MAJOR ARTICLE

Increased Risk of Preterm Delivery Among HIV-Infected Women Randomized to Protease Versus Nucleoside Reverse Transcriptase Inhibitor-Based HAART During Pregnancy

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(See the editorial commentary by Kourtis, on pages 493–4.)

Background. Protease inhibitor (PI)-based highly active antiretroviral therapy (HAART) use in pregnancy has been associated with preterm deliveries in some observational studies.

Methods. HIV-infected, HAART-naive pregnant women with CD4+ counts ≥200 cells/mm^3 were randomized between 26 and 34 weeks gestation to lopinavir/ritonavir/zidovudine/lamivudine (PI group) or abacavir/zidovudine/lamivudine (NRTI group) in a clinical trial to prevent mother-to-child HIV transmission. Risk factors for preterm delivery (<37 weeks) and differences by randomization arm were evaluated for live infants by logistic regression.

Results. Preterm delivery rates were higher among 267 women in the PI group than 263 women in the NRTI group (21.4% vs 11.8%, $P = .003$). PI-based HAART was the most significant risk factor for preterm delivery [odds ratio = 2.03, 95% confidence interval 1.26–3.27, $P = .004$]. Mean change in maternal body mass index (BMI) 1 month after HAART initiation was lower in the PI group ($P < .001$); however, this was not significantly associated with preterm delivery. Neither infant hospitalizations nor mortality through 6 months of life differed by maternal regimen.

Conclusions. PI-based HAART was associated with increased preterm delivery but not increased infant hospitalizations or mortality in a clinical trial setting. The association between PI use and lower increase in BMI in late pregnancy warrants further study.

Highly active antiretroviral therapy (HAART) during pregnancy and breastfeeding for the prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) is a highly efficacious public health intervention [1–5]. The World Health Organization (WHO) now recommends HAART in pregnancy for all HIV-infected women with CD4+ cell counts <350 cells/mm^3 and as a PMTCT option for all HIV-infected women [6]. However, many uncertainties remain regarding potential adverse effects of HAART use in pregnancy, including the association between PI-based HAART regimens and preterm births. Some studies reported an increased risk of preterm delivery (<37 weeks gestational age) with PIs [7–9], whereas others have not found this association [10–12]. Although the majority of studies have been performed in developed countries, most women who require HAART in pregnancy live in resource-limited settings where access to neonatal care may be limited, and where

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the effect of any increase in preterm deliveries on infant survival may be magnified. Therefore, identifying risk factors for preterm deliveries, and quantifying the contribution of PI-based HAART is of critical importance to public health policy makers.

We investigated risk factors for preterm delivery in a cohort of HIV-infected pregnant women with CD4+ cell counts $\geq$200 cells/mm^3 who were randomized to receive either PI-based or NRTI-based HAART for PMTCT. We also evaluated maternal weight gain in late pregnancy, and infant morbidity and mortality through 6 months, by maternal randomization group and preterm delivery status.

METHODS

Study Population

The Mma Bana Study, which enrolled 730 HIV-1 infected HAART-naive pregnant women, has been described in detail elsewhere [1]. The 560 participants who had CD4+ cell counts $\geq$200 cells/mm^3 and no AIDS-defining illnesses at enrollment, between 26 and 34 weeks gestation, were randomized to receive either abacavir/zidovudine/lamivudine coformulated as Trizivir (GlaxoSmithKline) (TZV) twice daily or lopinavir/ritonavir with zidovudine/lamivudine coformulated as Kaletra (Abbott)/Combivir (GlaxoSmithKline) (KAL/CBV) twice daily. The analysis and results described in this report concern these 560 women. Women were randomized to initiate HAART between 26 and 34 weeks gestation and continued through a period of breastfeeding not to exceed 6 months postpartum; HAART was continued for maternal health if indicated. All mothers in the study received the same antenatal care from study nurses at 1 of 4 study sites, in keeping with Botswana antenatal care guidelines. In addition, based upon the Mma Bana study protocol, each woman was evaluated by a study nurse and physician at enrollment, 2 weeks postenrollment, and monthly thereafter until delivery, unless pregnancy gestational age exceeded 38 weeks and then participants were evaluated weekly until delivery. Participants were also encouraged to present to the study sites for any concerning health issues between scheduled antenatal visits. Maternal weight and blood pressure were monitored at each visit, and interval illnesses were documented.

HIV-infected pregnant women and their infants were included in the preterm delivery analysis if the participant had a live, singleton birth. Gestational age was calculated from an algorithm that relied on maternal reported last menstrual period (LMP) and ultrasound performed prior to randomization. All study physicians received standardized ultrasound training. Ultrasound-identified fetal femur length and biparietal diameter were used to determine gestational age. Where the estimated gestational age of a first trimester ultrasound differed by more than 1 week from the woman's reported LMP, a second trimester ultrasound differed by more than 2 weeks, or a third trimester ultrasound differed by more than 3 weeks, the ultrasound dating was employed. Otherwise, the LMP was employed. If a woman was unable to recall her LMP, the ultrasound results determined the gestational age. Once the gestational age was ascertained using this algorithm, it was not altered later in the pregnancy. Women who experienced a preterm delivery were only included in the analysis if obstetric records documented spontaneous preterm birth, including the presence of either preterm labor with intact fetal membranes or preterm rupture of fetal membranes. The three Cesarean sections resulting in preterm deliveries were excluded from the primary analysis but were evaluated in a sensitivity analysis and did not significantly change the results.

The Botswana Health Research Development Committee and the Harvard School of Public Health Human Subjects Committee approved the Mma Bana study. Women who enrolled in the Mma Bana study provided written informed consent, and human subject research guidelines of Harvard School of Public Health were followed in the conduct of this clinical research.

Statistical Analyses

We performed a retrospective analysis of qualifying Mma Bana mother-infant pairs among the 560 mothers in the randomized treatment arms, a planned secondary analysis of the study. Statistical analyses were performed using SAS, version 9.2 (SAS Institute). Preterm delivery was defined as a spontaneous delivery occurring before 37 weeks gestation, and very preterm delivery was defined as a spontaneous delivery occurring before 32 weeks gestation. Continuous variables were compared using a Wilcoxon rank sum test. Ordinal variables were compared using an exact Kruskal-Wallis test. Categorical variables were compared using a Fisher exact test or χ^2 test. A literature search was conducted to identify maternal and infant characteristics associated with preterm delivery [13–19]. Univariate logistic regression models were used to test for associations, including maternal age, number of pregnancies, baseline maternal CD4+ cell count, HIV-1 viral load and hemoglobin at study enrollment, HAART regimen, presence of an STI during the antenatal period, maternal education level and income, and infant gender. Gestational age at maternal HAART initiation, hepatitis B coinfection, maternal hospitalization during the antenatal period, and site of enrollment were also included in the univariate analysis. Predictors of preterm birth with a likelihood ratio test P value of $\leq$ .10 in a univariate model were included in multivariate regression analysis. Variables with a likelihood ratio test P value $>$ .10 but $\leq$ .20 were introduced into the multivariate model to test for confounding and collinearity and retained in the model if an effect estimate or standard error was altered by 20% or greater.

Poor weight gain during pregnancy is also known to be a risk factor for preterm delivery [14, 19], and PI-based HAART regimens are known to have gastrointestinal and metabolic adverse effects. Therefore, maternal change in BMI 1 month after HAART

initiation was compared by treatment arm and by timing of delivery (preterm versus term) using a Wilcoxon rank sum test. Women who delivered <1 month after HAART initiation were excluded from this analysis.

Infant morbidity and mortality by preterm or full-term status were compared using a Fisher exact test. Morbidity was defined as either the need for 1 or more hospitalizations in the first 6 months of life including hospitalization at time of delivery, or the presence of 1 or more episode of a severe or life-threatening (grade 3 or 4) adverse event involving respiratory tract infections, diarrheal disease, meningitis, or sepsis in the first 6 months of life, using Division of AIDS (DAIDS) toxicity tables [20].

All testing used a 2-sided significance level of 0.05, with no correction for multiple testing.

RESULTS

Baseline Characteristics of Comparison Groups

Of 560 women in the randomized treatment arms of the Mma Bana Study, 530 qualified for the preterm risk factor analysis (Figure 1), with 88 (16.7%) experiencing spontaneous preterm deliveries. Baseline demographic and clinical characteristics of women in this analysis did not differ by HAART randomization arm (Table 1).

Estimated Delivery Dates

The estimated date of delivery was based on maternal reported LMP for 394 (74.3%) women, 199 (75.7%) of the women randomized to triple NRTIs and 195 (73.0%) of the women randomized to PI-based HAART. A total of 54 women, 27 from each arm, were unable to recall their LMP, and dating was based on the ultrasound. Per the prespecified algorithm, ultrasound was also used for an additional 82 women (37 in the triple NRTI arm and 45 in the PI-based arm) due to disparities between the LMP and ultrasound. Of ultrasound-established estimated dates of delivery, 1 (0.7%) ultrasound was conducted in the first trimester, 53 (39.0%) were conducted in the second trimester, and 82 (60.3%) were conducted in the third trimester.

Association of Maternal HAART Regimen and Preterm Delivery

All but 2 women were still receiving their originally assigned HAART regimen at the time of delivery. The median gestational age at delivery was 39.0 weeks for women taking PI-based HAART and 39.1 weeks for women taking triple NRTI-based HAART. However, women randomized to PI-based HAART experienced a significantly higher rate of preterm deliveries (21.4%) than women randomized to triple NRTI-based HAART (11.8%) ($P = .003$ for Fisher exact test), regardless of gestational age at HAART initiation (Table 2).

Univariate Risk Analysis of Preterm Deliveries

Use of a protease inhibitor-based HAART regimen was significantly associated with preterm delivery in univariate analysis (OR = 2.03; 95% CI, 1.26–3.27; $P = .004$) (Table 3). Maternal income was the only other factor significantly associated with preterm deliveries ($P = .02$ for 3 df), primarily reflecting a lower odds among categories of women reporting income versus women who reported no income. Maternal CD4+ cell count, viral load at enrollment, and gestational age at HAART initiation were not found to be associated with preterm deliveries.

Multivariate Risk Analysis

In multivariate logistic regression analysis, use of protease inhibitor-based HAART regimen was associated with a 2-fold higher rate of preterm delivery compared with triple NRTI-based HAART [AOR = 2.02; CI 1.25–3.27], after adjustment for self-reported maternal income ($P = .02$ for 3 df). When

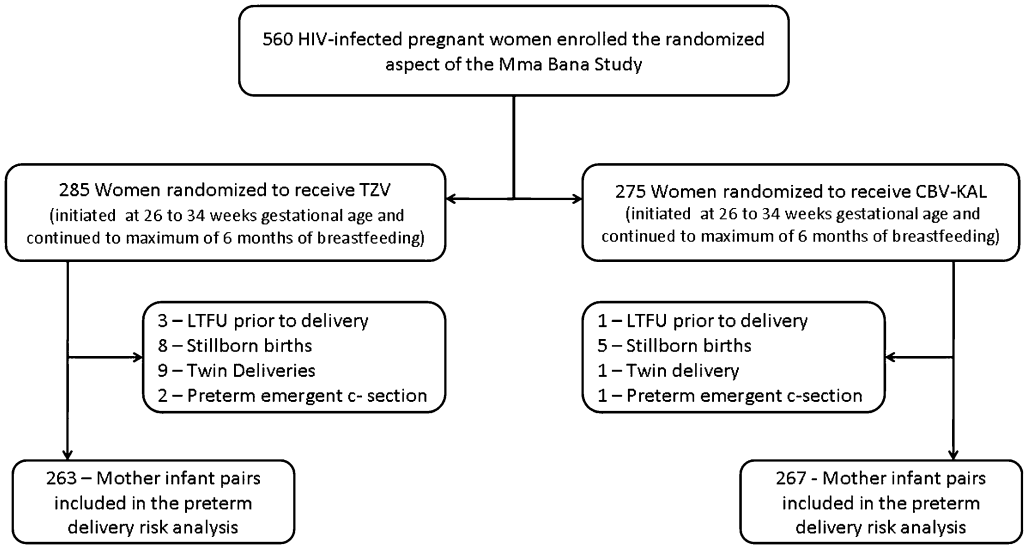

Figure 1. Study eligibility.

Table 1. Maternal Baseline Characteristics by Randomized HAART Treatment Arm

Maternal baseline characteristics	TZV (n = 263)	CBV-KAL (n = 267)	P value
Median age, years [IQR]	26.8 [23.0–31.6]	26.0 [23.0–30.4]	.31[a]
Gravida including current pregnancy, no. (%)			.69[b]
1	61 (23.2%)	71 (26.6%)	
2	93 (35.3%)	88 (33.0%)	
3	57 (21.7%)	51 (19.1%)	
4 or more	52 (19.8%)	57 (21.3%)	
Baseline labs			
Median HIV-1 RNA, $\log_{10}$ copies/mL [IQR]	3.94 [2.94–4.58]	3.92 [3.20–4.56]	.64[a]
Median CD4+ count, cells/μL [IQR]	388 [305–516]	405 [297–519]	.89[a]
Median hemoglobin, g/dL [IQR]	10.9 [10.0–11.7]	10.7 [10.0–11.5]	.16[a]
Gestational age at study enrollment			.57[b]
26–28 weeks	177 (67.3%)	180 (67.4%)	
29–31 weeks	44 (16.7%)	63 (23.6%)	
32–34 weeks	42 (16.0%)	24 (9.0%)	
Median time on HAART prior to delivery, weeks [IQR][c]	11.6 [8.3–13.3]	11.0 [8.1–12.7]	.13[a]
Enrollment site, no. (%)			.85[d]
Molepolole (village)	75 (28.5%)	79 (29.6%)	
Mochudi (village)	48 (18.2%)	41 (15.4%)	
Lobatse (town)	47 (17.9%)	49 (18.3%)	
Gaborone (city)	93 (35.4%)	98 (36.7%)	
Marital status, no. (%)			.55[d]
Single	213 (81.0%)	219 (82.0%)	
Married/cohabitating	48 (18.2%)	47 (17.6%)	
Divorced	2 (0.8%)	0 (0.0%)	
Other	0 (0.0%)	1 (0.4%)	
Education, no. (%)			.48[b]
None or primary	51 (19.4%)	54 (20.2%)	
Secondary	196 (74.5%)	203 (76.0%)	
University	16 (6.1%)	10 (3.8%)	
Employment, no. (%)			.34[e]
Housewife	12(4.6%)	9 (3.4%)	
Salaried—government	14 (5.3%)	10 (3.7%)	
Salaried—private	42 (16.0%)	38 (14.2%)	
Paid domestic worker	18 (6.8%)	25 (9.4%)	
Self employed	18 (6.8%)	10 (3.7%)	
Student	6 (2.3%)	2 (0.8%)	
Unemployed	151(57.4%)	171 (64.0%)	
Other	2 (0.8%)	2 (0.8%)	
Income, no. (%)[f]			.53[b]
None	133 (50.8%)	141 (52.8%)	
1–100 $/month	72 (27.5%)	75 (28.1%)	
Greater than 100 $/month	57(21.7%)	51 (19.1%)	
Electricity in home, no. (%)			.31[c]
Yes	83 (31.6%)	96 (36.0%)	
No	180 (68.4%)	171 (64.0%)	

NOTE. [a] P value from Wilcoxon Rank Sums test.

[b] P value from exact Kruskal-Wallis test.

[c] While ''Median time on HAART prior to delivery'' is not a baseline characteristic, it has been incorporated into this table.

[d] P value from a Fisher's Exact test.

[e] P value from a χ^2 test.

[f] Adjusted for inflation using 2001 as the base year per Botswana Central Statistics Office and using a Pula to US dollar conversion ratio of 0.22360 in effect on 1 January 2001. NB: Some demographic information was missing for women in this study, and totals within categories may not add up to the totals by randomized arm.

Table 2. Preterm Deliveries by Gestational Age at HAART Initiation and Treatment Arm

Gestational age at HAART initiation	Triple NRTI HAART regimen (no.)	% Delivering preterm	PI-based HAART regimen (no.)	% Delivering preterm
26–28 weeks	177	10.2%	180	21.7%
29–31 weeks	44	13.6%	63	19.1%
32–34 weeks	42	16.7%	24	25.0%
Total	263	11.8%	267	21.4%

maternal enrollment CD4+ cell count and HIV viral load were introduced into the model, there was no evidence of confounding or collinearity.

Change in Maternal BMI During Pregnancy

We evaluated weight gain in pregnancy by HAART randomization group, and as a potential risk factor for preterm delivery. Median change in BMI 1 month after HAART initiation was 0.5 kg/m^2 for the women in the TZV arm and 0.3 kg/m^2 in the CBV-KAL arm (P value $< .001$). However, no significant association was found between change in BMI 1 month after HAART initiation and odds of preterm delivery (OR = 0.81, 95% CI 0.53–1.24 for each 1 kg/m^2 increase in BMI).

Very Preterm Delivery

Of the 464 women who initiated HAART prior to 32 weeks gestational age, 12 (2.6%) delivered very preterm infants (<32 weeks gestation). Of these, 8 (3.3%) were born to mothers on PI-based HAART, while 4 (1.8%) were born to mothers taking a triple NRTI ($P = .39$). Median gestational age at HAART enrollment did not differ significantly between women with very preterm versus preterm deliveries (27.1 weeks vs. 28.1 weeks, $P = .47$). Only 3 of the 12 mothers who gave birth to very preterm infants completed at least 30 days of HAART prior to delivery, limiting the interpretability of these findings.

Infant Morbidity and Mortality

Preterm infants were significantly more likely to experience at least 1 severe or life-threatening episode of respiratory tract infection in the first 6 months of life than term infants (9.1% vs. 2.0%, $P = .003$) (Table 4). Twelve infants died in the first 6 months of life, 6 of whom were born preterm. Three of the 6 preterm infants were extremely preterm (born at 29.9, 30.6, and 31.4 weeks gestation), and 6 of the 12 infants died in the first 28 days of life, 3 of whom were born preterm. Infant mortality was higher in the first 6 months of life for preterm infants compared with term infants (6.8% versus 1.4%; $P = .002$). Preterm infants had a 5-fold higher risk of death in the first 6 months of life compared with term infants [OR = 5.3; 95% CI 1.7–16.9].

When infant morbidity was analyzed by maternal HAART regimen, no adverse outcomes were significantly associated with PI-based HAART. Infants born to mothers randomized to the triple NRTI regimen were more likely to experience meningitis (1.9% vs. 0%, P value = .03), but the frequency of severe or life-threatening respiratory illness, diarrheal disease, sepsis, or hospitalizations did not differ between infants by maternal treatment arm ($P = .47$, .09, .20, and .62 respectively). During the first 6 months of life, death occurred among 7 (2.6%) infants born to women in the PI-group, and 5 (1.9%) infants born to women in the triple NRTI-group ($P = .77$).

DISCUSSION

Among women randomized to receive either PI-based or NRTI-based HAART during pregnancy, we found an association between PI use and preterm delivery. We noted less weight gain among women initiating PI-based HAART in late pregnancy, using change in BMI 1 month after HAART initiation as a surrogate for weight gain. The overall rate of prematurity in our study was comparable to rates identified in government hospitals in Botswana [21].

The results of this randomized trial help clarify previous observational studies related to PI use in pregnancy. Although some previous studies have reported an association between PI use and preterm delivery [7–9], others have reported no association [10, 11] or have been underpowered to detect a modest increase in preterm deliveries [12]. We believe that previous conflicting results are related to limited power, as well as potential confounders in observational studies [11, 22]. However, as Townsend et al [23] noted in their pooled analysis of 3 large cohorts, the differences may reflect substantial differences in the study populations and the data collected. Our randomized design allowed us to isolate the effect of PIs.

Despite association with preterm delivery, we were reassured by the lack of association between the type of HAART used in pregnancy and excess infant mortality. Although we noted increased odds of hospitalizations and mortality among preterm infants overall in the first 6 months of life, there was no significant increase in the PI group. These findings should be interpreted with caution, as the number of infant deaths was small, limiting statistical power to detect a true difference. Women and infants in our cohort may have had better access to medical care because of their participation in a randomized clinical trial, and this may have attenuated differences in infant mortality by preterm status. Although clinical care in our study was comparable to that available for the general population in Botswana, even small increases in the incidence of preterm deliveries in

Table 3. Univariate Analysis of Potential Risk Factors for Preterm Delivery

	Univariate analysis			
Analyzed risk factors	Preterm deliveries (n = 88)	Full Term deliveries (n = 442)	Odds ratio (CI)	P value
Maternal age[a]				
<20 years of age	9 (25.0%)	27 (75.0%)	Ref	NA
20–24 years of age	37 (21.1%)	138 (78.9%)	0.80 (0.35–1.86)	.15
25–29 years of age	20 (12.7%)	138 (87.3%)	0.44 (0.18–1.06)	.15
30–34 years of age	10 (10.6%)	84 (89.4%)	0.36 (0.13–0.97)	.07
>34 years of age	12 (17.9%)	55 (82.1%)	0.66 (0.25–1.74)	.78
Maternal education level				
None	2 (16.7%)	10 (83.3%)	Ref	
Primary	12 (12.9%)	81 (87.1%)	0.74 (0.14–3.80)	.72
Jr or Sr secondary	71 (17.8%)	328 (82.2%)	1.08 (0.23–5.05)	.92
Tertiary	3 (11.5%)	23 (88.5%)	0.65 (0.09–4.52)	.67
Maternal income[c]				
None	59 (21.5%)	215 (78.5%)	Ref	
1–500 pula/year	12 (9.9%)	109 (90.1%)	0.40 (0.21–0.78)	.007
501–1000 pula/year	9 (12.9%)	61 (87.1%)	0.54 (0.25–1.15)	.11
>1000 pula/year	8 (12.5%)	56 (87.5%)	0.52 (0.24–1.15)	.11
Site of enrollment				
Molepoloe (village)	29 (18.8%)	125 (81.2%)	1.11 (0.64–1.93)	.71
Mochudi (village)	12 (13.5%)	77 (86.5%)	0.75 (0.37–1.53)	.42
Lobatse (town)	14 (14.6%)	82 (85.4%)	0.82 (0.41–1.61)	.56
Gaborone (city)	33 (17.3%)	158 (82.7%)	Ref	NA
No. of pregnancies[b]				
1	25 (18.9%)	107 (81.1%)	Ref	NA
2	30 (16.6%)	151 (83.4%)	0.85 (0.47–1.53)	.59
3	15 (13.9%)	93 (86.1%)	0.69 (0.34–1.39)	.30
4 or more	18 (16.5%)	91 (83.5%)	0.85 (0.43–1.65)	.62
CD4+ cell count at enrollment[a]				
200–399 cells/mm^3	40 (45.4%)	228 (51.6%)	Ref	NA
400–599 cells/mm^3	32 (17.7%)	149 (82.3%)	1.22 (0.74–2.04)	.90
≥600 cells/mm^3	16 (14.9%)	65 (85.1%)	1.40 (0.74–2.67)	.44
Log viral load at enrollment[a,c]				
<10,000 cells/mL	44 (17.2%)	211 (82.8%)	Ref	NA
10,000–<100,000 cells/mL	29 (14.8%)	167 (85.2%)	0.83 (0.50–1.39)	.32
≥100,000 cells/mL	15 (19.5%)	62 (80.5%)	1.16 (0.61–2.22)	.45
Hgb at enrollment				
<9.5 g/dL	10 (14.7%)	58 (85.3%)	Ref	NA
9.5–<10.5 g/dL	21 (16.8%)	104 (83.2%)	1.17 (0.52–2.66)	.71
≥10.5 g/dL	57 (16.9%)	280 (83.1%)	1.18 (0.57–2.45)	.66
Hepatitis B co-infection at enrollment[c]				
No	84 (16.5%)	424 (83.5%)		
Yes	4 (20.0%)	16 (80.0%)	1.26 (0.41–3.87)	.68
Randomized HAART regimen				
Trizivir	31 (11.8%)	232 (88.2%)		
Combivir-Kaletra	57 (21.3%)	210 (78.7%)	2.03 (1.26–3.27)	.004
Gestational age at HAART initiation[a]				
26–28 weeks	57 (15.9%)	302 (84.1%)	Ref	NA
29–31 weeks	18 (17.1%)	87 (82.9%)	1.06 (0.60–1.90)	.83
32–34 weeks	13 (19.7%)	53 (80.3%)	1.29 (0.66–2.52)	.45
BMI Δ 1 month post HAART initiation[a,c]				
<−0.25 kg/m^2	4 (8.5%)	43 (91.5%)	Ref	NA

Table 3. (*Continued*)

Analyzed risk factors	Univariate analysis: Preterm deliveries ($n = 88$)	Full Term deliveries ($n = 442$)	Odds ratio (CI)	*P* value
−0.25 to +0.24 kg/m^2	24 (17.0%)	117 (83.0%)	2.21 (0.72–6.72)	.16
+0.25 to +0.74 kg/m^2	17 (10.5%)	145 (89.5%)	1.26 (0.40–3.95)	.69
+0.75 to +1.24 kg/m^2	11 (12.4%)	78 (87.6%)	1.52 (0.46–5.05)	.50
≥+1.25 kg/m^2	2 (5.1%)	37 (94.9%)	0.58 (0.10–3.36)	.54
Need for hosp before 32 weeks GA[d]				
No	83 (16.5%)	419 (83.5%)		
Yes	5 (17.9%)	23 (82.1%)	1.10 (0.41–2.97)	.85
Diagnosis of ≥1 STI(s) prior to 32 weeks GA[d]				
No	69 (14.9%)	394 (85.1%)		
Yes	7 (12.7%)	48 (87.3%)	0.83 (0.36–1.92)	.67
Infant gender				
Male	51 (19.0%)	218 (81.0%)		
Female	37 (14.2%)	224 (85.8%)	0.71 (0.45–1.12)	.14

NOTE. [a] Even when evaluated as a continuous variable, no statistical significance was noted when comparing the outcomes of preterm versus term births.

[b] Number of pregnancies includes all pregnancies of 20 weeks or greater, including the current pregnancy.

[c] Categorical totals will not match heading totals as data was missing for this variable or women were excluded including maternal income missing for 1 mother delivering at term, enrollment viral load missing for 2 mothers delivering at term, hepatitis B results missing for 2 mothers who delivered at term, 30 women excluded from the change in BMI analysis due to delivery prior to 1 month of antiretroviral treatment, as well as 22 women lacking height and/or weight data to calculate BMI.

[d] Excludes 12 women who gave birth to extremely preterm infants before 32 weeks gestational age.

low-resource settings may have important consequences for infant mortality. Our ability to evaluate very preterm deliveries was limited by our study design, which enrolled women in the third trimester of pregnancy. However, the high mortality risk in very preterm infants, particularly in resource-limited settings [24–26], suggests that further study of very preterm deliveries by HAART regimen is warranted.

Our study found that women in the PI group had reduced weight gain in late pregnancy compared with the NRTI group, an association that to our knowledge has not been reported previously. We do not have a biological explanation for this finding, and although severe adverse events did not differ by study arm, we cannot exclude nausea, vomiting, or poor oral intake as an explanation. Women who delivered preterm were noted to have a lower mean change in BMI 1 month after initiating HAART, and each 1 kg/m^2 increase in BMI 1 month after initiation of HAART was associated with a 19% decline in odds of preterm delivery. However, this difference was not significant in the univariate analysis, likely owing to the multifactorial etiology of preterm delivery. We believe that additional studies are warranted to determine whether poor weight gain in late pregnancy may, in part, explain preterm deliveries among PI-treated women, and whether BMI can be followed during pregnancy to predict risk for preterm delivery.

We did not detect associations with preterm delivery for many established risk factors, in part because of limited power. However, the provision of regular antenatal care, including management of sexually transmitted infections, hypertension, and preeclampsia, may have contributed to the lack of association with these important potential risks for preterm delivery

Table 4. Infant Morbidity and Mortality in the First 6 Months of Life by Delivery Timing and Maternal Treatment

Event	Timing of delivery: Preterm infant (no. [%])	Term infant (no. [%])	*P* value[a]	Maternal treatment arm: TZV (no. [%])	CBV-KAL (no. [%])	*P* value[a]
Respiratory tract infection	8 (9.1%)	9 (2.0%)	.003	10 (3.8%)	7 (2.6%)	.47
Diarrhea	0 (NA)	12 (2.7%)	.23	9 (3.4%)	3 (1.1%)	.09
Meningitis	1 (1.1%)	4 (0.9%)	.52	5 (1.9%)	0 (NA)	.03
Sepsis	4 (4.6%)	11 (2.5%)	.29	10 (3.8%)	5 (1.9%)	.20
Hospitalization	20 (22.7%)	56 (12.7%)	.02	40 (15.2%)	36 (13.5%)	.62
Death	6 (6.8%)	6 (1.4%)	.002	5 (1.9%)	7 (2.6%)	.77

NOTE. TZV, Trizivir; CBV-KAL, Combivir – Kaletra.

[a] *P* value from Fisher exact test.

[17, 18]. We could not evaluate the association between infant HIV infection and preterm delivery because there were only 4 infants (all born at term) included in this analysis with in utero HIV infection. Similarly, analysis of risk factors associated with very preterm deliveries via logistic regression was not possible because there were only 12 very preterm deliveries. We were also unable to analyze the association between hypertension, pregnancy induced hypertension, or preeclampsia as no mothers who delivered preterm were diagnosed with these conditions. While these diagnoses did exist among women in the Mma Bana study who experienced stillbirths, our study excluded all stillborn deliveries.

Our study had several limitations. Power was limited to detect an association with less prevalent potential risk factors, and limited risk factor data were available. For example, we did not collect data on maternal use of tobacco, alcohol. or illicit substances. However, the prevalence of these risk factors among women in Botswana is reported to be low (Botswana-Harvard Partnership, unpublished data, 2010) and would be unlikely to differ by HAART randomization group. We also had a limited ability to assess very preterm delivery, as discussed previously. To make use of the HAART regimen randomization, our analyses were limited to women with baseline CD4+ cell counts $\geq$200 cells/mm^3, limiting generalizability. However, we detected no confounding or collinearity from baseline CD4+ cell count or baseline HIV-1 RNA among the women who were included. Our study focused on 2 HAART regimens, with Kaletra as our PI-based regimen. While our results may not be generalizable to all PI and non-PI HAART regimens, we would not expect PI within class differences. Fiore et al [19] have proposed antiretroviral immunomodulation as a potential mechanism triggering preterm deliveries. The Mma Bana study did not measure change in maternal CD4+ cell counts at frequent intervals, limiting our ability to compare the rate of change in CD4+ cells between women experiencing preterm deliveries and those experiencing term deliveries. We believe that further study of this potential mechanism is important. The major strength of our study was the randomization by HAART regimen, which eliminated several potential confounders that limited the interpretability of previous studies.

In summary, PI-based HAART initiated in the third trimester of pregnancy was associated with a 2-fold higher odds of a preterm delivery compared with triple NRTI-based HAART, and with reduced weight gain in late pregnancy. Although PIs were not associated with increased infant morbidity or mortality in our study population, additional mortality data for PI-exposed infants are needed from other settings. PI-based HAART is a critical component of both PMTCT and treatment programs in the developed and developing world, and offers proven benefits to maternal and infant health [6]. However, skilled obstetrical and neonatal care may be required to manage preterm deliveries to maximize the benefits of PI-based HAART use during pregnancy.

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