PMTCT Option B+ Does Not Increase Preterm Birth Risk and May Prevent Extreme Prematurity: A Retrospective Cohort Study in Malawi

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Objective: To estimate preterm birth risk among infants of HIV-infected women in Lilongwe, Malawi, according to maternal antiretroviral therapy (ART) status and initiation time under Option B+.

Design: A retrospective cohort study of HIV-infected women delivering at ≥27 weeks of gestation, April 2012 to November 2015. Among women on ART at delivery, we restricted our analysis to those who initiated ART before 27 weeks of gestation.

Methods: We defined preterm birth as a singleton live birth at ≥27 and <37 weeks of gestation, with births at <32 weeks classified as extremely to very preterm. We used log-binomial models to estimate risk ratios and 95% confidence intervals for the association between ART and preterm birth.

Results: Among 3074 women included in our analyses, 731 preterm deliveries were observed (24%). Overall preterm birth risk was similar in women who had initiated ART at any point before 27 weeks and those who never initiated ART (risk ratio = 1.14; 95% confidence interval: 0.84 to 1.55), but risk of extremely to very preterm birth was 2.33 (1.39 to 3.92) times as great in those who never initiated ART compared with those who did at any point before 27 weeks. Among women on ART before delivery, ART initiation before conception was associated with the lowest preterm birth risk.

Conclusions: ART during pregnancy was not associated with preterm birth, and it may in fact be protective against severe adverse outcomes accompanying extremely to very preterm birth. As preconception ART initiation appears especially protective, long-term retention on ART should be a priority to minimize preterm birth in subsequent pregnancies.

Key Words: antiretroviral therapy, preterm birth, premature, HIV, option B, PMTCT

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INTRODUCTION

Preterm birth, often defined as birth before 37 weeks of gestation,[1] is the second-leading cause of death in children younger than 5 years,[2] and accounts for 75% of all perinatal mortality worldwide.[3,4] Of the estimated 15 million infants born preterm in 2010, more than 1 million died as a result of prematurity.[1–4] In sub-Saharan Africa, approximately 12% of live births are preterm, with Malawi registering the highest preterm birth prevalence worldwide (18%).[5]

HIV is also endemic in sub-Saharan Africa, with 59% of all prevalent HIV infections occurring among women.[6] Prevention of mother-to-child HIV transmission (PMTCT) is thus a major public health priority. Antiretroviral therapy (ART) for HIV-infected women during pregnancy can virtually eliminate the risk of vertical HIV transmission,[7–9] with the additional, important benefit of reduced maternal morbidity and mortality.[10–13]

In July 2011, Malawi became the first country to adopt a strategy of universal lifelong ART for pregnant and breastfeeding women regardless of HIV disease stage or CD4 count.[14] The scale-up of this approach, called "Option B+," is expected to help bring an end to new pediatric HIV infections and substantially improve maternal health in settings with high HIV burdens.[15] Since the introduction of Option B+ in Malawi, the number of pregnant or breastfeeding women on ART has increased dramatically,[16] and in 2013 the World

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Health Organization recommended it for all countries with a generalized HIV epidemic.[17]

Despite the clear benefits of Option B+ for maternal health and the prevention of vertical HIV transmission, the effects of ART exposure during pregnancy on fetal development and birth outcomes are still unclear.[18–24] In particular, few studies have examined the relationship between the timing of maternal ART initiation and preterm delivery.[18,25–29] In this study, we used data from the maternity unit of a large, urban hospital in Malawi to estimate preterm birth risk among HIV-infected women according to maternal ART status and time of ART initiation in the Option B+ era.

METHODS

Study Design, Setting, and Population

We conducted a retrospective cohort study using data collected at delivery from HIV-infected pregnant women for whom the date of last menstrual period (LMP) was available and who delivered a singleton live birth at Bwaila Hospital in Lilongwe, Malawi, from April 1, 2012 through November 15, 2015. Study data were obtained from a point-of-care electronic medical record system (POC-EMRS) developed by Baobab Health Trust and hosted at the hospital. All records in the POC-EMRS were entered directly by a health care worker at the time of delivery. Information about HIV status and ART (for HIV-infected women) was cross-checked with documentation in the mother's personal health passport, a government-issued document containing information on general history, diagnoses, treatments, antenatal consultations, and deliveries.

ART duration during pregnancy is intrinsically linked to length of gestation (and thus preterm birth): women initiating ART later in pregnancy are necessarily closer to reaching term and are therefore less likely to experience preterm birth. In an attempt to remove this potentially confounding relationship from our analysis, we constructed our study population such that the risk period for the outcome (preterm birth) was entirely separate from the eligible ART start times. Specifically, we restricted our analysis to women who (1) delivered on or after 27 weeks of gestation and (2) either started ART before 27 weeks or did not receive ART at all before delivery (Fig. 1). In other words, we chose a cutoff of 27 weeks to define the start of the risk period for preterm birth. This start point is at the upper end of values (which range from 20 to 28 weeks) that have been used in other settings[1]; this choice allowed us to minimize the number of women initiating ART during pregnancy that we would need to exclude to keep ART start times separate from the preterm risk period. Women with missing information on the main exposure (ART use) were also excluded.

This study was approved by the National Health Sciences Research Committee of Malawi and the Institutional Review Board at the University of North Carolina, Chapel Hill.

Variable Definitions and Classifications

HIV Status

Each woman's HIV status was determined on maternity unit admission. Women whose health passports indicated prior HIV-positive test results were considered to be HIV-infected; women without health passport documentation of HIV-positive status underwent HIV testing. Women found to be HIV-infected based on either the health passport or testing at delivery were recorded as such in the database and were eligible for study inclusion.

Main Outcome—Preterm Birth

Preterm birth status was based on gestational age at delivery, calculated as the difference between delivery date and the LMP date recorded in the health passport during the first antenatal visit. We defined preterm birth as birth on or after 27 weeks and before 37 weeks of gestation. Births occurring at 37+ weeks of gestation were considered full term.[1]

Main Exposure—ART

ART status and timing of initiation were determined at delivery according to maternal interview and information recorded in the health passport. Eligible HIV-infected women with no history of ART use before delivery comprised the "never initiated" group in our analysis. Women whose health passports indicated ART initiation at or after 27 weeks of gestation (but before delivery) were excluded from the analysis, as their ART exposure during pregnancy began after the start of the preterm birth risk period. The remaining ART-exposed women were assigned to one of 3 categories according to timing of ART initiation: (1) before pregnancy (on ART at conception), (2) during the first trimester, or (3) during the second trimester (specifically, the portion of the second trimester <27 weeks).

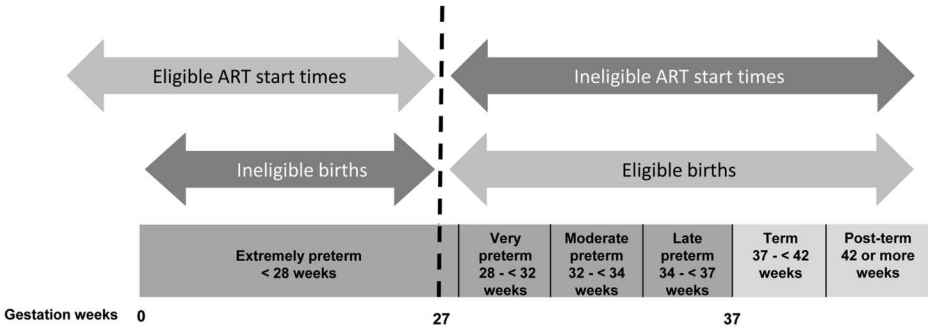

FIGURE 1. Study eligibility on the basis of maternal ART start time and gestational age at birth.

Confounders

We used a directed acyclic graph,[30,31] an epidemiological tool for encoding relationships among variables in studies of causal effects, to identify potential confounders. This tool helps to ensure that potential confounders are associated with both the exposure and the outcome, but are not on the causal pathway between them. In developing a directed acyclic graph with variables in our database, we identified mother's education, age, and parity as potential confounders for inclusion in the analysis. Based on the functional form of the relationship between each confounder and the outcome, we modeled mother's age as continuous and parity as ordinal. We used a manual, backward elimination, change-in-estimate strategy at a 10% retention threshold to assess the necessity of including each confounder in the final model.[32] We were unable to assess education as a confounder, as values for this variable were missing from 95% of records.

Statistical Analyses

We used Fisher exact tests to test differences in proportions between groups, and *t* tests and 1-way analysis of variance to test differences in means as appropriate. We used log-binomial regression models to estimate unadjusted and adjusted risk ratios (uRRs and aRRs, respectively) and 95% confidence intervals (CIs) of the association between ART exposure status and preterm birth (with those who were on ART as referent), and ART initiation time and preterm birth (with those initiating before conception as referent).

In subanalyses, we considered 3 preterm birth subcategories: extremely to very preterm (27 to <32 weeks), moderate preterm (32 to <34 weeks), and late preterm (34 to <37 weeks).[1] In the first subanalysis, we treated extremely to very preterm births (versus full term) as the outcome, excluding moderate to late preterm births. In a second subanalysis, we treated moderate to late preterm births (again versus full term) as the outcome, this time excluding extremely to very preterm births. In a third subanalysis, we dichotomized the outcome as <34 weeks versus ≥34 weeks (extremely to moderate preterm versus late preterm or full term), because births before 34 weeks' gestational age require advanced neonatal support, and their relationship with ART status and initiation time is thus of high clinical interest in this setting.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Among 66,029 women who delivered in the maternity ward at Bwaila Hospital during the study period, 6853 women (10.4%) were known to be HIV-infected (Fig. 2). Of these, 1733 (25.2%) were excluded because of missing LMP, 66 (1.0%) because of delivery before 27 weeks, and 66 (1.0%) because of multiple gestations. Among the women who were excluded for having delivered before 27 weeks, 17 had missing ART initiation time, 22 started ART before conception, 21 started ART during pregnancy, and 6 were not on ART, including 1 stillbirth. The remaining 4988 HIV-infected women (72.8%) had singleton live births at 27+ weeks of gestation and thus had eligible outcomes. After excluding 1264 women (25.3%) with missing ART initiation time and 650 (13.0%) who initiated ART at or after 27 weeks, 3074 women were included in the analyses. Compared with the 3724 women who had ART initiation time available, women who were excluded because of missing ART initiation time were on average slightly older and had similar parity, but a slightly lower percentage of preterm infants (19.4% versus 22.1%, see Table 1, Supplemental Digital Content,

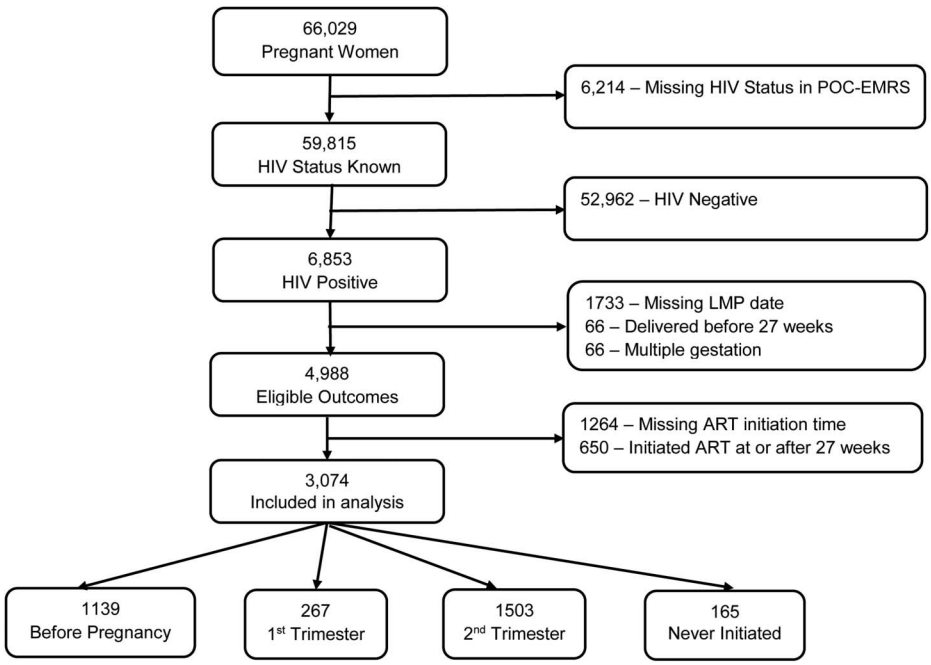

FIGURE 2. Flow diagram of the inclusion criteria for the women included in the analysis.

http://links.lww.com/QAI/A953). Among included women, most had initiated ART before pregnancy (N = 1139, 37.0%) or during the second trimester (N = 1503, 48.9%). Only 5.4% had not initiated ART before delivery (N = 165).

On average, women who did not start ART before delivery were younger than those who had received ART during pregnancy, and age at delivery increased with earlier ART initiation times ($P < 0.001$) (Table 1). The distribution of parity was different across the ART exposure categories ($P < 0.001$), and mean gestational age at delivery was similar between those who never initiated ART and those who were on ART, regardless of ART initiation time ($P = 0.05$). A total of 731 preterm births were observed during the study period (risk = 24%; 95% CI: 22% to 25%), with 149 being extremely to very preterm, 94 moderate preterm, and 488 late preterm. Women who delivered preterm babies were on average younger than those who delivered full term babies (mean age = 27.6 versus 28.4, $P < 0.001$).

Overall, preterm birth risk was similar in women who never initiated ART compared with those who had initiated ART at any point before delivery (24.8% versus 23.7%; aRR = 1.14; 95% CI: 0.84 to 1.55) (Table 2). Among women who initiated ART before delivery, preterm risk was lowest in those starting ART before conception, with aRRs for those initiating during the first and second trimester of 1.31 (95% CI: 1.03 to 1.68) and 1.17 (0.99 to 1.37), respectively. Preterm risk was also elevated in those never initiating ART versus those starting ART before pregnancy (aRR = 1.27; 95% CI: 0.92 to 1.76).

In subanalyses, we found a strong association between no ART use during pregnancy and extremely to very preterm birth versus full term birth (aRR = 2.33; 95% CI: 1.39 to 3.92) (Table 3). Among women who started ART before delivery, risk of extremely to very preterm birth was elevated in those starting ART in the first trimester (aRR = 1.30; 95% CI: 0.72 to 2.36) but not the second trimester (aRR = 1.00; 95% CI: 0.68 to 1.48) compared with women starting before conception. Not starting ART before delivery more than doubled the risk of extremely to very preterm birth compared with starting ART before pregnancy (aRR = 2.41; 95% CI: 1.36 to 4.24).

Risk of moderate to late preterm (versus full term) birth was similar in those not initiating ART before delivery and those who were on ART (aRR = 0.86; 95% CI: 0.55 to 1.34) (Table 3), but among those on ART at delivery, initiation in either the first trimester or second trimester was associated with a higher risk of moderate to late preterm birth compared with ART initiation before conception.

Finally, we found suggestion that not starting ART before delivery increased risk of birth at less than 34 weeks' gestation, although the estimate was imprecise (aRR = 1.42; 95% CI: 0.85 to 2.36) (Table 3). Among those initiating ART before delivery, risk of birth before 34 weeks was similar among those starting ART before pregnancy and those starting during the second trimester, but the point estimate for ART initiation during the first trimester suggested increased risk. The point estimate comparing no ART to ART initiated before pregnancy also suggested increased risk, but this estimate was similarly imprecise.

DISCUSSION

In this study of infants born to HIV-infected mothers in Malawi since the start of Option B+, we did not find a strong association between ART initiation before delivery and preterm birth overall. Importantly, we found ART to be quite strongly associated with a reduced risk of extremely to very preterm birth (birth between 27 and 32 weeks of gestation), and moderately associated with a reduction in preterm birth before 34 weeks. These results are encouraging because mortality increases as gestational age decreases, with only 30% of babies born between 28 and 32 weeks in low-income countries surviving.[1] In general, ART initiation before conception was associated with better outcomes relative to ART nonuse, particularly with respect to the more severe preterm birth outcomes. Among women who were on ART before delivery, initiation before conception or during the second trimester was associated with lower risk of the more severe preterm birth outcomes than was initiation during the first trimester.

Our findings related to early ART initiation and overall preterm birth risk are consistent with previous studies that have shown a protective effect of earlier maternal ART against preterm birth. A study of predominantly black African pregnant women delivering at a single hospital in London found a decreased odds of preterm delivery among women who conceived while receiving ART compared with women

TABLE 1. Characteristics of Study Population

	Birth Status		ART Initiation Time During Pregnancy			
Characteristics	**Preterm, N = 731**	**Full Term, N = 2343**	**Before Pregnancy, N = 1139**	**1st Trimester, N = 267**	**2nd Trimester,* N = 1503**	**Never Initiated, N = 165**
Mother's age, mean (SD)	27.6 (5.6)	28.4 (5.8)	30.4 (5.4)	27.2 (5.4)	26.9 (5.5)	25.6 (5.5)
Gestation weeks at delivery, mean (SD)	34.0 (2.2)	39.4 (1.3)	38.3 (2.7)	37.9 (2.9)	38.1 (2.8)	38.0 (3.3)
Parity, N (%)						
Nulliparity	20 (3.3)	46 (2.3)	12 (1.1)	9 (4.1)	40 (3.4)	5 (4.1)
Primiparity (1 child)	163 (26.9)	567 (28.6)	239 (22.3)	64 (29.2)	384 (32.7)	43 (35.5)
Low multiparity (2–4 children)	394 (65.0)	1243 (62.8)	739 (68.9)	140 (63.9)	695 (59.2)	63 (52.1)
Grand multiparity (≥5 children)	29 (4.8)	124 (6.3)	82 (7.7)	6 (2.7)	55 (6.7)	10 (8.3)

*Before 27 weeks.

TABLE 2. Associations Between ART Status and Timing of Initiation With Preterm Birth

	Preterm (N = 731), N (%)	Full Term (N = 2343), N (%)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)
ART initiation status				
On ART	690 (94.4)	2219 (94.7)	1.00	1.00
Never initiated	41 (5.6)	124 (5.3)	1.05 (0.80 to 1.38)	1.14 (0.84 to 1.55)
ART initiation time				
Before pregnancy	235 (32.2)	904 (38.6)	1.00	1.00
1st trimester	77 (10.5)	190 (8.1)	1.40 (1.12 to 1.74)	1.31 (1.03 to 1.68)
2nd trimester†	378 (51.7)	1125 (48.0)	1.22 (1.06 to 1.41)	1.17 (0.99 to 1.37)
Never initiated	41 (5.6)	124 (5.3)	1.20 (0.90 to 1.61)	1.27 (0.92 to 1.76)

*Adjusted for mother's age and parity.
†Before 27 weeks.

who received ART after conception.[27] Results from a study in Malawi and Mozambique showed a protective effect of a longer course of ART during pregnancy against preterm birth, although the investigators did not differentiate between those starting ART before conception and those starting during pregnancy.[28]

Other studies have found ART initiation before pregnancy to be associated with increased preterm birth

TABLE 3. Associations Between ART Status and Timing of Initiation With Alternate Preterm Categorizations

	Extremely to Very Preterm* (N = 149), N (%)	Full Term† (N = 2343), N (%)	Unadjusted RR (95% CI)	Adjusted RR‡ (95% CI)
ART initiation status				
On ART	133 (86.3)	2219 (94.7)	1.00	1.00
Never initiated	16 (10.7)	124 (5.3)	2.02 (1.24 to 3.30)	2.33 (1.39 to 3.92)
ART initiation time				
Before pregnancy	50 (33.6)	904 (38.6)	1.00	1.00
1st trimester	14 (9.4)	190 (8.1)	1.31 (0.74 to 2.32)	1.30 (0.72 to 2.36)
2nd trimester§	69 (46.3)	1125 (48.0)	1.10 (0.77 to 1.57)	1.00 (0.68 to 1.48)
Never initiated	16 (10.7)	124 (5.3)	2.18 (1.28 to 3.75)	2.41 (1.36 to 4.24)
	Moderate to Late Preterm‖ (N = 582), N (%)	**Full Term† (N = 2343), N (%)**	**Unadjusted RR (95% CI)**	**Adjusted RR‡ (95% CI)**
ART initiation status				
On ART	557 (95.7)	2219 (94.7)	1.00	1.00
Never initiated	25 (4.3)	124 (5.3)	0.84 (0.58 to 1.20)	0.86 (0.55 to 1.34)
ART initiation time				
Before pregnancy	185 (31.8)	904 (38.6)	1.00	1.00
1st trimester	63 (10.8)	190 (8.1)	1.47 (1.14 to 1.88)	1.36 (1.02 to 1.82)
2nd trimester§	309 (53.1)	1125 (48.0)	1.27 (1.08 to 1.49)	1.23 (1.02 to 1.48)
Never initiated	25 (4.3)	124 (5.3)	0.99 (0.68 to 1.45)	0.99 (0.63 to 1.57)
	<34 wk (N = 243), N (%)	**≥34 wk (N = 2831), N (%)**	**Unadjusted RR (95% CI)**	**Adjusted RR‡ (95% CI)**
ART initiation status				
On ART	227 (93.4)	2682 (94.7)	1.00	1.00
Never initiated	16 (6.6)	149 (5.3)	1.24 (0.77 to 2.01)	1.42 (0.85 to 2.36)
ART initiation time				
Before pregnancy	83 (34.2)	1056 (37.3)	1.00	1.00
1st trimester	24 (9.8)	243 (8.6)	1.23 (0.80 to 1.90)	1.24 (0.79 to 1.96)
2nd trimester§	120 (49.4)	1383 (48.9)	1.10 (0.84 to 1.43)	1.02 (0.76 to 1.37)
Never initiated	16 (6.6)	149 (5.3)	1.33 (0.80 to 2.22)	1.47 (0.86 to 2.52)

*Extremely to very preterm: 27 to <32 gestation weeks.
†Full term: ≥37 gestation weeks.
‡Adjusted for mother's age and parity.
§Before 27 weeks.
‖Moderate to late preterm: 32 to <37 gestation weeks.

risk. In an analysis of abstracted obstetrical records at 6 sites in Botswana, women starting highly active ART (HAART) before pregnancy had a higher odds of preterm delivery compared with HIV-infected women with no ART exposure and those initiating HAART or zidovudine monotherapy during pregnancy.[20] Similarly, results from a prospective cohort study in Brazil found that starting ART before conception increased the odds of preterm birth, although the effect estimate was very imprecise.[25] Most recently, a large prospective cohort study in Tanzania found that HAART before conception was associated with a higher risk of preterm birth overall and very preterm birth in particular.[29] Importantly, however, the referent population in that study was women starting zidovudine monotherapy after 28 weeks of gestation, so these women (by virtue of the fact that their pregnancies had survived to at least 28 weeks) may have been at lower preterm risk than any of the groups to whom we compared our own women who initiated ART before conception. We also note that all of these prior studies were performed in the era when ART initiation for health and PMTCT was only available to those with advanced disease. Advanced maternal HIV is associated with increased preterm birth risk[33] and these earlier findings may not be directly applicable to the Option B+ era in which lifelong ART is initiated during pregnancy regardless of HIV disease stage or CD4 count.

Findings around the relationship between preterm birth overall and any ART during pregnancy have been mixed. Preliminary results of the PROMISE trial,[34] which randomized HIV-positive pregnant women with high CD4 counts to one of 2 triple antiretroviral regimens versus antepartum zidovudine, found an association between the triple antiretroviral arms and birth before 37 weeks, but not birth before 34 weeks. However, a recent study from South Africa reported significantly lower odds of preterm birth among women receiving any ART under Option B+ versus those not receiving ART.[35] In general, heterogeneities across studies, particularly with respect to ART regimens, analytical choices around referent populations, and inclusion of women starting ART after preterm risk began, make direct comparison between our findings and those of previous studies difficult.

To our knowledge, our study is the first to provide evidence that ART initiation before conception is protective against preterm birth in the era of Option B+. As the Option B+ program matures and the proportion of women on lifelong ART after a prior pregnancy grows, we expect that increasing proportions of women will be on ART before conception. Our finding that preterm risk was lowest in this group suggests that preterm prevalence among HIV-infected mothers is likely to decrease as the time since Option B+ implementation increases. Our results also suggest that being on ART during pregnancy is protective against extremely to very preterm birth, regardless of time of ART initiation. These findings suggest that increased ART uptake in the Option B+ era could have a profound impact on preterm birth and neonatal mortality in developing countries where fertility rates are high, HIV is endemic, and advanced nursery facilities are not readily available.

Several mechanisms have been hypothesized for possible adverse effects of ART on birth outcomes. Specifically, it has been proposed that protease inhibitor (PI)-based ART could induce preterm birth by a cytokine-mediated regulation of the immune system through increased Th1 and decreased Th2 cytokines production.[36,37] Women with recurrent pregnancy losses have been observed to have increased Th1 and decreased Th2 cytokines.[38,39] Compared with non-PI-based ART, women on PI-based ART have a higher risk of having preterm birth.[20,21] However, the same cytokine mechanism has been hypothesized to be protective against HIV disease progression.[40,41] Women who are on established ART before conception may have a stabilized cytokine environment due to long exposure to ART, which can be one reason we observed ART initiation before pregnancy being protective against preterm birth. In addition, the ART regimen used in Malawi, tenofovir/lamivudine/efavirenz, is not PI-based, which may explain the similar preterm birth risk we observed in women who initiated ART at any point before 27 weeks and those who never initiated ART.

Studies focusing on the association between ART exposure duration in utero and other fetal outcomes have also suggested that earlier ART is not detrimental. Earlier ART initiation during pregnancy was not associated with increased risk of stillbirth or low birthweight (LBW) in South Africa (with ART initiation dichotomized at <28 weeks or ≥ 28 weeks of pregnancy)[18] or with LBW in the United States (with ART initiation dichotomized at ≤ 25 weeks or ≥ 32 weeks of gestation).[24] A recent cohort analysis in Zambia among infants born at term also did not find increased risk of LBW or decreased mean birthweight because of longer ART duration during pregnancy.[42]

ART duration during pregnancy is intrinsically linked to length of gestation and thus preterm birth. To confine the preterm risk period to an interval in which women were either always or never on ART, and to maximize the number of ART initiation intervals (before pregnancy, during the first trimester, during the second trimester) before the start of the risk period that we could examine, we restricted our analysis to births that occurred on or after 27 weeks and to women who either started ART before 27 weeks or did not receive ART at all before delivery. We are therefore unable to draw any conclusions about the effects of early ART on extremely early preterm birth (before 27 weeks) or the effects of ART initiated at or after 27 weeks on subsequent preterm births.

We note that there may have been some misclassification of preterm status and ART initiation time within pregnancy because of inaccurate estimates of the LMP. The general consistency of our findings across analyses suggests that such misclassification may not be a large concern, and our specific finding that women initiating ART at any point during pregnancy were less likely to experience extremely to very preterm birth (versus term birth) may be especially robust, given the 5-week difference between the upper gestational age limit of very preterm (32 weeks) and the lower limit of full term (37 weeks).

Information on several covariates was either unavailable or insufficient. In particular, we did not have information on the interrelated covariates of ART adherence, CD4

count, and viral load. Poor ART adherence can result in drug resistance,[43,44] lower CD4, and higher viral loads, leading to adverse maternal and birth outcomes. In general, ART adherence is high during pregnancy,[45] and we expect that the fixed-dose tenofovir/lamivudine/efavirenz combination of 1 tablet per day in our study population would have encouraged high adherence.[14] Furthermore, we would consider viral load and CD4 count to be casual intermediates between ART and preterm birth, and thus statistical adjustment would have been inappropriate even if viral load and CD4 data had been available. We also note that there may have been data entry errors, but we do not expect such errors to have been differential according to exposure or outcome status. It is, however, possible that some exclusions due to missing LMP or ART initiation time resulted in selection bias, but it is difficult to predict the magnitude and direction of any such biases. Furthermore, we note that some of our comparisons suffered from low precision due to small numbers of births, particularly in the analyses of preterm subcategories.

ART initiation in pregnancy is an indicator of access to prenatal care and other health care services. In Malawi, HIV-infected women not on ART are initiated on lifelong ART during an antenatal care visit,[46] in addition to receiving treatment for anemia, malaria, and other infections as standard prenatal care. Women who attend antenatal care are less likely to deliver LBW infants, especially from preterm births.[47,48] In the likely event that the women who had never initiated ART before delivery were less likely to have had access to prenatal care, then the higher preterm birth risk among those who did not initiate ART may not be fully attributable to lack of ART during pregnancy. No information on dates or numbers of antenatal visits, or of treatments received during such visits, was available in the POC-EMRS to allow control for antenatal care or specific components thereof.

Nevertheless, our results suggest that ART initiation before delivery does not increase preterm birth risk, and that it may in fact be protective against extremely to very preterm birth. Our results further suggest that ART initiation before conception may provide the optimal benefit. As the era of Option B+ continues, postweaning ART retention should thus be a priority. These findings also suggest that HIV testing of women who wish to become pregnant, followed by ART initiation before conception in those testing HIV-positive, could be beneficial. If adequate uptake and retention can be achieved, then Option B+ may not only dramatically reduce vertical HIV transmission and improve maternal health, but also reduce preterm birth in settings with heavy, overlapping burdens of HIV and neonatal mortality.

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