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Impact of Antiretroviral Regimen on Pregnancy and Infant Outcomes in Women With HIV/ HBV Coinfection

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Background: There are limited data on the impact of antenatal antiretroviral regimens (ARV) on pregnancy and infant outcomes in HIV/HBV coinfection. We compared outcomes among 3 antenatal antiretroviral regimens for pregnant women with HIV/HBV.

Methods: The PROMISE study enrolled ARV-naive pregnant women with HIV. Women with HBV were randomized to (no anti-HBV)-zidovudine (ZDV) + intrapartum nevirapine and 1 week of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC); (3TC)-3TC + ZDV + LPV/r; or (FTC-TDF)-FTC + TDF + LPV/r. Pairwise group comparisons were performed with Fisher exact, *t*, or log rank tests. Adverse pregnancy outcome (APO) was a composite of low birth weight, preterm delivery, spontaneous abortion, stillbirth, or congenital anomaly.

Results: Of 138 women with HIV/HBV, 42, 48, and 48 were analyzed in the no anti-HBV, 3TC, and FTC-TDF arms. Median age was 27 years. APOs trended lower in the no anti-HBV (26%) vs 3TC (38%), and FTC-TDF arms (35%), $P \geq 0.25$). More infant deaths occurred among the FTC-TDF [6 (13%)] vs no anti-HBV [2 (5%)] and 3TC [3 (7%)] arms. There were no differences in time-to-death, HIV-free survival, birth or one-year WHO Z-score length-for-age, and head circumference. Hepatitis B e antigen (HBeAg) was associated with an increased risk of APO, 48% vs 27% (odds ratio 2.79, 95% confidence interval: 1.19 to 6.67, *post hoc*).

Conclusion: With HBV/HIV coinfection, the risk of an APO was increased with maternal ARV compared with ZDV alone, although the differences were not statistically significant. Maternal HBeAg was associated with a significantly increased risk of APO. Infant mortality was highest with FTC + TDF + LPV/r. Early assessment of HBeAg could assist in identifying high-risk pregnancies for close monitoring.

Key Words: HIV, HBV, antiretroviral therapy, infant outcomes

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INTRODUCTION

About 3%–12% of pregnant women are living with HIV and HBV yet data on the impact of antiretroviral (ARV) regimens on pregnancy and infant outcomes in HIV/HBV coinfection are limited.[1,2] Tenofovir disoproxil fumarate (TDF) is the preferred agent for treating HBV in pregnancy, given its high barrier to resistance, favorable safety profile, and efficacy for HIV and HBV.[3–5] Previously a cornerstone ARV, lamivudine (3TC) decreases perinatal HBV transmission and is safe in pregnancy.[6,7] Similarly, emtricitabine (FTC) possesses anti-HBV activity.[8]

The PROMISE study demonstrated that infant mortality was increased with ritonavir-boosted lopinavir (LPV/r)+TDF/FTC compared with antepartum zidovudine (ZDV) alone, but whether such differences also exist in the context of HBV-active regimens in HIV/HBV coinfection is unknown. In this secondary analysis, our objective was to compare the impact of ARV regimen on pregnancy and infant adverse outcomes among people living with HIV and HBV. We further assessed the association of maternal baseline HBeAg status and HBV viral load with pregnancy and infant outcomes.

METHODS

Study Population and Eligibility Criteria

PROMISE 1077BF/1077FF was a multisite randomized open-label trial examining strategies for preventing perinatal HIV transmission and for preserving maternal and infant health, implemented between April 2011 and September 2016. The protocol was approved by relevant ethics committees in the collaborating countries, and reviewed by an independent data and safety monitoring board. All women provided written informed consent for study participation. The study population included women with high $CD4^+$ cell counts ($\geq$350/mm^3) who had not met country-specific criteria for initiating ART. Women with elevated ALT (>2.5x ULN) were excluded. Additional details are referenced here.[9] Women who were HBsAg-positive were randomized 1:1:1 to receive zidovudine (ZDV) plus intrapartum single-dose nevirapine followed by 6–14 days of TDF and FTC postpartum (no anti-HBV), 3TC + ZDV+ Lopinavir/ritonavir (LPV/r) (3TC), or FTC + TDF + LPV/r (FTC-TDF).

Clinical and safety evaluations occurred at entry, week 2, 4, 8, every 4 weeks until labor and delivery; at labor and delivery; at postpartum week 1, week 6, 14, and Q12 weeks thereafter. Screening HBsAg was performed at local laboratories. Maternal HBV DNA levels were measured at Quest with COBAS AmpliPrep/COBAS TaqMan HBV Test, v2.0 assay (lower limit of quantification (LLQ) 20 IU/mL), and later with the COBAS HBV/Roche 8800 (LLQ 10 IU/mL) assay.

Adverse pregnancy outcome (APO) was defined as a composite of low birth weight (LBW) (<2500 g), preterm delivery (<37 weeks), spontaneous abortion (<20 weeks), stillbirth (≥20 weeks), or a congenital anomaly.[9] Infant outcomes were: mortality (time to), HIV-free survival (time to earlier of HIV infection or death), weight and hemoglobin level (primary focus at birth), and weight and WHO-Z score for length-for-age (primary focus at 1 year) and head circumference (primary focus at 1 year), grade 3 or 4 adverse events, graded for severity per the DAIDS toxicity table 2009.[10]

Pairwise group comparisons between regimens and their outcomes were performed with Fisher exact, *t*, or log rank tests. The primary comparison was between FTC-TDF and 3TC arms. Infant time-to-event analyses were censored at the earlier of last clinic visit, last laboratory measurement, or end of infant follow-up of visit week 104, or site notification of the START study results, which recommended initiation of ARVs for all women.[11]

We applied logistic and Cox proportional hazards regression models to further assess p*ost hoc* whether there was treatment effect modification by maternal baseline HBeAg status and HBV DNA level (< or ≥ 1 million IU/mL), and their association, with APO, infant hemoglobin at birth, birth weight, infant weight at 1 year, and time-to-infant mortality. The statistical significance level was set at 0.05.

RESULTS

Socio-Demographic and Clinical Characteristics

Of 3543 women, 139 (3.9%)[12] were HBsAg-positive and 42, 48, and 49 randomized to the no anti-HBV, 3TC, and FTC-TDF-containing arms, Table 1. One participant was excluded from analyses. Half of the women had a CD4 ≥ 500 cells/mm^3 (51%). Median baseline HBV DNA level was 2.6 log_{10} IU/mL; 23% had HBV DNA ≥ 1 million IU/mL, whereas 24% had a level < 20 IU/mL. Thirty-four (26%) women were HBeAg-positive, and among these, 28 (93%) of 30 with data had HBV VL≥ 1 million IU/mL (Table 1).

Pregnancy Outcomes

Among 132 (96%) of 138 pregnancies with outcomes, there were no spontaneous abortions, 5 singleton stillbirths, and 127 pregnancies with 126 live singleton births and 1 twin birth (in FTC-TDF arm).The risk of an APO was not statistically different in the primary pairwise comparison of the FTC-TDF vs 3TC arms (35%) and (38%) of pregnancies, estimated odds ratio {[OR, 3TC reference] 0.86, 95% confidence interval (CI): [0.34 to 2.17], $P = 0.83$, Table 2}, but were numerically higher when compared with no anti-HBV arm (26%); FTC-TDF vs no anti-HBV [1.55 (0.55 to 4.47), $P = 0.48$; 3TC vs no anti-HBV 1.80 (0.65 to 5.13), $P = 0.25$]. The most common APOs were preterm delivery and LBW. Among 127 live birth pregnancies, preterm delivery (<37 weeks' gestation) was 11% in the no anti-HBV arm and higher in 3TC and FTC-TDF arms with 20% and 28% [OR (95% CI) 2.12 (0.52 to 10.26) and 3.25 (0.87 to 14.92)]The proportion with LBW (<2500 g) was 16% (6/37) in the no anti-HBV arm and, 20% (9/44) and 17% (8/46) in the 3TC and FTC-TDF arms, and did not differ between arms, $P \geq 0.78$.

TABLE 1. Baseline Characteristics of Pregnant Women Living With HIV and HBV in the PROMISE Study

Characteristic	No anti-HBV (N = 42)	3TC (N = 48)	FTC-TDF (N = 48)	Total (N = 138)
Country				
South Africa	9 (21%)	14 (29%)	12 (25%)	35 (25%)
Malawi	19 (45%)	20 (42%)	22 (46%)	61 (44%)
Zambia	1 (2%)	2 (4%)	1 (2%)	4 (3%)
Uganda	4 (10%)	4 (8%)	5 (10%)	13 (9%)
Zimbabwe	7 (17%)	6 (13%)	8 (17%)	21 (15%)
Tanzania	2 (5%)	2 (4%)	0 (0%)	4 (3%)
Age (years)				
N	42	48	48	138
Median (IQR)	24 (21–29)	28 (24–31)	28 (25–30)	27 (23–30)
Gestational age (wk)				
N	42	47	48	137
Median (IQR)	28 (23–32)	25 (22–31)	26 (21–31)	27 (22–31)
<14	0 (0%)	1 (2%)	0 (0%)	1 (1%)
14 to <28	21 (50%)	27 (57%)	27 (56%)	75 (55%)
28 to <34	14 (33%)	13 (28%)	11 (23%)	38 (28%)
34 to <37	4 (10%)	4 (9%)	7 (15%)	15 (11%)
≥37	3 (7%)	2 (4%)	3 (6%)	8 (6%)
Missing	0	1	0	1
Weight (kg)				
N	42	48	48	138
Median (IQR)	61 (56–69)	65 (59–72)	69 (61–81)	64 (59–76)
$CD4^+$ cell count (cells/mm^3)				
N	42	48	48	138
Median (IQR)	506 (420–695)	507 (433–620)	496 (420–607)	505 (420–634)
<350	0 (0%)	2 (4%)	2 (4%)	4 (3%)
350 to < 400	6 (14%)	8 (17%)	7 (15%)	21 (15%)
400 to <450	12 (29%)	4 (8%)	7 (15%)	23 (17%)
450 to <500	3 (7%)	9 (19%)	8 (17%)	20 (14%)
500 to <750	15 (36%)	18 (38%)	18 (38%)	51 (37%)
≥750	6 (14%)	7 (15%)	6 (13%)	19 (14%)
Log_{10}HIV RNA (copies/mL)				
N	42	48	48	138
Median (IQR)	3.8 (3.2–4.6)	4.1 (3.3–4.5)	4.0 (3.3–4.6)	4.0 (3.2–4.5)
HIV RNA (copies/mL)				
<400	5 (12%)	8 (17%)	4 (8%)	17 (12%)
400 to 1000	3 (7%)	2 (4%)	2 (4%)	7 (5%)
1000 to <10,000	15 (36%)	12 (25%)	21 (44%)	48 (35%)
10,000 to <100,000	12 (29%)	24 (50%)	16 (33%)	52 (38%)
100,000 to <200,000	4 (10%)	0 (0%)	2 (4%)	6 (4%)
≥200,000	3 (7%)	2 (4%)	3 (6%)	8 (6%)
HBV DNA (Log_{10} IU/mL)				
N	40	48	46	134
Median (IQR)	2.47 (1.30–7.61)	2.62 (1.45–5.79)	2.55 (1.89–4.15)	2.58 (1.38–5.34)
HBV DNA IU/mL				
≥1 million	11 (28%)	12 (25%)	8 (17%)	31 (23%)
< 20	12 (30%)	12 (25%)	8 (17%)	32 (24%)
HBeAg				
N	41	44	46	131
Positive	13 (32%)	11 (25%)	10 (22%)	34 (26%)
Anti-HBe				
N	36	38	41	115
Positive	21 (58.3%)	23 (60.5%)	25 (61%)	69 (60%)

TABLE 2. Pregnancy Outcomes Among Women Living With HIV and HBV in the PROMISE Study

Variable	Total (N = 132)	No anti-HBV (N = 39)	3TC (N = 47)	FTC-TDF (N = 46)	Estimated Odds Ratio (95% CI), P§		
					3TC vs No anti-HBV (Ref)	FTC-TDF vs No anti-HBV (Ref)	(Primary) FTC-TDF vs 3TC (Ref)
No. of infants							
Singleton	131 (99%)	39 (100%)	47 (100%)	45 (98%)			
Twins†	1 (1%)	0 (0%)	0(0%)	1 (2%)			
Any adverse* pregnancy outcome							
No	88 (67%)	29 (74%)	29 (62%)	30 (65%)			
Yes	44 (33%)	10 (26%)	18 (38%)	16 (35%)			
Prob. any outcome (95% CI)		25.6% (14.6, 41.1)	38.3% (25.8, 52.6)	34.8% (22.7, 49.2)	1.80 (0.65, 5.13) $P = 0.25$	1.55 (0.55, 4.47) $P = 0.48$	0.86 (0.34, 2.17) $P = 0.83$
Outcome of delivery							
Live birth	127 (96%)	37 (95%)	44 (94%)	46 (100%)			
Stillbirth (IUFD ≥ 20 weeks)	5 (4%)	2 (5%)	3 (6%)	0 (0%)			
Prob. Stillbirth (95% CI)		5.1% (1.4, 16.9)	6.4% (2.2, 17.2)	0.0% (0.0, 7.7)	1.26 (0.14, 15.8) $P = >0.99$	0.00 (0.00, 2.9) $P = 0.21$	0.0 (0.0, 1.7) $P = 0.24$
Preterm delivery (<37 weeks)‡							
No	101 (80%)	33 (89%)	35 (80%)	33 (72%)			
Yes	26 (20%)	4 (11%)	9 (20%)	13 (28%)			
Prob. preterm (95% CI)		10.8% (4.3, 24.7)	20.5% (11.2, 34.5)	28.3% (17.3, 42.5)	2.12 (0.52, 10.26) $P = 0.36$	3.25 (0.87, 14.92) $P = 0.06$	1.53 (0.52, 4.63) $P = 0.47$
Low birth weight (LBW) (<2500 grams)†							
No	104 (82%)	31 (84%)	35 (80%)	38 (83%)			
Yes	23 (18%)	6 (16%)	9 (20%)	8 (17%)			
Prob. LBW (95% CI)		16.2 (7.7, 31.1)	20.5% (11.2, 34.5)	17.4% (9.1, 30.7)	1.33 (0.37, 5.07) $P = 0.78$	1.09 (0.29, 4.24) $P = >0.99$	0.82 (0.25, 2.70) $P = 0.79$
Congenital anomaly†							
No	124 (98%)	36 (97%)	43 (98%)	45 (98%)			
Yes	3 (2%)	1 (3%)	1 (2%)	1 (2%)			

ZDV alone = no anti-HBV, Lamivudine/zidovudine/Lopinavir-ritonavir (3TC + ZDV + LPV/r) = 3TC, Emtricitabine/tenofovir disoproxil fumarate/Lopinavir–ritonavir (FTC/TDF//LPV/r) = FTC-TDF arms.

Unit of analysis is mother–infant pair, if ≥1 event among twins counted as one event.

*Adverse pregnancy outcome was defined as a composite of low birth weight (<2500 g), preterm delivery (<37 weeks), spontaneous abortion (<20 weeks), stillbirth (≥20 weeks), or a congenital anomaly.

†Both twins were preterm live births, with low birth weight.

‡Live birth infant only.

§Exact 95% CI for Odds ratio, and 2-sided Fisher exact test *P*-value.

Infant Outcomes

Through 2 years, more infant deaths occurred among the FTC-TDF [6 (13%)] vs no anti-HBV [2 (5%)] and 3TC [3 (7%)] arms. More infant deaths occurred among the FTC-TDF [6 (13%)] vs no anti-HBV [2 (5%)] and 3TC [3 (7%)] arms, Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/B914. Two, 1, and 0 deaths in the FTC-TDF, 3TC, and no anti-HBV arms were preterm. One death in each of the 3TC and FTC-FDF arms occurred in infants born at 34 weeks of gestation (very preterm delivery infants). One, 2, and 0 deaths in each arm had LBW (<2500 g), and none had very LBW (<1500 g). There were no significant differences in time-to-death, HIV-free survival, or mean WHO Z-score length-for-age, and head circumference at birth or 1 year.

The risk of a grade 3 or 4 infant adverse event was not different between arms. Infants in the FTC-TDF arm had significantly higher mean hemoglobin level at birth vs those in 3TC (1.31 g/dL, 95% CI: 0.38 to 2.25, $P < 0.01$), but not vs no anti-HBV arm (−0.77 g/dL, 95% CI: −1.75 to 0.22, $P = 0.12$); 3TC vs no anti- HBV arm (0.54 g/dL, 95%

CI: −0.39 to 1.48, $P = 0.25$, see Figure 2 and Tables 1 and 2, Supplemental Digital Content, http://links.lww.com/QAI/B914.

Pregnancy and Infant Outcomes by Maternal HBeAg Status and Baseline HBV Viral Load

In *post hoc* analyses, treatment effects did not differ by maternal HBeAg for APO, infant hemoglobin level at birth, birth weight, weight at 1 year, and time-to-infant mortality ($P \geq 0.12$, see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B914). Adjusted for treatment arm, HBeAg positivity was associated with an increased risk of an APO [48% (15/31) vs 27% (25/94)] in HBeAg-negative women [OR 2.79 (95% CI: (1.19 to 6.67), $P = 0.019$)], Table 3, Supplemental Digital Content, http://links.lww.com/QAI/B914.

Higher percentages were observed for pregnancies among HBeAg-positive women for each of stillbirth (10% vs 2%), preterm (32% vs 15%) and LBW (21% vs 14%). Results were similar when we compared outcomes by baseline maternal HBV DNA above and below 1 million IU/mL, Tables 2 and 3, Supplemental Digital Content, http://links.lww.com/QAI/B914. There was no evidence of an association between HBeAg or maternal HBV DNA and infant hemoglobin at birth, infant birth weight, and infant weight at 1 year, Table 3, Supplemental Digital Content, http://links.lww.com/QAI/B914.

DISCUSSION

This is one of the first studies to evaluate whether ARV regimens affected pregnancy and infant outcomes in HIV/HBV coinfection. The proportion of women with any APO was numerically higher with antepartum TDF containing ART, although differences were not statistically significant. Infant mortality at 2 years was higher in the TDF-ART arm, with two-thirds of deaths occurring within the first month of life in ART arms. However, event numbers were small. Although these results were not statistically significant, they follow previous results from similar results from the overall PROMISE trial. Use of 3TC plus ZDV resulted in significantly lower infant mean hemoglobin at birth compared with TDF-ART. Maternal baseline HBeAg positivity and HBV DNA ≥1 million IU/mL were associated with increased risk of an APO.

Similar point estimates for APO treatment differences were observed in the much larger parent PROMISE study, where higher rates of APO were observed with 3TC + ZDV + LPV/r and FTC + TDF + LPV/r than with ZDV alone, but not between the 2 PI-containing ART regimens. Although the exact mechanisms responsible for the relationship between maternal ART and the elevated risk of APO are unclear, one possible mechanism is through modulation of the immune response. Use of ART may induce APOs by altering circulating cytokine levels through ART-associated immune reconstitution.[13,14] In addition, use of protease inhibitors during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to LBW and preterm deliveries[15] as observed in the PROMISE primary analysis.[9]

Similar to the PROMISE study, we observed that infant mortality was highest with FTC + TDF + LPV/r initiated during pregnancy. In HIV/HBV coinfection, one may have hypothesized that non-HBV active therapy would have led to worse infant outcomes given 2 viral infections in pregnancy, but we did not see this effect, and instead, saw the same interesting association with infant mortality with TDF-ART. As in HIV, the mechanism is unknown but may be related to an additive deleterious impact of TDF and LPV/r. Of note, we did not assess the impact of postpartum maternal ART status on infant outcomes, and factors beyond antepartum ARV receipt may have contributed to infant outcomes.

In *post hoc* analyses, APOs were more pronounced among women with positive HBeAg, consistent with other studies.[16,17] Although the mechanism is unclear, maternal HBeAg is associated with high HBV viral load.[18] HBeAg serves as a qualitative and cheaper surrogate marker of viral load.[19] Data from HPTN-046, a randomized controlled of HIV vertical transmission in sub-Saharan Africa that evaluated 6 months of infant nevirapine vs. placebo for perinatal HIV prevention showed that HBsAg-positive women with high HBV viral loads (defined as HBV VL≥ 1 million IU/mL) had a higher risk of delivering a LBW infant compared with those with HBV VL < 1 million IU/mL. Similarly, in a large retrospective cohort study of 26,350 pregnant Thai women, 1446 (5.5%) of whom had HBV, preterm births and LBW were higher among women with positive HBeAg status (21.9% vs 14.1%, $P = 0.005$) and (8.6% vs 13.6%, $P = 0.028$).[17]

Major strengths of our study include the randomized design, including a no anti-HBV ZDV-alone regimen, and the relatively long two-year infant follow-up. We also include data from a variety of SSA countries where WHO has noted a paucity of data.[3] Study limitations include *post hoc* analyses, inability to distinguish between acute and chronic HBV infection with a single timepoint assessment, and the use of LPV/r as backbone for the regimen containing TDF + 3TC. This agent is being replaced by dolutegravir as a first-line regimen, and therefore extrapolating our results to other TDF + 3TC-containing regimens needs caution. Finally, this analysis had a relatively small sample size and few events, limiting our precision on estimating treatment effects.

In HIV/HBV coinfection, maternal ART (3TC + ZDV + LPV/r and FTC + TDF + LPV/r) initiated during pregnancy was associated with higher risk of APO compared to use of ZDV alone though the difference were not statistically significant.[9] Baseline positive HBeAg or high baseline HBV DNA (≥1 million IU/mL) was associated with higher risk for an APO. Early antenatal diagnosis of HBV, followed by assessment of HBeAg in pregnancy as a surrogate for high HBV DNA levels, particularly in resource limited settings, could assist in identifying high-risk pregnancies for close monitoring. As was demonstrated in PROMISE overall, among this subgroup of women with HIV and HBV, infant mortality was also highest with FTC + TDF + LPV/r. Future research

should evaluate the safety of newer ART/HBV drug-containing regimens including tenofovir alafenamide fumarate and dolutegravir in pregnant women living with HIV/HBV.[20]

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