

Program Implementation of Option B± at a President's Emergency Plan for AIDS Relief-Supported HIV Clinic Improves Clinical Indicators But Not Retention in Care in Mbarara, Uganda

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Abstract

2013 WHO guidelines for prevention of mother to child transmission recommend combination antiretroviral therapy (ART) for all pregnant women, regardless of CD4 count (Option B/B+). We conducted a retrospective analysis of data from a government-operated HIV clinic in Mbarara, Uganda before and after implementation of Option B+ to assess the impact on retention in care. We limited our analysis to women not on ART at the time of their first reported pregnancy with CD4 count >350. We fit regression models to estimate relationships between calendar period (Option A vs. Option B+) and the primary outcome of interest, retention in care. One thousand and sixty-two women were included in the analysis. Women were more likely to start ART within 6 months of pregnancy in the Option B+ period (68% vs. 7%, $p < 0.0001$) and had significantly greater increases in CD4 count 1 year after pregnancy (+172 vs. -5 cells, $p < 0.001$). However, there was no difference in the proportion of women retained in care 1 year after pregnancy (73% vs. 70%, $p = 0.34$). In models adjusted for age, distance to clinic, marital status, and CD4 count, Option B+ was associated with a nonsignificant 30% increased odds of retention in care at 1 year [adjusted odds ratio (AOR) = 1.30, 95% CI 0.98–1.73, $p = 0.06$]. After transition to an Option B+ program, pregnant women with CD4 count >350 were more likely to initiate combination therapy; however, interventions to mitigate losses from HIV care during pregnancy are needed to improve the health of women, children, and families.

Keywords: PMTCT, pregnancy, retention in care

Introduction

ELIMINATING PERINATAL TRANSMISSION of HIV and improving care for women living with HIV and their children is a goal of the World Health Organization (WHO), the President's Emergency Plan for AIDS Relief (PEPFAR), and others.^{1,2} This goal has begun to be realized through the provision of antiretroviral therapy (ART) during pregnancy and breastfeeding for HIV-infected women, which reduces the risk of perinatal HIV transmission from 15% to 40% to less than 1% in optimal conditions.³ Although progress has been made toward the goal of eliminating perinatal transmission, more than 100,000 children are born with HIV each year in sub-Saharan Africa.⁴

In 2013, the WHO issued updated guidelines for prevention of mother to child transmission (PMTCT). These guidelines recommend initiation of triple drug ART for pregnant or breastfeeding HIV-infected women, either during pregnancy and breast-feeding periods (termed PMTCT Option B) or for life (termed PMTCT Option B+), regardless of CD4 count. This recommendation supplanted the prior 2006 recommendation, which called for zidovudine starting at 28 weeks of pregnancy or as soon as possible thereafter, nevirapine and zidovudine plus lamivudine during the intrapartum period, and zidovudine plus lamivudine for 7 days during the postpartum period for women who had higher CD4 counts (termed Option A). The change in guidelines reflected a push to simplify service delivery, reduce perinatal transmission,

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avoid drug resistance that arises with episodic use of ART, reduce maternal morbidity and mortality, and reduce transmission to sexual partners.⁵

The guideline changes are beginning to affect clinical outcomes. In 2016, the WHO published the results of the PROMISE study, which enrolled over 3500 women in several Sub-Saharan countries and demonstrated a lower rate of mother to child HIV transmission among women on triple drug regimens (0.5%) than on Option A (1.8%).⁶ Early data from the PROMISE study also demonstrate maternal health benefits, with risk of WHO stage 2 and 3 events significantly lower among women who continued ART postpartum [hazard ratio (HR) 0.47, 95% CI 0.32–0.68].⁷ However, rates of death, AIDS defining illness, and serious non-AIDS events did not differ by study arm, and virologic failure was high (23%) in the continuing ART group. In addition, retention in care outcomes of Option B+ have been mixed^{8–11} and both poor ART adherence and decreased maternal retention in care have been reported among pregnant women with HIV.^{12,13} We present additional programmatic data on clinical outcomes and retention in care for pregnant women after implementation of Option B+ in Uganda, an early adopter of the strategy.

In January 2010, the HIV clinic at the Mbarara Regional Referral Hospital (MRRH) changed its PMTCT policy from Option A to Option B+. This change in policy avails an opportunity to investigate the independent clinical and programmatic impacts of the policy change at a PEPFAR-supported publicly operated clinic in rural sub-Saharan Africa. We conducted a retrospective analysis of data collected at the MRRH HIV clinic before and after the policy change from Option A to Option B+ to assess the impact of the implementation of an Option B+ ART program on maternal health outcomes, including CD4 count, the likelihood of starting ART, and maternal retention in HIV care.

Methods

Study design

We conducted a retrospective analysis of deidentified data collected at the HIV clinic at the MRRH before and after the policy change from Option A to Option B+. Mbarara, Uganda is in southwestern Uganda, where HIV prevalence is estimated to be 7% among the adult population.¹⁴ Approximately 75% of pregnant women receive ART for PMTCT in the area.¹⁵ MRRH was founded in 1998 and serves the population of Mbarara, as well as the surrounding areas. The HIV clinic has an active patient census of over 10,000 HIV-infected individuals and provides HIV-related care, including ART at no cost to patients.

We included all women in care at the HIV Clinic during 2007–2013 who had at least one pregnancy recorded in the database. At each visit, clinicians ask women of child bearing age if they are currently pregnant and, if so, their expected date of delivery. Those who are pregnant remain in the adult HIV clinic for PMTCT services and are referred to antenatal clinic for additional pregnancy care. For each woman included, we evaluated data during their first instance of pregnancy during the observation period. We excluded women who were on ART at the time of pregnancy and those women with a pretreatment CD4 count <350 cells/ μ L at the time of pregnancy, because they had a non-PMTCT indication for ART. We define ART use as use of triple therapy ART. We also excluded seven women who transferred care to a different site within the first year of treatment. For each woman, we

extracted data on age, marital status, distance from clinic, and CD4 count at the time of their incident pregnancy. All variables other than CD4 count were self-reported by the patients.

For the 50 women who had no pregnancy CD4 count, we imputed their CD4 count using the median CD4 count for the cohort during their year of enrollment.

Data analysis

Our primary explanatory variable of interest was calendar period, which we dichotomized into pre-Option B+ (from January 2007 to 2010) and post-Option B+ (after March 2010 to January 20, 2013). We excluded the period between January and March 2010 from the analysis, considering it as a washout period while the clinic was transitioning from Option A to B+ protocols. Women were allocated into a period based upon the date that their first pregnancy was noted in the clinic record. We abstracted data for this analysis in January 2014 and included all women who had a first pregnancy up until January 2013, to allow each woman a minimum of 1 year of data in the dataset after pregnancy detection. Secondary explanatory variables include age, distance from clinic, gestational age, and CD4 count at pregnancy.

We had one primary and three secondary outcomes of interest:

1. Retention in HIV care, as determined by one or more clinic visits 12 months after the date of pregnancy detection (primary).
2. Initiation of ART within 6 months of pregnancy detection (secondary).
3. CD4 count at 1 year after pregnancy (secondary).
4. Change in CD4 count over the year after pregnancy (secondary).

Outcomes (3) and (4) were restricted to those in care and with an available CD4 count for a minimum of 180 days after pregnancy detection. We did not include pediatric outcomes in the analysis because the pediatric clinic records are collected independent of the adult medical records, and linkage of mothers to children was not possible. We fit bivariable logistic and linear regression models to estimate relationships between calendar period (Option A vs. Option B+) and each of our outcomes of interest. We then fit a multivariable model for our primary outcome of interest, retention in care at 12 months, including calendar period, age, travel time to clinic, marital status, and CD4 count. We used postestimation margins to estimate adjusted proportions of women retained in care in the pre and post-Option B+ periods and graphed Kaplan–Meier survival plots to depict retention in care during both periods. We also conducted three sensitivity analyses: one excluding women with a missing CD4 count at the time of pregnancy (8% of included women) instead of imputing CD4 values, one including gestational age in the model, which was missing for 35% of women so not included in the primary model, and a final one restricted to pregnant women with CD4 counts <350 cells/ μ L, and therefore, who met ART initiation criteria at both periods, as a control group to assess for temporal changes in the HIV care program other than Option B+ implementation.

Results

A total of 1062 women were included in the analysis: 536 (50.5%) in the Option A period (January 2007 to 2010) and

TABLE 1. COHORT CHARACTERISTICS

Characteristics	Total cohort, n = 1062	Pre Option, B+, n = 536	Post Option B+, n = 526	p
Age (median, IQR)	26 (23–30)	26 (23–30)	25 (22–29)	0.004
Married, % (n)	70 (741)	68 (363)	72 (378)	0.302
Distance from clinic, % (n)				<0.001
<30 min	23 (239)	20 (108)	25 (131)	
30–60 min	28 (298)	21 (110)	36 (188)	
>60 min	30 (315)	28 (151)	31 (164)	
Missing	20 (210)	31 (167)	8 (43)	
Pregnancy CD4 count (median, IQR)	501 (414–637)	506 (414–639)	495 (419–630)	0.699
Categorized pregnancy CD4 counts, % (n)				0.790
Pregnancy CD4 count 350–450	39 (411)	38 (202)	40 (209)	
Pregnancy CD4 count 450–550	23 (241)	23 (124)	22 (117)	
Pregnancy CD4 count >550	39 (410)	39 (210)	38 (200)	
Gestational age weeks (median, IQR)	20 (12–24)	16 (8–24)	20 (16–28)	<0.001
Missing, % (n)	36 (385)	21 (110)	51 (271)	

Data on cohort characteristics were assessed at the time of detection of the first pregnancy in HIV care. IQR, interquartile range.

526 (49.5%) in the Option B+ period (March 2010 to January 2013). The median CD4 count at the time of first pregnancy for women was similar between periods (506 cells/ μ L in Option A period, 495 cells/ μ L in Option B+ period, rank sum testing $p=0.699$). Women in Option B+ period had slightly later gestational age at presentation (20 weeks vs. 16 weeks); however, the variable was missing in the database for 36% of women. The remainder of the cohort characteristics is summarized in Table 1. Women in the two groups were not significantly different in terms of marital status or pregnancy CD4 count, but women in the Option A period were slightly older (26 years old vs. 25 years old, $p=0.004$) and those in the Option A period were more likely to be missing data on their distance from the clinic (31% vs. 8%, $p<0.001$).

Women in the Option B+ period were more likely to start ART within 6 months of their first recorded pregnancy (68% vs. 7%, $p<0.0001$) and those who started treatment began it significantly earlier (28 days vs. 1026 days, $p<0.0001$) compared to the Option A group. Of those who initiated ART in the first 6 months in the Option A period, the most common regimen was AZT/3TC/NVP, started in 84% (31/37) of women. In contrast, in the Option B+ period, the most common regimens were TDF/3TC/EFV (55%, 198/358) and AZT/

3TC/EFV (34%, 120/358). Women retained in care (as defined by at least one clinic visit recorded 12 months after their first detected pregnancy) and with a CD4 result at least 180 days after pregnancy had significantly greater increases in CD4 count 12 months after pregnancy in the Option B+ period (+172 cells/ μ L vs. -5 cells/ μ L, $p\leq 0.001$) and had higher overall CD4 counts 12 months after pregnancy (684 cells/ μ L vs. 535 cells/ μ L, $p\leq 0.001$).

However, there was no significant difference in the crude proportion of women retained in care 1 year after pregnancy between the two periods (73% vs. 70%, $p=0.338$; Table 2 and Fig. 1). Women who started ART had a significant increased likelihood of remaining in care at 1 year post-pregnancy in both time periods compared to women who did not start ART (84% vs. 62%, $p<0.001$; Table 2). In addition, women in the Option B+ period who did not start ART had the lowest rates of retention in care (46% for women receiving Option B+ not on ART vs. 84% for women in Option B+ receiving ART) at 1 year after pregnancy. In multivariable models adjusted for age, marital status, and clinic travel time, the Option B+ period was associated with a nonsignificant 30% increased odds of retention in care at 1 year (AOR 1.30, 95% CI 0.98–1.73, $p=0.06$; Table 3). Using

TABLE 2. CLINICAL AND RETENTION IN CARE OUTCOMES 1 YEAR AFTER DETECTION OF PREGNANCY AMONG WOMEN ENROLLED IN CARE AT A PUBLIC HIV CLINIC IN SOUTHWESTERN UGANDA BEFORE AND AFTER IMPLEMENTATION OF AN OPTION B+ PREVENTION OF MOTHER TO CHILD TRANSMISSION PROGRAM

	n	Pre Option B+	Post Option B+	p
CD4 count 1 year after report of pregnancy (median, IQR)	776	535 (400–738)	684 (553–900)	<0.0001
Change in CD4 count from report of pregnancy to 1 year after pregnancy (median, IQR)	776	-5 (-107 to 137)	+172 (36–335)	<0.0001
ART initiation within 6 months of report of pregnancy (n, %)	1062	37/536, 7	358/526, 68	<0.0001
Retention in care 1 year after report of pregnancy (n, %)	1062	375/536, 70	382/526, 73	0.338
Retention in care 1 year after report of pregnancy if started ART (n, %)	420	41/47, 87	312/373, 84	0.527
Retention in care 1 year after report of pregnancy if not started ART (n, %)	642	334/489, 68	70/153, 46	<0.001

Retention in care defined as one or more clinic visits 12 months after detection of first pregnancy detection.

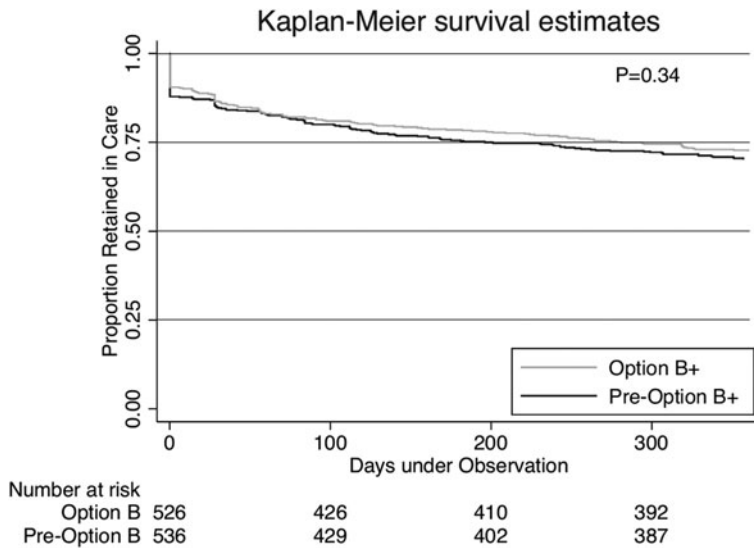


FIG. 1. Kaplan–Meier estimates for proportion retained in HIV care 1 year after pregnancy detection at a public HIV clinic in Southwestern Uganda before and after implementation of an Option B+ PMTCT Program. PMTCT, prevention of mother to child transmission.

adjusted postestimation margins, we estimated that 69% (95% CI 65–73) of women were retained in care in the Option A period versus 74% in the Option B+ period (95% CI 70–78). We found no significant differences in the effect of observation period on retention in care at 1 year in sensitivity analyses with models excluding women with missing CD4 count at the time of presentation (AOR 1.14, 95% CI 0.84–1.55, $p=0.399$) or including gestational age at the time of pregnancy detection (AOR 1.26, 95% CI 0.87–1.82, $p=0.230$). In multivariable analyses, increasing age (AOR 1.49, 95% CI 1.15–1.93, $p=0.002$; Table 3) and being married (AOR 1.34, 95% CI 1.02–1.75, $p=0.034$; Table 3) were associated with significant increases in retention in care. In a second analysis restricted to women with a CD4 count <350 cells/ μL at the time of their first pregnancy (who met criteria for ART in both periods independent of the PMTCT policy), we found a nonsignificant increase in the proportion of women retained in care 12 months after report of pregnancy (72% vs. 78%, $p=0.085$).

Discussion

After transition to an Option B+ program, pregnant women enrolled in care in a government-run, PEPFAR-supported HIV clinic, and not otherwise eligible for ART (i.e., with a CD4 count >350 cells/ μL), were more likely to initiate combination ART, began combination ART therapy faster, and had improved CD4 cell counts in the following year. These data are reassuring and in keeping with data from elsewhere in sub-Saharan Africa demonstrating important benefits in maternal health indicators among mothers living with HIV and initiating ART during pregnancy.^{16–18} It is also an important contrast to data in the general HIV population, demonstrating a lack of improvement in ART initiation despite increasing CD4 count thresholds in the sub-Saharan African region.¹⁹ Despite improvements in clinical indicators in the Option B+ period, we found suboptimal rates of retention in HIV care both before and after the change in policy, with $\sim 30\%$ and 27% of women lost to follow-up 1 year after

TABLE 3. LOGISTIC REGRESSION MODELS FOR CORRELATES OF RETENTION IN HIV CARE 1 YEAR AFTER PREGNANCY DETECTION AT A PUBLIC HIV CLINIC IN SOUTHWESTERN UGANDA BEFORE AND AFTER IMPLEMENTATION OF AN OPTION B+ PREVENTION OF MOTHER TO CHILD TRANSMISSION PROGRAM

Characteristic	Univariable estimate		Multivariable estimate	
	HR (95% CI)	p	AHR (95% CI)	p
Age (each 10 years)	1.51 (1.17–1.94)	0.001	1.49 (1.15–1.93)	0.002
Distance from Clinic (30–60 min)				
<30 min	Ref	—	Ref	—
30–60 min	1.11 (0.77–1.61)	0.583	1.10 (0.76–1.60)	0.609
>60 min	1.04 (0.73–1.50)	0.819	0.99 (0.69–1.44)	0.978
Missing	1.58 (1.04–2.42)	0.033	1.65 (1.06–2.57)	0.027
Married	1.31 (1.01–1.71)	0.046	1.34 (1.02–1.75)	0.034
CD4 count at report of pregnancy (each 100 cells)	1.06 (0.98–1.14)	0.162	1.06 (0.98–1.14)	0.165
Enrollment period				
Option A	Ref	—	Ref	—
Option B+	1.14 (0.87–1.49)	0.338	1.30 (0.98–1.73)	0.064

One thousand and sixty-two women were included in the cohort, 536 pre Option B+ and 526 post Option B+. HR, hazard ratio; AHR, adjusted hazard ratio.

pregnancy in the Option A versus Option B+ time periods, respectively. After adjustment for potential confounders, we found that the Option B+ period was associated with a non-significant 30% increased odds of retention in care at 1 year, which corresponded to an estimated 5% increase in retention. There was also a nonsignificant increase (72% vs. 78%) in retention in care among women with low CD4 counts, indicating that there might also be other factors influencing retention in care between the two observation periods. These data suggest that Option B+ might minimally improve retention in care, but also signal an important need to consider additional components of care for pregnant and postpartum women in HIV care to ensure the long-term benefits of ART to women, their children, and families.

Previous data on the impact of the Option B+ on retention in care have also shown mixed benefits. For example, a recent clinical review in Botswana found that although implementation of Option B+ was associated with increased likelihood of receiving full ART therapy, it was also associated with an increased likelihood of receiving no type of ART at all, and as a result was predicted to lead to increased perinatal transmission.²⁰ The lack of significant improvement in retention rates we report in this study is also consistent with preliminary data on Option B+ from Malawi, where one study found that Option B+ increased maternal ART initiation by 748% but rates of maternal retention in care at 12 months remained approximately the same.^{8,9} A second study in Malawi found relatively high losses to follow-up in women using Option B+, particularly in facilities with a high patient volume.¹⁰ In contrast, a study in Lilongwe, Malawi, found a significantly greater proportion of women were retained through delivery post-B+ (51% vs. 65% post-B+) although they did not find an increase in the proportion initiating ART (79% vs. 82%).¹¹ A thorough understanding of differences in the programs, including secondary support interventions such as counseling, family planning, and/or antenatal care services which might differentiate them will be critical in helping to understand these divergent results.

Formative data on reasons for poor follow-up among pregnant and postpartum women living with HIV highlight the role of structural and psychosocial barriers and suggest that providing ART alone might be insufficient to retain women in the long term. For example, access to transportation is a central barrier for many women and may contribute to loss to follow-up, particularly in the postpartum period, when caring for a newborn heralds many new economic costs for the mother.²¹ Other studies have reported transportation costs, stigma of being HIV positive and pregnant, fear of HIV serostatus disclosure, lack of partner support, lack of understanding of the health benefits of HIV treatment for the mother, postpartum depression, poor communication from providers, confusion about breastfeeding guidelines, and long wait times at the clinic as significant factors affecting retention in care during this time.^{10,22–24} In keeping with these findings, our study found that women who were older and married had improved retention in care, putatively due to more stable social support mechanisms. In addition, others have demonstrated increased challenges to ART adherence in the postpartum period, which may also impact retention in care.²⁵ For example, a meta-analysis of ART adherence rates during pregnancy in low, middle, and high income countries found that adherence was higher in the antepartum than the post-

partum periods. However, another study on women in Uganda found relatively high adherence in the antepartum, pregnant, and postpartum periods (90% adherence antepartum, 92% during pregnancy, and 88% postpartum), although 72-h gaps in adherence were also most common in the postpartum period.²⁵ A third study in Uganda found that the median ART adherence during pregnancy was as high as 96%, indicating that women may have improved adherence during pregnancy.²⁶ Barriers to adherence in the meta-analysis included postpartum depression, life stressors in the postnatal period, and additional burden of ART medications.¹³

In addition to the challenge of retention in care and adherence for women who start ART, a further challenge arises from the fact that a significant proportion of women who did remain in care under Option B+ do not start ART during their pregnancy (32% in our data in the Option B+ period). This may be due to loss to follow-up before ART initiation, as at the MRRH HIV clinic same day initiation was not common at the time (average initiation time in Option B+ was 28 days post-pregnancy detection). A small 2016 study in Uganda evaluating adherence for women in the Option B+ period found that 36% of women never returned to care after their first visit and, thus, did not start ART, similar to our rate of not starting ART in the Option B+ period.²⁶ Many of the same barriers to retention in care outlined above are relevant for women who do not start ART.²¹ However, patient preference, concerns about ART toxicity, and unreported transfers out to other clinics are also possible etiologies for why women in the Option B+ period did not have a record of starting ART during pregnancy. More data are needed to further understand the reasons for suboptimal rates of ART initiation in this population.

These data and ours reinforce the fact that effective PMTCT programs will need to consider a multi-faceted approach, in addition to providing ART, to improve retention in care and promote durable health benefits for pregnant women living with HIV and their children. Fortunately, data are emerging that these barriers are not insurmountable. A recent study in rural Uganda found that HIV serostatus disclosure to the primary partner facilitated retention in care with viral suppression in postpartum women under Option B+.²⁷ In addition, some sites have implemented “family clinic days,” in which care is provided to both mother and child, in an effort to ameliorate the many challenges which are compounded in the postpartum period, such as additional visits for immunizations, as well as HIV follow-up. Two recent studies have tested the ability of such interventions to improve retention in care—one which focused on the use of a lay-counselor led intervention with home visits and appointment reminders and another that implemented a family-focused care package that integrated mother-infant care and included active male partner and community involvement. Both led to an improvement in the proportion of women retained in care by ~10% in the intervention arms.^{28,29} Other interventions, such as consolidated cash transfers,³⁰ have had mixed results—with some improvements in retention without alterations in clinical outcomes. Finally, multi-faceted programs designed to “engineer” interventions based on tailored clinic need assessments have shown recent promise in improving both ART coverage and infant testing.^{31,32} A redoubled effort by donors and ministries of health is underway to combine best practices from the variety of strategies and develop implementation guidelines to reduce PMTCT and improve maternal and child health.^{33–35}

Our study was strengthened by the use of routinely collected programmatic data, which augments generalizability to other PEPFAR-supported, publically operated HIV clinics in the region. However, the study also has several limitations. As this is a retrospective design of a nonrandomly allocated intervention, it can be challenged by both unmeasured and residual confounding. For example, preferred regimens changed from nevirapine-based to efavirenz-based therapy during 2008 and 2010 at the clinic. However, we know of no other major policy or structural changes to take place at the clinic during this time that would have confounded associations between retention in care and time period. In addition, although high rates of loss to follow-up in our studies and others are sobering, they may overestimate losses from care for failure to account for transfer to other facilities.³⁶ Other limitations include study of the first year of a new program, which might miss a lag in impact on the longer term outcomes, the lack of ability to measure whether loss to follow-up was during pregnancy or the postpartum period, the lack of ability to measure adherence, and the lack of linked data on child outcomes, which are key indicators for PMTCT programs that should be considered in future work.

In summary, at the Mbarara, Uganda HIV Clinic, women with higher CD4 counts in the Option B+ period were more likely to initiate combination therapy, were more likely to receive combination therapy faster, and had higher CD4 counts a year after pregnancy compared to women with higher CD4 counts in the Option A period. However, we estimated a nonsignificant 3% absolute difference in retention in care in the Option B+ period compared to the pre Option B+ period, suggesting that retention in care remains a significant barrier to providing high-quality HIV care for women and their children in sub-Saharan Africa. Efforts to improve health for women living with HIV and their children in the region must focus on additional support systems to support women to remain in care and maximize the health benefits of ART for women and their families.

Author Disclosure Statement

No conflicting financial interests exist.

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