Safety and efficacy of Option B+ ART in Malawi: few severe maternal toxicity events or infant HIV infections among pregnant women initiating tenofovir/lamivudine/efavirenz

Bryna J. Harrington[1,*], Bethany L. DiPrete[1,*], Allan N. Jumbe[2], McNeil Ngongondo[2], Laura Limarzi[2], Shaphil D. Wallie[2], Maganizo B. Chagomerana[2], Mina C. Hosseinipour[2,3] and on behalf of the S4 Study Team

1 *Department of Epidemiology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*
2 *UNC Project-Malawi, Kamuzu Central Hospital, Lilongwe, Malawi*
3 *Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Abstract

OBJECTIVES Malawi's Option B+ universal antiretroviral therapy (ART) program for pregnant and breastfeeding women does not include routine laboratory monitoring. We report safety outcomes of pregnant women who initiated ART through Option B+.

METHODS We analysed 12-month data from an observational cohort study on Option B+ among women newly initiating tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) at a government antenatal clinic in Lilongwe, Malawi. Proportions of women engaged in care, incidence of DAIDS grade ≥ 2 laboratory toxicity, grade ≥ 3 adverse events (AEs), viral suppression (<1000 copies/mL), birth outcomes and infant HIV infections are reported.

RESULTS At ART initiation, participants (n = 299) had a median age of 26 years (IQR 22–30), median CD4 count of 352 cells/μl (IQR 231–520) and 94% were in WHO Stage 1. We noted 76 incident DAIDS Grade ≥ 2 laboratory results among 58 women, most commonly elevated liver function tests (n = 30 events) and low haemoglobin (n = 27). No women had elevated creatinine. Clinical AEs (n = 45) were predominantly infectious diseases and Grade 3. Five participants (2%) discontinued TDF/3TC/EFV due to virologic failure (3) or toxicity (2). Twelve months after ART initiation, most women were engaged in care (89%) and had HIV RNA < 1000 copies/ml (90%). 8% of pregnancies resulted in preterm birth, 9% were low birthweight (<2500 g), and 2% resulted in infant HIV infection at 6 weeks post-delivery.

CONCLUSION Most women remained on ART and were virally suppressed 12 months after starting Option B+. Few infants contracted HIV perinatally. While some women experienced adverse laboratory events, clinical symptom monitoring is likely reasonable.

keywords pregnancy, HIV infection, Malawi, Option B+, prevention of mother to child transmission, safety and efficacy

Introduction

In 2011, Malawi became the first country to implement Option B+, a program for preventing maternal-to-child transmission (PMTCT) of HIV by providing lifelong antiretroviral therapy (ART) to all pregnant and breastfeeding women regardless of CD4 count or other health conditions [1–3]. Option B+ incorporates the test-and-treat approach to HIV management, following evidence of the benefits of earlier ART initiation [2,3]. Taking ART reduces HIV viral load, and sustained viral suppression dramatically reduces the risk of transmitting HIV to infants or sexual partners [4–7].

First-line ART for Option B+ in Malawi is a combination of tenofovir, lamivudine and efavirenz (TDF/3TC/EFV) in a single tablet taken once daily, which is readily available and endorsed by the WHO. The regimen is considered safe in the general adult population [8,9], yet its long-term safety and efficacy have not been systematically evaluated in pregnant and breastfeeding women. This population may be more susceptible to toxicity due to physiologic changes that occur during pregnancy [10–12]. Specifically, pregnancy is associated with increased risk of abnormal liver function tests [12] and anaemia [13],

*Contributed equally.

especially among pregnant women living with HIV [10,14,15]. While there are concerns regarding the risk of adverse birth outcomes among women taking ART during pregnancy, several studies have shown that ART, including TDF/3TC/EFV, is not associated with a higher risk of preterm birth [16], neonatal death or low birth weight [17,18].

Current laboratory monitoring guidelines for Option B+ care do not include routine assessments for toxicities such as haematologic, hepatic or renal abnormalities [19] Studies have demonstrated that some patients on regimens containing tenofovir – especially those in resource-limited settings or with risk factors for renal dysfunction – would benefit from screening for renal impairment [20,21]. However, the evidence is mixed [22,23]. Accurate estimates of potential risks and benefits associated with an ART regimen are important evidence for both patients and practitioners.

In this analysis, we assess the proportion of pregnant and breastfeeding women who had incident laboratory-confirmed adverse events through 12 months post-ART initiation, and adverse birth outcomes including infant HIV infections through 6 weeks of age.

Methods

Study setting and population

Pregnant women living with HIV who reported for antenatal care at the public Bwaila Maternity Hospital in Lilongwe, Malawi in 2015–16 were invited to enroll in an observational cohort study ('Safety, Suppression, Second-line, Survival – S4', ClinicalTrials.gov identifier: NCT02249962) that evaluated the long-term safety and efficacy of Option B+. All women were offered opt-out HIV testing during antenatal care, per Ministry of Health standards, with two rapid tests (Alere Determine™ and Unigold™). Women in any trimester of pregnancy who tested positive for HIV or were known to be living with HIV were approached by study staff to enroll in the S4 study.

Women eligible for S4 were pregnant, at least 18 years old (or emancipated minor), planned to give birth in Lilongwe, and able to provide informed consent. Participants represented women newly initiating first-line ART (TDF/3TC/EFV) on the day of their first antenatal visit. Participants had interviews with study nurses in Chichewa, the predominant local language, and received ART on the day of their first antenatal visit, monthly for 6 months, then quarterly for up to 36 months after delivery. The S4 study schedule for dispensing ART was identical to that of the Malawi Ministry of Health ART guidelines, including cotrimoxazole preventive therapy (CPT) for *Pneumocystis jiroveci* pneumonia [19]. Isoniazid preventive therapy was not part of the guidelines at inception of the study. Women received ART from the S4 study unless they transferred care to a non-study clinic. All participants received counselling about the Option B+ program and were encouraged to continue taking ART for life.

Measurements

The definition of 'engaged in care' was women who attended clinic within 60 days of their scheduled date for receiving ART at 12 months post-ART initiation. Similarly, the Malawi Ministry of Health defines a person as lost to follow-up when she has not returned to clinic 2 months after running out of ART, if there is no report of transfer to another clinic, stopping ART or death [19].

Participants received routine laboratory monitoring at enrollment, quarterly thereafter and at labour and delivery. All assays were performed at the UNC Project-Malawi accredited laboratory facility. Viral load was measured with the Abbott m2000rt real-time PCR system. Laboratory results were graded using the National Institute of Allergy and Infectious Diseases Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [24]. In the present study, we focus on blood chemistries and haematologic values with DAIDS grade of 2 or higher as indicative of toxicity. Laboratory assays evaluated comprised: alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin, creatinine, haemoglobin, platelet count, absolute lymphocyte count, absolute neutrophil count, total white blood cell count, phosphate and CD4 cell count. Individuals who had any toxicity events were identified, with incident toxicity defined as the first toxicity instance after enrollment. Laboratory events were considered to be incident toxicity events only among women who did not have a persistent condition at baseline. Frequencies and proportions of incident toxicity events are presented by laboratory assay, using the total number of enrolled participants as the denominator for each assay.

Adverse events (AE) are unfavourable and unintended signs, symptoms or diseases associated with the medical treatment [24]. In our analysis, AE were graded from 3 (severe) to 5 (death), and we noted those that occurred specifically during childbirth or post-partum ('obstetrical/post-partum'), and new WHO Stage 3 or 4 conditions as defined by Appendix 60 of the Adult AIDS Clinical Trials Group (ACTG) or other toxicity requiring ART modification [24]. We present frequencies and proportions of characteristics at enrollment and toxicities or AE in the first 12 months post-ART initiation.

Non-live outcomes for infants were classified as miscarriages (<20 weeks gestation); stillbirths or intrauterine foetal demises (non-live born foetus of ≥20 weeks gestation); and neonatal deaths (live born infants who died within 28 days of delivery). Preterm infants were those born <37 weeks gestation according to Ballard examination when available or obstetrical estimate based on last menstrual period. Low birth weight was defined as <2500 g. Early infant HIV infection was defined as a positive infant HIV DNA result using dried blood spots collected at the infant's 6-week study visit and analysed with the Abbott M2000 system (lower limit of quantification: 40 copies/ml). Frequencies and proportions are presented for each of the infant outcomes using the total number of pregnancies (i.e. number of women enrolled) as the denominator for proportions.

All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA) and Stata version 14.2 (College Station, TX, 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 May 2015 and June 2016, 16 255 women presented to Bwaila antenatal clinic, of whom 15 121 (93%) were tested for HIV and 935 (6%) tested newly positive for HIV (Figure 1). S4 study nurses were able to approach about 50% of the newly positive women and enrolled 299 women into the study. Those who were approached and did not enroll did not meet eligibility requirements (being pregnant and living in Lilongwe) or were not interested in participation. Most women (89%, $n = 267$) were still engaged in HIV care through the study at 12 months post-ART initiation.

At the time of ART initiation, participants had a median age of 26 years (IQR 22–30) and were at 22 weeks gestation (IQR 18–26) (Table 1). Most women (88%, $n = 263$) were married, and 42% ($n = 122$) had finished primary school. At ART initiation, median CD4 count was 352 cells/mm^3 (IQR 231–520), median viral load was 14 539 copies/mL (IQR 2883–45 324), and median haemoglobin was 10.9 g/dl (IQR 10.0–11.7). Nearly all women were in WHO HIV clinical stage 1 (94%, $n = 282$). 17% ($n = 51$) had baseline laboratory values grade 2 or higher, the majority of which were low haemoglobin (82%, $n = 42$).

In the first 12 months post-ART initiation, 19% of women ($n = 58$) without a persistent condition at baseline had any incident laboratory adverse events grade 2 or higher. Among these 58 women, 76 incident laboratory adverse events grade ≥ 2 occurred (Table 2A) of which 64% were grade 2, 26% were grade 3 and 9% were grade 4. The most common new toxicity event was low haemoglobin ($n = 27$), followed by elevated ALT ($n = 21$). New hepatotoxicity (elevated ALT, AST or bilirubin) occurred in 8% of women ($n = 23$). Some women had grade 2 or higher values at more than one evaluation from baseline through 12 months in the following tests: low haemoglobin ($n = 28$), high ALT ($n = 5$), high AST ($n = 1$), high bilirubin ($n = 1$), low platelets ($n = 2$) and low WBC ($n = 1$). None had new elevated creatinine levels during the follow-up period.

In the first 12 months post-ART initiation, 45 clinical adverse events grade 3 or higher were reported (Table 2A), with the most common being pneumonia, sepsis and malaria. Three women died: one from liver failure, one from tuberculosis (TB) and one from unknown causes. Overall, five women had laboratory values or clinical adverse events that led to an ART regimen change: three women due to virologic failure, one due to elevated ALT and one due to multiple clinical toxicities including a rash. New WHO stage 3 conditions occurred in five women, including severe bacterial infection (pneumonia) and oral candida. Eleven women had obstetric or post-partum complications, including puerperal sepsis, pre-eclampsia, retained products of conception, placental abruption, infected caesarian section wound and trichomoniasis.

The proportion of women who had viral suppression post-ART initiation was high: 89% and 90% of women had viral loads <1000 copies/mL at 6 and 12 months, respectively. 81% and 85% of women achieved <50 copies/ml at 6 and 12 months post-ART initiation, respectively (Figure 2).

Birth outcomes were unknown for 6% ($n = 19$) of women (Table 2B). Most births were live born (88%, $n = 264$), with the remainder being stillbirths or neonatal deaths (4%, $n = 12$) and miscarriages (2%, $n = 5$). One in 12 pregnancies resulted in preterm birth (8%, $n = 24$), and 9% were low birth weight ($n = 27$). Four pregnancies were multiple gestations. Of these four twin births, one pregnancy resulted in one stillborn and one live born infant that was low birth weight, and two pregnancies resulted in one infant that was low birth weight and one infant that weighed >2500 g. Few pregnancies (2%, $n = 7$) resulted in infant HIV infection by 6 weeks post-delivery. Only three mothers of these infants infected with HIV by 6 weeks of age had viral loads <1000 copies/ml at delivery.

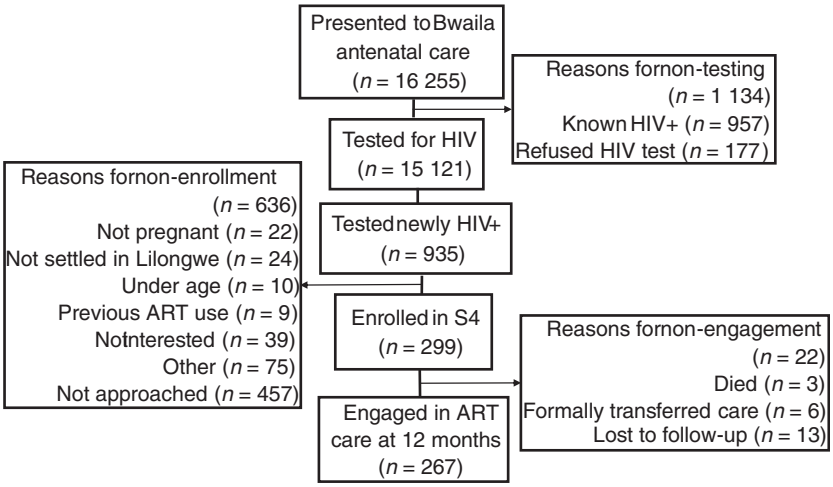

Figure 1 Consort diagram of participant recruitment and engagement in S4 study through 12 months post-ART initiation.

Table 1 Baseline maternal characteristics at ART initiation

Characteristic	Median (IQR)	Total *N* (%)
Age (years)	26 (22–30)	
Gestational age (weeks)	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)
WHO HIV clinical stage		
Stage 1		282 (94)
Stage 2–4		17 (6)
CD4 count (cells/mm^3)	352 (231–520)	
Viral load (copies/ml)	14 539 (2883–45 324)	
Haemoglobin (g/dl)	10.9 (10.0–11.7)	

Discussion

In this prospective cohort of pregnant women newly diagnosed with HIV and initiating ART on TDF/3TC/EFV in Malawi, adverse outcomes were observed in less than one-fifth of study participants, and ART regimen changes due to toxicity or virologic failure were rare.

Our encouraging finding of few adverse events is consistent with many previous studies of TDF/3TC/EFV among non-pregnant adults that showed the ART regimen is well tolerated [8,25–27]. The most frequent adverse event among S4 participants was low haemoglobin. Given that pregnancy is associated with haematological changes and HIV infection puts pregnant women at higher risk of anaemia [13,14,28], the frequency of anaemia among participants is unsurprising. Pregnancy is associated with increased risk of hepatotoxicity among women living with HIV who are managed on ART regimens [10,11,29,30]. Studies of pregnant women on different ART regimens in the US [10,31], France [29], the United Kingdom [11] and Côte d'Ivoire [30] found frequencies of hepatotoxicity ranging from 0.5% (grade 3–4) to 14% (grade 1–4), comparable to our finding of new hepatotoxicity events grade 2 or higher in 7% of women enrolled in S4 and managed on TDF/3TC/EFV. Among S4 participants who had elevated liver enzymes, only one ART regimen change occurred due to hepatotoxicity. Three women died during the study period, with one death attributed to liver failure. Laboratory monitoring was helpful to promptly identify liver failure in this woman; however, the efforts were not enough to prevent her passing.

Adult patients managed on TDF/3TC/EFV have a low prevalence of renal insufficiency [27], and no participants in the current study developed elevated creatinine to indicate renal insufficiency during 12 months of follow-up. Checking glomerular filtration rate (eGFR) or creatinine clearance (CrCl) is recommended instead of serum creatinine to monitor renal function because serum creatinine changes are the least sensitive marker of renal function decline [32]. However, serum creatinine may still be a useful measure of renal function during pregnancy [33]. Our study was only able to use serum creatinine to

Table 2 Maternal and infant safety outcomes in first 12 months: incident DAIDS Grade ≥ 2 laboratory values or Grade ≥ 3 adverse events, birth outcomes, and transmission events

A. Maternal outcomes	*N*	%*
Incident laboratory event grade ≥ 2†		
Haemoglobin	27	8
Platelets	6	2
WBC	2	1
Absolute lymphocyte count	2	1
Absolute neutrophil count	8	3
Phosphate	1	<1
Creatinine	0	0
ALT	21	7
AST	5	2
Bilirubin (total)	4	1
Clinical adverse events grade ≥ 3		
Grade 3 – Severe	24	8
Grade 4 – Life threatening	3	1
Grade 5 – Death	3	1
Obstetric/post-partum complication	11	4
New WHO Stage 3 or 4 condition	4	1
Total ART regimen changes	5	2

B. Infant outcomes‡	*N*	%*
Live born	264	88
Preterm (<37 weeks)	24	8
Birthweight < 2500 g§	27	9
HIV infections by 6 weeks	7	2
Stillborn/intrauterine foetal demise (≥20 weeks)	12	4
Miscarriage (<20 weeks)	5	2
Missing birth outcome	19	6

*Denominator is 299 participants/pregnancies.
†An individual can experience ≥ 1 laboratory event.
‡Four pregnancies were multiple gestations (twins) and are included.
§Missing birth weight: $n = 22$.

monitor renal function, thus the data may have underestimated true reduced renal function among participants.

Other rarer toxicity outcomes may not have been observed due to the current study's small sample size. Despite high engagement in care, women who were lost to follow-up may have had qualifying laboratory or clinical adverse events that were not observed, meaning our data may underestimate the true occurrence of adverse events from TDF/3TC/EFV. Drug adverse event monitoring systems are important for ongoing safety data and patient care.

Engagement in care is necessary for optimal maternal and infant health, and links closely with viral suppression. One of the UNAIDS 90-90-90 goals to end the HIV epidemic by 2020 is to have 90% of those on ART maintain viral suppression, which reduces transmission to partners and infants [34]. Engagement in care tends to decrease over time, especially in the post-partum period [35]. Interruptions in care and ART adherence can lead to rebounds of high viremia: episodes of high viremia were frequent in the 12 months post-partum among women initiating ART through Option B+ in a South African cohort [36]. Additional efforts to help mothers continue their outpatient HIV care and viral suppression beyond the perinatal period are needed. Engagement in care among our participants (89% and 90% at 6 and 12 months, respectively) was higher than published estimates from other studies of women enrolled in Option B+ in Malawi, which ranged from 75% to 83% over 6–12 months after ART initiation [35,37,38], even using the same Malawi Ministry of Health definition of lost to follow-up (>60 days since attending a scheduled clinic visit for ART) [19]. The current study's participants may have been more motivated to return for their clinic visits and adhere to their ART regimen because they received a transport stipend provided as part of study participation, had positive view of care received from study staff, because the study clinic was less crowded than the government clinic, or because they desired to be part of a research program. Future investigation of continued engagement in care after exiting research studies could help inform efforts to increase long-term engagement in HIV care after the perinatal period in the general population.

Overall, infant outcomes were reassuring with regards to maternal-to-child transmission (MTCT) of HIV. MTCT occurred in only 2% of women enrolled in this cohort, comparable to MTCT among participants managed on this same regimen in other studies [39–41], and lower than the overall MTCT rate of >4% in Malawi [42]. Most MTCT events in our cohort occurred in mother-infant pairs where the mother had an unsuppressed viral load. Expectant mothers are less likely to transmit HIV to their infants if they initiate ART with enough time to achieve viral suppression by delivery [43,44]. Ongoing support during the perinatal period is needed to further decrease MTCT of HIV.

Birth outcomes may vary by timing of ART initiation (pre-conception *vs.* during pregnancy) – earlier ART initiation is associated with worse birth outcomes [16,17,45–48]. EFV-based regimens have demonstrated a null or protective relationship with preterm birth when compared to nevirapine- or dolutegravir-based regimens [49–53] and are widely available. Among infants in our study, birth outcomes were comparable to or more favourable than results from other sub-Saharan African countries for both preterm birth [52,54–57] and low

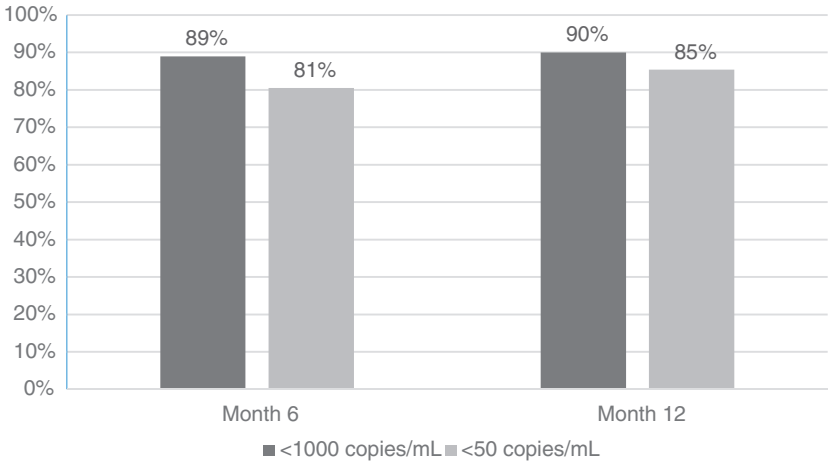

Figure 2 Viral suppression at 6 and 12 months post-ART initiation among women in HIV care.

birth weight [55,56,58]. We did not observe pregnancy outcomes for women lost to follow-up, so our results may underestimate adverse birth outcomes and MTCT events. Further evaluation of the potential effects of ART exposure on infants as they age is needed, given that HIV-exposed but uninfected infants have worse outcomes than HIV-unexposed infants [59].

In summary, most women who initiated TDF/3TC/EFV remained engaged in HIV care with little maternal-to-child transmission of HIV, few toxicities requiring regimen change, and few deaths. While laboratory monitoring provides objective information useful for clinicians, routine management per Ministry of Health guidelines is reasonable under a public health approach.

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Corresponding Author **Bryna J. Harrington**, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 2101 McGavran-Greenberg Hall CB#7435, Chapel Hill, NC 27599, USA. Tel.: +1-919-966-7430; Fax +1-919-966-2089; E-mail: bryna_harrington@med.unc.edu