

# Impact of Option B+ on the Infant PMTCT Cascade in Lilongwe, Malawi

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**Abstract:** This observational study compared uptake of infant prevention of mother-to-child transmission of HIV services pre/post implementation of Option B+ in Lilongwe, Malawi. There were 845 (pre) and 998 (post) births. Post-B+, infants had longer median pre-delivery maternal antiretroviral therapy {62 days [interquartile range (IQR): 38–94] pre-B+ vs. 95 days [IQR: 61–131] post-B+;  $P < 0.0001$ } and improved polymerase chain reaction testing (82.0% vs. 86.5%;  $P = 0.01$ ) at younger median age [7.6 weeks (IQR: 6.6–10.9) vs. 6.9 (IQR: 6.4–8.1);  $P < 0.0001$ ]. Proportion testing polymerase chain reaction positive decreased (4.6% vs. 2.6%;  $P = 0.03$ ). Proportion of HIV-infected infants starting antiretroviral therapy (75% vs. 77.3%) and age at initiation [19.7 weeks (IQR: 15.4–31.1)

vs. 16 (IQR: 13.3–17.9)] remained unchanged. These findings suggest modest improvements in infant care with Option B+.

**Key Words:** HIV, PMTCT, Option B+, Africa, antiretroviral, early infant diagnosis, Malawi

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## INTRODUCTION

Antiretroviral medications are highly effective for preventing mother-to-child transmission of HIV (PMTCT). However, in 2013, over 240,000 children worldwide were infected with HIV; the majority in sub-Saharan Africa.<sup>1</sup> Incremental losses along the PMTCT cascade have been a significant challenge to optimizing PMTCT outcomes.<sup>2–5</sup> Furthermore, a majority of HIV-exposed infants do not receive HIV testing, contributing to inadequate antiretroviral therapy (ART) coverage for children that is estimated to be 24%.<sup>1,6</sup>

In July 2011, the Malawi Ministry of Health (MOH) implemented Option B+ (B+), an innovative approach to improve uptake of PMTCT.<sup>7,8</sup> In addition to offering *lifelong* ART to all pregnant and breastfeeding women, HIV-exposed infant care was integrated with maternal ART follow-up to improve retention.<sup>9</sup> Infants receive 6 weeks of nevirapine starting at birth, early infant HIV DNA polymerase chain reaction (PCR) diagnosis using dried blood spots after 6 weeks of age and clinical follow-up until determination of final infection status.<sup>10,11</sup>

Several studies have examined the impact of B+ on the PMTCT cascade, particularly uptake and retention of women on ART.<sup>12,13</sup> However, little attention has focused on infant outcomes,<sup>14–18</sup> particularly HIV diagnosis, transmission, and treatment.<sup>19,20</sup> We assessed the impact of the change to B+ on the infant PMTCT cascade, by comparing service uptake pre- and post-B+ implementation (post-B+) at 2 large health centers in urban Lilongwe.

## METHODS

### Study Design

A pre/poststudy using routinely collected program data of infants born to women enrolled in the PMTCT program during two 18-month periods pre-B+ (October 2009–March 2011) and post-B+ (October 2011–March 2013). Our primary objective was to compare uptake of early infant HIV diagnosis (EID) with

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HIV DNA PCR testing (PCR test) and infant ART initiation pre- and post-B+. We also compared uptake of maternal/infant ART/antiretroviral medications for PMTCT and duration of maternal ART predelivery and evaluated maternal factors associated with failure to obtain an infant PCR test.

### Study Setting, Patient Population, and Routine PMTCT Program Services

Program data were available for Area 25 and Kawale, 2 large urban communities in Lilongwe, Malawi. All PMTCT care including the Tingathe community health worker (CHW) support was provided in accordance with WHO and Malawi MOH guidelines as has been previously.<sup>8,21–26</sup> To align support services with the policy of ART for all HIV-infected pregnant women (B+), CHWs were trained on the new national guidelines.<sup>8</sup> In compliance with national policy change to B+, HIV-exposed infant follow-up was integrated with maternal ART follow-up. Other than these modifications, service activities were unchanged.

### Statistical Analysis

Service uptake along the infant PMTCT cascade was compared between infants of women enrolled pre-B+ and post-B+. Wilcoxon rank-sum test was used for continuous and  $\chi^2$  test or Fisher exact test for categorical variables.

Logistic regression was used to identify maternal factors associated with failure to obtain an infant PCR test among births post-B+. We considered the following 5 factors: maternal age, trimester of pregnancy, HIV status at enrollment, ART initiation, and partner disclosure. We excluded women who transferred out before infant PCR. Univariate analysis was followed by multiple logistic regression to simultaneously evaluate the effects of these factors on failure to obtain infant PCR. Two-way interactions were not significant and therefore not retained in the model. The final model was checked by goodness-of-fit and influential statistics. We reported crude and adjusted odds ratio (OR) and 95% confidence intervals (CIs) to evaluate the associations between covariates and the outcome with and without adjustment of covariates, respectively.

Additionally, we examined the association between maternal ART outcome 6 months after initiation and failure to obtain an infant PCR test among women newly initiating ART post-B+. Only infants born to women enrolled while pregnant were included. Women who transferred out before infant PCR were excluded. We used Fisher exact test to compare infant PCR completion rates among the maternal 6-month ART outcome categories, and univariate logistic regression was performed to obtain OR estimates.

A  $P < 0.05$  was considered statistically significant, and SAS software version 9.3 (SAS Institute, Cary, NC) was used for all analyses.

### Ethics Statement

The National Health Sciences Research Committee of Malawi and the Baylor College of Medicine Institutional

Review Board approved the study. Data were deidentified before analysis.

## RESULTS

There were 845 (pre) and 998 (post) infants born to women enrolled in the PMTCT program. Post-B+, a greater proportion of infants were born to women who enrolled earlier in pregnancy, were known to be HIV-infected (30.2% vs. 48.4%;  $P < 0.0001$ ), and on ART at enrollment (20.6% vs. 32.6%;  $P < 0.0001$ ) (Table 1). There was no change in the proportion of mothers and infants who newly received antiretrovirals for PMTCT pre- and post-B+. However, among women newly initiating ART, median duration on ART before delivery was significantly longer post-B+ (62 vs. 95 days;  $P < 0.001$ ).

A greater proportion of infants received a PCR test and at a younger median age post-B+ (Table 1). However, post-B+, 13.5% of infants failed to receive a PCR test, and, of those tested, 216 of 863 (25%) were tested after 2 months of age. There was no change in the median time for delivery of results to caregivers. A smaller proportion of infants tested were diagnosed as HIV-infected post-B+ (all infants: 4.6% vs. 2.6%;  $P = 0.03$ ); the difference remained significant after including only those tested at 4–12 weeks (4.7% vs. 2.3%;  $P = 0.01$ ).

There was neither a change in the proportion of HIV-infected infants started on ART [75% (24/32) vs. 77.3% (17/22);  $P = 0.85$ ] nor median age at ART initiation [19.7 weeks, (interquartile range: 15.4–31.1) vs. 16 (interquartile range: 13.3–17.9);  $P = 0.08$ ].

Sensitivity analysis evaluating changes in outcomes after excluding women already on ART at PMTCT enrollment remained significant (see Appendix A, Supplemental Digital Content, <http://links.lww.com/QAI/A692>).

Multivariate logistic regression, examining maternal factors associated with failure to obtain an infant PCR test post-B+, found that being newly diagnosed as HIV-infected was marginally associated with failure and not starting ART was significantly associated with failure while adjusting for other covariates (Table 2). Enrolling in the second trimester, compared with later enrollment, and starting ART after enrollment were protective.

In the post-B+ cohort, we also examined the relationship between maternal outcomes 6 months after ART initiation and failure to obtain an infant PCR test. Of the 626 infants born to women newly initiating ART after enrollment, 34 transferred out and were excluded leaving 592 infants in the analysis. Infant PCR completion rates were significantly different by maternal outcome category: ( $P < 0.0001$ ). Compared with those whose mothers were alive on ART at 6 months, those whose mothers were lost to follow-up/died or stopped ART were much more likely to fail to get an infant PCR (OR 14.7; 95% CI: 7.0 to 30.8) and (OR 27.5; 95% CI: 10.9 to 69.4), respectively.

## DISCUSSION

In this first study to carefully examine infant outcomes postimplementation of Option B+ in Malawi, we found

**TABLE 1.** Baseline Maternal Characteristics and Changes in Service Uptake in the Infant PMTCT Cascade Pre- and Post-Implementation of Option B+

STEP in the Infant PMTCT Cascade	Description	Pre-Option B+ October 2009–March 2011	Post-Option B+ October 2011–March 2013	P
	Infants born to women enrolled in the PMTCT program	845	998	—
Characteristics of infants' mothers at program enrollment during antenatal care	Gender male, n/N (%)	402/844 (47.6)	464/998 (46.5)	0.63
	Median maternal age, yrs (IQR)	27.1 (23.9–31.0)	28.0 (24.2–31.8)	0.07
	Trimester of pregnancy, n (%)			
	First	24 (2.8)	44 (4.4)	<0.0001
	Second	449 (53.1)	627 (62.9)	—
	Third	372 (44.0)	326 (32.7)	—
	Missing data	0	1	—
	HIV status at enrollment, n (%)			
	Already known to be HIV-infected	254 (30.2)	483 (48.4)	<0.0001
	Newly diagnosed as HIV-infected	588 (69.8)	515 (51.6)	—
Missing	3	0	—	
Mom on ART at enrollment into PMTCT program, n (%)	174/845 (20.6)	325/998 (32.6)	<0.0001	
Maternal ART/ARVs for PMTCT	Mom received ART/ARVs* for PMTCT, n (%)	801/845 (94.8)	951/998 (95.3)	0.62
	Newly initiated ART/ARVs for PMTCT	627/671 (93.4)	626/673 (93.0)	0.76
	New ART initiation	206/627 (32.9)	626/626 (100)	<0.0001
	Days on ART before delivery among those newly initiating, median (IQR)	62 (38–94)	95 (61–131)	<0.0001
Infant ARVs for PMTCT	Infant received ARVs† for PMTCT, n/N (%)	817/845 (96.7)	957/998 (95.9)	0.37
Infant HIV DNA PCR testing, transmission, and ART initiation	Infant received HIV DNA PCR test, n/N (%)‡	693/845 (82.0)	863/998 (86.5)	0.01
	Median weeks of age at time of test, (IQR)	7.6 (6.6–10.9)	6.9 (6.4–8.1)	<0.0001
	PCR test result available, n/N (%)	691/693 (99.7)	860/863 (99.7)	1.00
	Median weeks from test taken to result given to caregiver, (IQR)	8 (4.7–10)	8 (4.3–10)	0.53
	Of infants with positive PCR test, median weeks of age at PCR test, (IQR)	7.5 (6.5–10.7)	6.9 (6.4–8.0)	0.32
	Infants found have be HIV-infected at first PCR (number positive/number of available first PCR results), n/N (%)	32/691 (4.6)	22/860 (2.6)	0.03
	PCR done at 4–12 wks of age, n/N (%)	26/549 (4.7)	18/793 (2.3)	0.01
	HIV-infected infants started on ART, n/N (%)	24/32 (75.0)	17/22 (77.3)	0.85
	Median weeks of age at ART initiation, (IQR)	19.7 (15.4–31.1)	16 (13.3–17.9)	0.08

\*Pre-B+, this included lifelong ART (stavudine-lamivudine-NVP) if CD4+ <350 cells per cubic millimeter, or ZDV from 28 wks gestation to delivery + single-dose NVP at delivery if CD4+ ≥350 cells per cubic millimeter. Post-B+, all HIV-infected pregnant women were automatically eligible for lifelong ART (tenofovir-lamivudine-efavirenz).

†Pre-B+, infants received single-dose NVP and ZDV for 1 week after birth. Post-B+, infants received NVP for 6 weeks after delivery.

‡During both observation periods, EID with DNA PCR testing on dried blood spot specimens was offered at ≥ 6 weeks of age.

ARVs, antiretroviral medications; IQR, interquartile range; NVP, nevirapine; ZDV, zidovudine.

modest improvement along the infant PMTCT cascade. There was a significant improvement in duration of maternal ART pre-delivery and smaller proportion of infants testing positive. However, ongoing challenges such as prompt delivery of EID results to caregivers and timely infant ART initiation remained.

There was a significant improvement in the duration of maternal ART during pregnancy (median, 62 vs. 95 days) and smaller proportion of infants with a positive PCR test on early testing post-B+ (4.6% vs. 2.6%). The lower transmission may be secondary to increased proportion of eligible women receiving ART and longer duration of maternal ART during pregnancy. This is reassuring preliminary evidence of B+'s impact on MTCT through extended maternal ART coverage

and the impact of the ART scale-up in Malawi with increasing numbers of women entering PMTCT on ART. However, studies measuring population-level vertical transmission post-B+ implementation are needed.<sup>27</sup>

Our study suggests modest improvements in the uptake of infant HIV testing (82% vs. 86.5%) and younger median age at testing (7.6 vs. 6.9 weeks) post-B+. With B+, more women initiated ART and therefore may have been more likely to bring their infants in for testing. The linked mother–infant data enabled us to provide preliminary insights on the impact of maternal ART outcomes on infant PCR testing uptake post-B+. Women who were lost to follow-up or died or stopped ART were much more likely to fail to have a recorded infant PCR test. These findings

**TABLE 2.** Maternal Factors Associated With Failure to Obtain Infant HIV DNA PCR Test Post Option B+ Implementation

	n/N (%), Total 977	OR of Failure (95% CI)	P	Adjusted OR of Failure (95% CI)* (N = 976)	P
Maternal age, yrs					
<20	11/80 (13.8)	1.00 (ref)	—	1.00 (ref)	—
20+	103/897 (11.5)	0.81 (0.42 to 1.59)	0.55	1.03 (0.49 to 2.17)	0.95
Trimester of pregnancy, n (%)					
First	6/43 (14.0)	0.86 (0.34 to 2.13)	0.74	0.96 (0.36 to 2.59)	0.94
Second	57/613 (9.3)	0.54 (0.36 to 0.81)	0.003	<b>0.55 (0.36 to 0.83)</b>	<b>0.005</b>
Third	51/320 (15.9)	1.00 (ref)	—	1.00 (ref)	—
Missing data	1	—	—	—	—
HIV status at enrollment, n (%)					
Already known to be HIV-infected	44/473 (9.3)	1.00 (ref)	—	1.00 (ref)	—
Newly diagnosed as HIV-infected	70/504 (13.9)	1.57 (1.05 to 2.35)	0.03	1.94 (0.89 to 4.23)	0.09
Time to maternal ART initiation					
On ART before enrollment	30/320 (9.4)	1.00 (ref)	—	1.00 (ref)	—
Initiated the same day of enrollment	50/331 (15.1)	1.72 (1.06 to 2.78)	0.03	0.97 (0.47 to 2.03)	0.94
Initiated after the day of enrollment†	25/314 (8.0)	0.84 (0.48 to 1.46)	0.53	<b>0.45 (0.20 to 1.01)</b>	<b>0.05</b>
Did not start ART	9/12 (75.0)	28.99 (7.40 to 112.88)	<0.0001	<b>18.59 (4.46 to 77.59)</b>	<0.0001
Partner disclosure status at enrollment, n (%)*					
Partner involved and disclosed	39/412 (9.5)	1.00 (ref)	—	1.00 (ref)	—
Partner involved, not disclosed	74/542 (3.7)	1.51 (1.00 to 2.28)	0.05	1.11 (0.60 to 2.08)	0.73
Partner not involved	1/23 (4.4)	0.44 (0.06 to 3.31)	0.42	0.41 (0.05 to 3.20)	0.40

The analysis was conducted among HIV-infected pregnant women with a recorded birth who were enrolled during the post-option B+ period. Those transferred out without PCR testing were excluded.

All covariates were tested for entry into the multivariate model. No 2-way interaction was found in the multivariate logistic regression model using significance level of 0.05.

\*Partner disclosed defined as partner having knowledge of maternal HIV status. Partner noninvolved defined as a partner who has died, or is otherwise separated from the mother. Hosmer and Lemeshow goodness-of-fit:  $P = 0.93$ , supporting the model's adequacy and no evidence of lack of fit.

†Among those who started ART after the day of enrollment, median to ART start was 23 (IQR: 7–53) days.

Bold  $P$  values are  $\leq 0.05$ .

highlight the need for targeted efforts to better understand and address women's choices around engagement in care and adherence to ART, as well as where and how infant care is best delivered. Women starting ART after enrollment at antenatal clinic (ANC) were more likely to get an infant PCR test. This may indicate that women<sup>13</sup> and infants by extension may benefit from more time to prepare for ART initiation and infant testing. However, additional research is needed to explore if delayed initiation may be protective or if women who delay are inherently different.

Despite the improvements in duration of maternal ART, transmission, and timely EID uptake, we did not see improvement along other critical points in the infant cascade. A sizeable portion of infants failed to receive a PCR test (13.5%) post-B+, and 25% were tested after 2 months of age. Furthermore, there was no change in the median time to delivery of test results, proportion of infants started on ART, or age at ART start, which remained at a median of 16 weeks. There is increasing evidence that, for some infants, ART initiation even by 12 weeks of age may not adequately prevent disease progression or death.<sup>28</sup> Delays in diagnosis because of late testing and slow turnaround of results lead to late ART initiation and subsequent increases in infant morbidity and mortality.<sup>17,29</sup> There is a need to develop and evaluate strategies not only for earlier identification of HIV-infected infants<sup>6</sup> but more rapid ART initiation to further reduce infant mortality.<sup>29</sup>

The study is limited in that it used a historical control group. Because of the rapid and widespread scale-up of Option B+ throughout the country, contemporary controls were not available. Therefore, improvements in maternal ART coverage predelivery and transmission post-B+ may represent maturity of the ART, PMTCT, and EID programs or may be secondary to other unknown contemporary influences or epidemiologic trends. However, other than training on the new national B+ protocols,<sup>8</sup> service activities were unchanged. Furthermore, we report data from large urban health centers in Malawi within a CHW-supported program with better outcomes pre-B+ than those reported nationally. Therefore, generalizability to centers in rural Malawi or with less support may be limited. Indeed, the impact of B+ on EID uptake and infant ART initiation may be more robust at sites with worse PMTCT uptake before B+. Finally, this study is limited to early infant outcomes. We can report on survival and final infant infection status postweaning as the cohort matures.

This preliminary evidence suggests that post-B+ there have been improvements in maternal ART coverage predelivery, decreased proportion of infants testing HIV-positive, and modest improvements in uptake and timing of EID. However, despite these noteworthy successes, additional strategies to increase EID testing coverage, improve timely delivery of results, and expedite prompt ART are still needed.

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