, such as antenatal depression, may fail to capture the nuance of a complex health behavior such as engagement in HIV care.[173,174]

Our results were consistent under two sensitivity analyses addressing potential inappropriate selection into the study and misclassification, and under two secondary analyses that extended the period of follow up, and relaxed the visit attendance definition. In our sensitivity analysis for potential inappropriate selection into the study, the magnitude and precision of the point estimates were comparable, suggesting that even if some of the women in our sample were not ART-naïve, our substantive conclusions about the effect of probable antenatal depression on either engagement in care outcome did not change. Our sensitivity analysis that accounts for outcome misclassification (undocumented transfer of HIV care) did not yield estimates considerably different from the main analyses. One source of potential misclassification we were not able to address was for probable antenatal depression. The EPDS is a screening rather than diagnostic assessment, and we did not have inter-rater reliability for EPDS scores. Some of the women classified as having or not having probable antenatal depression may have been classified differently with a diagnostic depression assessment. In our secondary analyses, probability of engagement in care did not depend on the definition of visit attendance or follow up duration.

Depression symptoms can be dynamic over time, and measurement at one point (at time of ART initiation) may be a crude characterization of a woman's trajectory of psychosocial well-being. However, we focus on antenatal rather than postpartum depression with regards to HIV care engagement for multiple reasons: antenatal depression predicts postpartum depression and could be treated in the context of antenatal care[71]; in routine postpartum care, the focus is typically on the infant's rather than the mother's health; most all Malawian women have an antenatal visit, which allowed a more representative group than sampling from postpartum women[1]; and for programmatic reasons, we wanted to know whether women with antenatal depression have lower engagement in postpartum HIV care.

Screening for antenatal depression is not part of routine antenatal care in Malawi or most sub-Saharan African countries. Although the present analysis does not suggest an association between probable antenatal depression and engagement in HIV care, identification and treatment of antenatal depression likely has other important benefits for the mother and child. With untreated antenatal depression, mothers may experience impaired functioning, poor quality of life, increased risk of postpartum depression, or death.[79] Infants of mothers with untreated antenatal depression have increased risk of low birth weight,[88] preterm birth,[89,90] behavioral difficulties,[89] malnutrition,[91] and altered neurotransmitter profiles.[98]

Overall, most women initiating ART through Option B+ in Malawi remained engaged in care through 12 months, and probable antenatal depression did not appear to affect HIV care engagement. Despite similar probability of desirable HIV care outcomes by depression status, our finding that one in ten women had probable antenatal depression suggests screening for antenatal depression in Option B+ could be appropriate. Additionally, although most women remained in care through 12 months postpartum, nearly one in five women were not able to adequately engage in HIV care during the perinatal period critical for reducing maternal to child HIV transmission. Exploration of the psychosocial and practical factors that compromise consistent engagement in care is warranted.

Table 9. Participant demographics (n=299)

Characteristic at enrollment	Median (IQR)	EPDS <6 (n=269)	EPDS ≥6 (n=30)
Age in years	26 (22-30)	26 (22-30)	27 (24-32)
Weeks gestation	22 (18-26)	22 (18-26)	23 (17-25)
	Total N (%)		
Marital status			
Currently married	263 (88)	241 (90)	22 (73)
Not currently married	36 (12)	28 (10)	8 (27)
Education attained			
None/some primary	133 (44)	121 (45)	12 (40)
Finished at least primary	166 (56)	148 (55)	18 (60)
Employment status			
Unemployed	190 (64)	178 (66)	12 (40)
Employed	108 (36)	91 (34)	18 (60)
Current pregnancy intendedness			
Intended	132 (44)	121 (45)	11 (37)
Not intended	167 (56)	148 (55)	19 (63)
Ever experienced IPV			
No	242 (81)	223 (83)	19 (63)
Yes	57 (19)	46 (17)	11 (37)
History of depression or anxiety			
No	184 (62)	173 (64)	11 (37)
Yes	115 (38)	96 (36)	19 (63)
WHO HIV Clinical Stage			
Stage I	282 (94)	254 (94)	28 (93)
Stage II-IV	17 (6)	15 (6)	2 (7)

Figure 10. Comparison of engaged in care with viral suppression (<1000 copies/mL) by probable antenatal depression status (EPDS score)

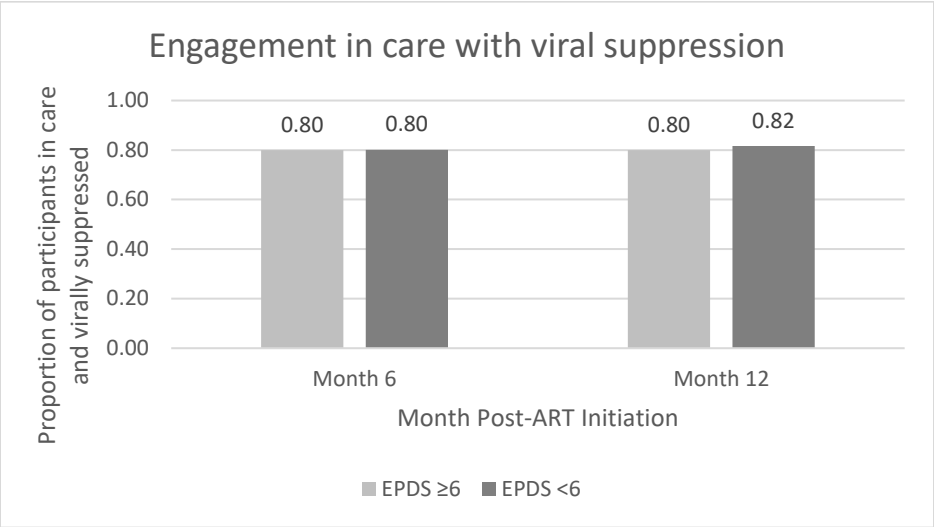
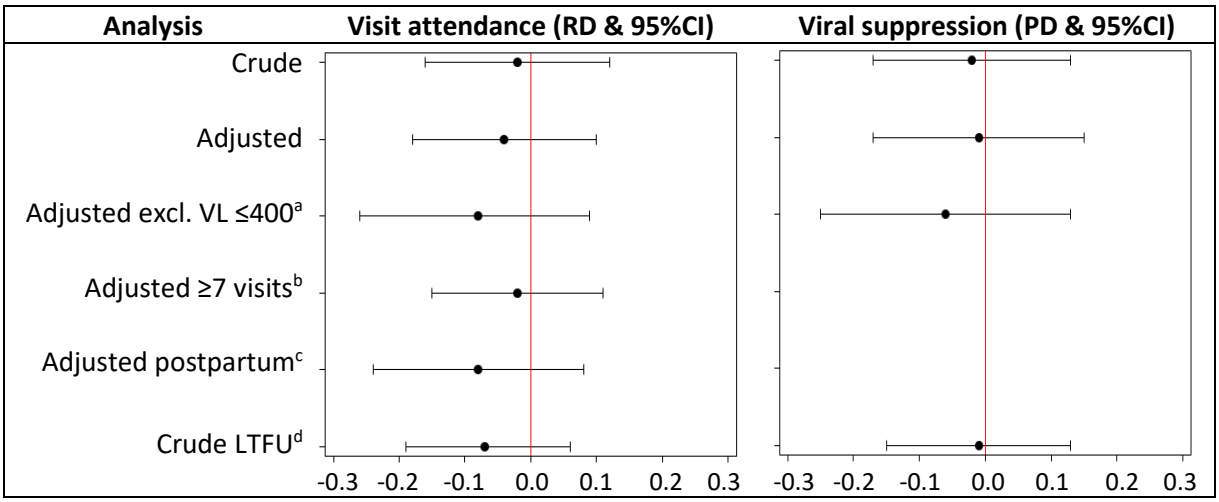


Figure 11. Risk and prevalence differences of engagement in HIV care outcomes comparing women with and without probable antenatal depression at time of ART initiation



[a]*Excluding women whose baseline viral load was ≤400 copies/mL*

[b]*Adequate visit attendance defined as attending ≥7 visits in the first 12 months post-ART initiation*

[c]*Adequate visit attendance defined as attending all scheduled visits through 12 months postpartum*

[d]*Accounting for potential outcome misclassification among those lost to follow up (LFTU)*

CHAPTER VII: DISCUSSION AND CONCLUSIONS

Perinatal depression is a common condition of pregnancy and the postpartum period, yet screening for the condition is not part of routine care in much of sub-Saharan Africa, including Malawi.[42] The existing prevalence and incidence estimates for perinatal depression vary, but are comparable or higher among women who are living with HIV.[12,21] With the scale up of ART programs under test-and-treat care models such as Option B+, an increasing number of people living with HIV are eligible for ART. Despite the success of more women initiating ART in the perinatal period, challenges with sustained engagement in care have emerged. Long-term engagement in HIV care is a critical component of preventing HIV transmission to infants and partners, and multiple factors may contribute to adequate engagement in care, including psychosocial factors such as depression. To better understand the role of perinatal depression in Option B+ HIV care for pregnant and postpartum women, we characterized the burden, timing, and factors associated with probable perinatal depression, and evaluated the relationship between probable antenatal depression and engagement in care postpartum.

Summary of Results

Our data come from a cohort study of women living with HIV in Malawi who participated in the national Option B+ prevention of maternal to child transmission of HIV ART program. In 2015-2016, participants were enrolled at their first antenatal care visit, and followed through at least 12 months postpartum. For the first aim, we included women initiating ART (n=299) and women who had been on ART for at least 6 months (n=426). For the second and third aims, we focused on women who were initiating ART (n=299).

From the first aim, we identified factors associated with probable antenatal depression. Among women initiating ART or who had been on ART for ≥6 months (n=725), about 10% screened positive on

the EPDS for probable antenatal depression, and almost half self-reported a history of depression or anxiety (46%). A positive screen for probable antenatal depression was more likely among women who reported a history of depression or anxiety (adjusted PR [aPR] 2.42; 95%CI 1.48-3.95) and who had experienced intimate partner violence (1.77; 1.11-2.81). Having an unintended current pregnancy (1.78; 0.99-3.21), being unmarried (1.66; 0.97-2.84), or employed (1.56; 1.00-2.44) had suggestive associations with probable depression.

In the second aim, we estimated the prevalence and incidence of probable perinatal depression at enrollment and through the first 12 months postpartum among women initiating ART. At enrollment, 10% of women screened positive on the EPDS and 13% on the PHQ-9, whereas 2-6% of women screened positive on either instrument during the postpartum period. Given that some women did not complete all study visits when postpartum depression was assessed, we conducted a sensitivity analysis to examine the potential for biased estimates due to missing data. Under three scenarios of low, intermediate, or high depression prevalence among those who were missing assessments, we estimated that the prevalence of probable postpartum depression could have ranged from 2-11%. The agreement between the EPDS and PHQ-9 assessments was high (95%).

In the third aim, we quantified the difference in risk of postpartum engagement in care between women who had probable antenatal depression and those who did not. Our participants demonstrated high engagement in care at 12 months as measured by visit attendance (85%) and engaged in care with viral suppression (81%). The probability of attending all visits in the first 12 months post-ART initiation was comparable between women with and without probable antenatal depression in crude and adjusted analyses (RD: -0.02; 95%CI -0.16-0.12; aRD: -0.04; 95%CI -0.18-0.10). For viral suppression at 12 months, we noted no appreciable differences comparing women with and without probable antenatal depression (PD: -0.02; 95%CI -0.17-0.13; aPD: -0.01; 95%CI -0.17-0.15).

Estimates from the two secondary analyses and two sensitivity analyses all had estimates substantively similar to the main analyses. When the definition for visit attendance through 12 months post-ART initiation was relaxed, or when we extended the follow up time through 12 months postpartum, no notable difference in visit attendance was present by probable antenatal depression status. In sensitivity analyses, when we excluded women with particularly low viral loads at enrollment who might have already been on ART, or accounted for the possibility that some women who were not engaged in care through the study might have been receiving ART from another clinic and thus were in care elsewhere with viral suppression, the point estimates were similar in magnitude and precision to those from main analyses, and had confidence intervals that contained the null value, leading to no substantive differences in conclusions.

Interpretation and Implications of Results

The research presented in this dissertation contributes to our understanding of the magnitude of and factors associated with probable antenatal depression among perinatal women living with HIV in Malawi, as well as the relationship of depression and engagement in HIV care. Routine screening for depression during the perinatal period or more widely as part of HIV care does not exist in Malawi, so our results provide new information that can assist with care provision and potential policy considerations regarding mental health in the context of HIV programs.

The factors that were associated with probable antenatal depression in the first aim (chapter 4) were broadly indicative of current or past life stress: a history of depression or anxiety, history of intimate partner violence, being unmarried, not intending the current pregnancy, and being employed. It is possible that being employed was a stressor rather than representative of socioeconomic resources. Our results echo those of other studies in neighboring countries. Women in our study who screened positive for probable antenatal depression endorsed characteristics that may represent an unstable social situation or low social support. Of note, nearly half of women said they had been depressed or

had anxiety in the past, which suggests any interventions to improve perinatal depression should take into account the psychosocial context of women who endorse multiple stressors and may not have adequate social support.

Disclosure of HIV status to sexual partners can be challenging. Among women who had been on ART for at least 6 months, those who had not disclosed their status had a prevalence of probable antenatal depression nearly twice that among women who had disclosed their status. The positive association between non-disclosure of HIV status and probable antenatal depression could also be a marker of relationship instability and lack of social support from the partner.[155] For the other half of the participants who were initiating ART, they had just received their HIV diagnosis at their antenatal care visit. Thus, in addition to the potential joy and stress of a pregnancy, women also received a diagnosis that historically carried a death sentence in Malawi. Currently, few male partners attend antenatal care visits, so the onus is on women to disclose their HIV status to their partners, which can carry the risk of relationship dissolution, and potentially intimate partner violence.[175,176] Increasing the implementation of male-friendly and couples-based HIV services, including in the perinatal context, could be important options for improving HIV status disclosure and engagement in care.

While this first aim's analysis was not designed to identify causal relationships between the variables and probable antenatal depression, the results highlight the complex social fabric in which pregnancy occurs and suggest that multiple items likely influence the occurrence of antenatal depression.

Our results from the second aim (chapter 5) show that one in ten women have probable antenatal depression at their first antenatal care visit, and one in twenty postpartum. The prevalence and incidence of probable depression during the postpartum period were low relative to other countries in sub-Saharan Africa, even when we assumed that those lost to follow-up had a particularly high prevalence of unobserved depression.[21,107–109,143] Our data do not provide definitive clues as to why our

postpartum estimates were so low. Our participants may have had particularly robust postnatal support from family or friends compared to other settings, or there may have been some cultural difference in depression manifestation that our interviews did not capture. Estimates of prevalence and incidence were similar on the EPDS and PHQ-9, and nearly all women had concordant scores on the two tools when using a dichotomous threshold for presence of probable perinatal depression. On both tools, the most frequently endorsed symptoms were depressed mood or sadness, and the least endorsed symptoms were of self-harm or suicidal ideation. Many participants endorsed the somatic symptom items present on the PHQ-9, which be important manifestations of depressive symptoms,[159–162,177] or that our pregnant and newly postpartum participants had physiological reasons for somatic symptoms due to being in the perinatal period, or a combination thereof.

In the third aim (chapter 6) we hypothesized that women who had probable antenatal depression would have worse postpartum engagement in care as measured by visit attendance and viral suppression. The results from our study population showed no significant differences in HIV care visit attendance or viral suppression between those with and without probable antenatal depression. Adjustment for confounders and several secondary and sensitivity analyses did not change the interpretation that in our population, probable antenatal depression was not associated with differences in postpartum engagement in HIV care. The sample size was reasonable but modest, and did lead to sparse cells in a multivariable model. Despite the similar HIV care engagement profiles of women with and without probable antenatal depression, our results do not mean that depression in the context of HIV care is unimportant. There may be more nuance to the relationship between depression and HIV care than our study assessments were able to ascertain.

Our study participants met all three 90-90-90 targets at 12 months post-ART initiation: 100% knew their HIV status, 91% of women attended the 12 month visit, and 90% of those who attended the 12 month visit were virally suppressed.[11] Overall, engagement in our study was slightly higher than or

comparable to what has been reported in other studies in Malawi,[10,31,44] which was encouraging because women need to have sustained viral suppression through the end of breastfeeding to prevent transmission to their infants, and long-term to preserve their own health and avoid transmission to their sexual partners. However, using our stricter definition of attended all 8 scheduled ART visits in the first 12 months, 85% of women were "engaged in care," and 82% attended all visits through 12 months postpartum. Thus, engagement in care is a dynamic and sustained process. Furthermore, the women who were not engaged in care are likely not a random sample of all women who started ART through Option B+, and individualization of HIV care may improve long-term engagement for a wider group of women with diverse needs.[178,179]

It is no surprise that engagement in care is complex. Numerous difficulties may impede consistent engagement in care, including lack of transport to the clinic, lack of partner support, facility-based issues (poor rapport with providers, long wait times, inconvenient clinic hours), side effects from ART, other health issues that render a person sick or weak, HIV-related stigma, intimate partner violence, and maladaptive coping skills.[38,40,51–55] Women likely had their own motivating reasons to continue engaging in care, whether to optimize their own health, or to avoid a bad outcome such as transmitting the virus to their infants.[48–50] Our study did not fully evaluate each of these items at baseline or longitudinally.

We have incomplete information on women who disengaged from care soon after initiating ART. Some of these women could have transferred to another HIV clinic without reporting their move to the study staff. In our sensitivity analysis to address potential outcome misclassification, however, the point estimate and confidence interval for difference in engagement in care between those with or without probable antenatal depression did not appreciably change. Thus, even with some potential outcome measurement error, our conclusions are consistent with the results of the main analysis estimate.

Depression can be dynamic over time, and measurement at one antenatal time point may be a crude characterization of a woman's trajectory of psychosocial well-being. Antenatal depression on its own may not be sufficient to noticeably affect long-term engagement in HIV care. Researchers and clinicians may need to identify a suite of psychosocial stressors that are more indicative of women who may have challenges engaging in HIV care consistently. However, we focus on antenatal rather than postpartum depression with regards to engagement in HIV care for multiple reasons: antenatal depression predicts postpartum depression, and could be treated in the context of antenatal care [71]; in routine care postpartum, the focus is typically on the infant's rather than the mother's health; most all Malawian women have an antenatal visit, which allowed a more representative sample of women than sampling from postpartum women [1]; and for programmatic reasons, we wanted to know whether women with antenatal depression have lower engagement in postpartum HIV care.

One source of misclassification we were not able to address was exposure misclassification for probable antenatal depression. The EPDS is a screening rather than diagnostic assessment of antenatal depression, and we did not have inter-rater reliability for EPDS scores. Some of the women classified as having probable antenatal depression did not necessarily have diagnosable antenatal depression, and some women classified as not having probable antenatal depression may have indeed been suffering with the condition. However, the EPDS tool and score threshold used in our analyses were chosen based on a validation study in Malawi, there was high agreement between the EPDS and PHQ-9 scores, and scores over the calendar months were relatively stable (data not shown).[103] The exposure misclassification could bias our estimates if it were differential by outcome, meaning if women's probable antenatal depression status varied with whether they remained engaged in care. We do not have reason to believe that women who remained engaged in care or who disengaged from care over or under reported their depressive symptoms.

Women who participated in our study were recruited from a busy public hospital that served about 20% of all women seeking antenatal care in the Lilongwe district, and a much higher proportion of those seeking care within urban Lilongwe. Women at Bwaila hospital were a population with a higher HIV prevalence compared to the overall Lilongwe district, but a prevalence consistent with previous estimates for urban Lilongwe. While we do not have demographic data on how our participants compare to non-participants from Bwaila, the eligibility criteria for the S4 parent study were broad, and the HIV care visit schedule was identical to that of women in Option B+ who were not in the study. We believe our participants are representative of women living with HIV in the urban Lilongwe area, and potentially similar to other urban areas as well. Further information is needed on similarities and differences between urban and rural women regarding engagement in HIV care and perinatal depression.

Despite a lack of difference in risk of desirable HIV care outcomes between women with and without probable antenatal depression, our finding that one in ten women had a positive EPDS score suggests screening for antenatal depression in the HIV care context could be appropriate because it would help to identify and address an important and prevalent concern for pregnant women. Additionally, despite the fact that the majority of women remained in care through 12 months post-ART initiation or 12 months postpartum, nearly one in five women were not able to adequately engage in HIV care during the perinatal period critical for reducing maternal to child transmission of HIV.

Considering the results of all three aims together, we have learned five main items about women participating in Option B+ HIV care in Malawi: as high as one in ten women have probable perinatal depression; nearly half report a history of depression or anxiety; factors associated with probable antenatal depression broadly reflect past or current life stressors; postpartum engagement in HIV care was relatively high but nevertheless showed important room for improvement; and probable

antenatal depression does not appear to be positively or negatively associated with postpartum engagement in HIV care.

Future Directions

Through the current research, we have identified multiple opportunities for additional studies. Some specific options described below broadly address ways to learn about three areas relevant to mental health and HIV care: improving the measurement of depression; exploring a broader set of psychosocial factors that may affect engagement in care; and examining targets for engagement in care that are most meaningful in the Malawian context.

Improving the measurement of depression

In each of the study aims, we used a dichotomous cut-point on screening tools to measure probable perinatal depression. As is the case with any continuous measure that is categorized into a smaller number of units, some information is lost and women who scored just above the threshold are considered to have the same exposure level as women who had a much higher score that fell into the same category. Similarly, women who scored a 5 versus a 6 on the EPDS, or a 4 versus a 5 on the PHQ-9 may have had comparable intensity and nature of depressive symptoms but ended up in our analyses as "negative for probable depression" versus "positive for probable depression" due to their answers to the EPDS or PHQ-9 questions or how the study staff interpreted their answers. Our estimate for the prevalence of probable antenatal depression was within the plausible range expected based on prior literature, but only when we used a EPDS score threshold that was lower than the most widely used threshold (although the same threshold that was validated in Malawi), and our estimates for the postpartum period were lower than expected. Future researchers in perinatal depression in Malawi could consider re-validating the EPDS, or conducting cognitive interviews to better assess what women comprehend when they hear the questions on the EPDS and PHQ-9. It is possible that some of the

wording on the questions does not fully translate the original meaning, and that there are expressions of depression culturally relevant to Malawi that should be included to best capture depressive symptoms.

Given the distribution of depression scores in the postpartum period, we were not able to evaluate the relationship between depression trajectories and engagement in HIV care. Multiple factors could explain our low scores. Few of our participants may have truly had probable postpartum depression; the fidelity of the depression assessments may have been uneven during the study period; participants may have tired of answering the EPDS and PHQ-9 assessments, or did not fully understand the questions; and the EPDS and PHQ-9 may not be adequately adapted to the Malawian context. Administering the EPDS and PHQ-9 in Malawi required multiple steps that might have had error in them: nurse reading the questions to the participant, the participant processes the questions and responds, and the nurse interpreting the participant's response into a score. Thus, it may be important to ensure the fidelity of EPDS and PHQ-9 administration through trainings and periodic refresher trainings that could help ensure that study staff remain familiar with the tools and how to score them in a standardized way. Trainings would also provide the opportunity to discuss any confusions, challenging cases, or trends providers are noticing in participants and the scores. A study could evaluate the performance of the screening tools between providers who receive training once versus those who receive refresher trainings. Participant comprehension of and interest in answering the depression assessment questions could be evaluated via qualitative interviews. Adequate adaptation of the EPDS and PHQ-9 to the Malawian context would likely require a study with a qualitative component to identify culturally relevant expressions of depression, and a quantitative component to evaluate the performance of the two tools relative to a reference standard such as the MINI or evaluation by a psychiatrist using criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Depression is dynamic: people can have depression that is active, in remission, relapsed, or not present. Almost half of our participants endorsed having a history of depression or anxiety. Inquiry into

what women were referring to as their prior experience with depression or anxiety and how that affected their past and present functioning could be fruitful.

In Malawi, women are not screened antenatally for depression, regardless of HIV status. [42,111] The 10% of women in our study endorsing probable antenatal depression could benefit from prompt mental health treatment. Compared to other maternal morbidity conditions during pregnancy, only anemia and HIV infection are more prevalent in Malawi than antenatal depression.[142] Moreover, efavirenz is commonly one of the drugs in first-line ART regimens, and the drug has been linked with neuropsychiatric side effects including depression.[156] Thus, ART prescribing practices and symptom monitoring of women who have underlying depression may need revision to avoid potential exacerbation of psychiatric symptoms. Quantifying both the cost effectiveness of depression screening and any improved outcomes due to treatment in the perinatal period would be useful for programmatic planning in the Option B+ care model.

One logistical item we were not able to incorporate in our study given constraints with the informed consent process and the volume of clients at the governmental clinic was to assess depression prior to HIV testing. Some women may have screened positive for depression in part due to their reaction to their HIV diagnosis (acute adjustment disorder with a depression reaction).[180] Screening for depression prior to HIV diagnosis would also allow for the evaluation of depression in women who do not have HIV. Perinatal depression occurs in women living with and without HIV, and can negatively affect infant outcomes. Gathering data on all perinatal women may provide evidence on the need for mental health services in the context of perinatal care.

Exploring a broader set of psychosocial factors that may affect engagement in care

Depression is one of many mental health conditions that may affect engagement in HIV care. Other conditions that have not been widely examined in sub-Saharan Africa include anxiety and post-traumatic stress disorder. Outside of diagnosable mental illnesses, psychosocial factors such as coping

style, social support, HIV-related stigma, intimate partner violence, HIV status disclosure, stressful life events, trauma history, and self-efficacy may affect engagement in care. Most studies have examined one of these items as the exposure, rather than consider multiple factors in concert. It is possible that each person has a different threshold for whether they are able to fully engage with HIV care. Thus, it could be less the effect of any one of these items, but rather the sum of what is happening in a given person's life along with contextual factors that enable or impede a health behavior such as engagement in care.[63,174,181] Methodologically, it is more challenging to evaluate a multifaceted exposure as described. Researchers interested in decision making around engagement in long-term HIV care could consider discrete choice experiments, behavioral economic approaches, or a comprehensive intervention package to better understand how Malawian adults view and interact with their HIV care.[182,183] Ultimately, studies would need to then develop and test interventions that may facilitate better engagement in HIV care.

Examining targets for engagement in care that are most meaningful in the Malawian context

A relatively high proportion of our participants remained engaged in care, defined as visit attendance at ART dispensing appointments and viral suppression. The fact that most women kept returning to their HIV care appointments is encouraging. Having regular contact with health providers allows women to have concerns addressed that may impede ART adherence, such as medication side effects.[52,184] Consistent contact also allows for any routine screening and assessment of opportunistic infections indicative of advancing HIV. The biologic goal of regular HIV care is to ensure access to ART medicines so viral suppression can occur. Specific to the perinatal context, a major purpose of HIV care is to prevent infants from contracting HIV. Future studies could examine which definitions of engagement in care most closely track with viral suppression and with low infant HIV acquisition. Such data could reframe programmatic targets that often focus on visit attendance regardless of ART medication adherence, viral load, or infant infections. The Option B+ population of perinatal women

may or may not have the same definitions of 'engaged in care' as non-pregnant or breastfeeding adults that ultimately promote viral suppression.

Until recently, ART was reserved for the sickest people living with HIV who had symptoms consistent with AIDS or met other criteria indicating severe immunosuppression. Thus, ART became associated with death because many who started ART when so immunocompromised had little reserve and succumbed to opportunistic infections or other AIDS complications. With the growing evidence supporting a 'test and treat' approach for HIV, Option B+ was developed. One reason Option B+ was able to be rapidly deployed in Malawi and neighboring countries is that it was designed to do so: all perinatal women were eligible for the first-line ART regimen. While some women were given second-line ART for various indications, Option B+ is largely a standard care package. Growing attention is now on 'differentiated care' models for HIV,[178,179] which could be particularly important to improve care engagement in the perinatal population, especially those who reluctantly start ART when they were feeling healthy.

Social norms around ART are changing in Malawi as ART becomes available to more people who are asymptomatic, but as with other chronic diseases like hypertension and diabetes, taking pills daily can be burdensome. Thus, future work should involve programmatic reviews, evaluation of new technologies, and community awareness about HIV and ART with a goal of making it easier and more appealing to initiate and stay on ART long term. In addition to differentiated models of care, other initiatives include long-acting injectables or implants for ART delivery to reduce pill burden, introduction of pre-exposure prophylaxis (PrEP), couples HIV counseling and testing, and peer support programs to help newly diagnosed persons navigate their HIV and ART care. Likely, a concert of approaches and ongoing evaluation will be needed to help serve those already living with HIV, and prevent future infections in infants and partners.

Conclusions

In summary, in a sample of women living with HIV and engaged in ART care through Option B+, probable depression was present in one in ten women antenatally and one in twenty postpartum. Our estimates of perinatal depression were lower than in some comparable populations, and there was no appreciable difference in engagement in perinatal HIV care between women with or without probable antenatal depression. However, a sizable proportion of participants reported characteristics consistent with heightened mental health vulnerability, such as a personal or family history of depression or anxiety, and intimate partner violence. Efforts to scale up Option B+ treatment programs should give careful consideration to psychosocial screening and support services that patients may need to facilitate their successful engagement in HIV care long-term.

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