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Comparison of Antiretroviral Therapies in Pregnant Women Living With Human Immunodeficiency Virus and Hepatitis B Virus: A Randomized Controlled Trial

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Abstract

Objective: To describe the anti–hepatitis B virus (HBV) efficacy, HBeAg serologic changes, HBV perinatal transmission and safety in pregnant women living with human immunodeficiency virus (HIV) and hepatitis B (HBV) coinfection who were randomized to various antiretroviral therapy (ART) regimens.

Methods: The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial was a multicenter randomized trial for ART-naive pregnant women with HIV. Women with HIV/HBV at 14 or more weeks of gestation were randomized to one of three ART arms; one without

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HBV treatment (Group 1) and two HBV treatment arms with single (Group 2) or dual anti-HBV activity (Group 3). The primary HBV outcome was HBV viral load (VL) antepartum change from baseline (enrolment) to 8 weeks; safety assessments included ALT, AST, and anemia (Hb <10 g/dl). Primary comparison was for the HBV- active treatment arms. Pairwise comparisons applied t- and Fisher's exact tests.

Results: Of 3543 women, 3.9% (138) were HBsAg+; with 42, 48, and 48 randomized to Groups 1, 2, and 3. Median gestational age at enrolment was 27 weeks. Among HBV viremic women, mean antepartum HBV VL change at week 8 was −0.26, and −1.86 and −1.89 $\log_{10}$ (IU/ml) in Groups 1, 2, and 3, respectively. In those who were HBeAg positive, HBeAg loss occurred in 44.4% at delivery. Two perinatal HBV transmissions occurred in Group 2. During the antepartum period, 1 (2.4%), 2 (4.2%) and 3 (6.3%) women had > grade 3/4 ALT/AST elevations in Groups 1, 2, and 3, respectively.

Conclusions: Over a short period of time, HBV DNA suppression was not different with one or two HBV-active agents. HBeAg loss occurred in a substantial proportion of participants. Perinatal transmission of HBV was low. HBV-active ART was well tolerated in pregnancy with few grade 3/4 ALT/AST elevations.

Precis

Hepatitis B virus (HBV)-active antiretroviral therapy is safe and effective for pregnant women living with human immunodeficiency virus and HBV, with low perinatal HBV transmission.

Keywords

HIV; HBV; Viral Load Decline; Antiretroviral Therapy

Introduction:

Three to 12% of pregnant women with HIV in Sub-Saharan Africa have Hepatitis B (HBV) infection[1–5]; yet there are limited data on antiretroviral therapy (ART) outcomes, particularly in sub-Saharan Africa

There are also few randomized studies evaluating different ART strategies in HIV/HBV women during pregnancy and its effect on HBV viral load (VL) reduction.[6] Current recommendations for ART in women living with HIV and HBV include therapy with two active anti-HBV agents, usually tenofovir disoproxil fumarate combined with either lamivudine or emtricitabine, yet some women may be unable to receive tenofovir containing regimens due to pre-existing conditions. Similarly, although HBV perinatal transmission in HIV/HBV coinfection has been reported in 5–29% [3, 7–9], these cohorts of women with HIV and HBV coinfection varied with regards to receipt and duration of ART.

Adverse events, particularly hepatotoxicity, are a concern in pregnant women living with both viral hepatitis and HIV. In one study from South Africa, in people living with HIV and HBV, high baseline HBV DNA was associated with hepatotoxicity with ART initiation[10]. In contrast, two large studies of pregnant women living with HBV alone did not report any antepartum hepatotoxicity during antiviral therapy [11, 12] but there are limited data on

adverse events from pregnant HIV/HBV coinfected women [13, 14]. Similarly, HBeAg and anti-HBe seroconversions may be common in the peripartum period and often accompany hepatic flares [15, 16]. These phenomena may be indicators of immunologic benefit of HBV control [17], but there are limited data for those with HIV/HBV coinfection.

The Promoting Maternal and Infant Survival Everywhere (PROMISE) study was a randomized ART strategy trial conducted in sub-Saharan Africa and India. In this nested sub-study to explore HBV related outcomes, we describe the anti-HBV efficacy, HBeAg serologic changes, HBV perinatal transmission, and safety in pregnant women with HIV/HBV coinfection who were randomized to various ART regimens, including short-term lamivudine (3TC)-containing therapy where 3TCwas the single HBV active agent. Acknowledging that universal ART is recommended for all people with HIV/HBV coinfection with two HBV-active agents, there remain limited comparative data on the safety and efficacy of these agents in pregnant women with HIV/HBV, particularly relevant with the availability of the co-formulated HIV regimen dolutegravir/lamivudine which affords single HBV active therapy. Hence data from this trial will help shed light on these important questions.

Methods:

PROMISE was a multicenter trial using sequential randomization comparing open-label ART strategies that proved efficacious for reducing the risk of perinatal HIV transmission among ART-naive pregnant HIV women.[18] Detailed methodology is presented elsewhere [18]. At screening, women were tested for HBsAg. Positive HBsAg denoted HBV infection.

At the time of study design, there was equipoise on a) whether persons living with HIV and HBV who did not meet criteria for HBV treatment should be treated for HBV and b) whether ART should be continued postpartum for all women with HIV for HBV, similar to the current debate in HBV monoinfection and pregnancy.[19–21] As such, antiretroviral therapy agents were selected based on the need for both HBV and HIV antiviral efficacy and women were randomized to strategies that included ART discontinuation. Lopinavir/ritonavir and zidovudine (ZDV), which do not have inherent anti-HBV activity, had previously been studied in persons living with HIV, with demonstrated anti-HIV activity and safety.[22, 23] Tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and emtricitabine (FTC) have all been studied in HIV infection and HBV monoinfection and had demonstrated safety and efficacy.[24–26]

The PROMISE nested HBV substudy randomized open-label, in an unblinded fashion, pregnant women with HIV/HBV to receive one of three ART arms; one **without** HBV treatment [Group 1- zidovudine (ZDV) and intrapartum nevirapine], one with **single** HBV treatment [Group 2- **3TC**, ZDV, and lopinavir/ritonavir] and one with **dual** HBV treatment [Group 3- **FTC**, **TDF**, and lopinavir/ritonavir] or dual anti-HBV activity (Group 3). All women in the untreated HBV arm received one week of daily FTC-TDF, from labor onset or as soon as possible thereafter. HBV-active ART was defined as containing either single therapy with 3TC as the only HBV active agent (Group 2) or dual therapy (Group 3) with two HBV active agents with FTC-TDF. All participants provided written informed consent.

The study was approved by local country and collaborating institutional review boards, including at the University of California, Los Angeles.

Eligibility criteria included CD4 count ≥350 (or a country-specific threshold for initiating triple-drug ART if higher), gestation of ≥14 weeks, no previous use of triple-drug ART unless for prevention of HIV perinatal transmission, no clinical or immune-related indication for triple-drug ART, a hemoglobin level of ≥ 7.5 g/dL, an absolute neutrophil count ≥750 cells/mm^3, an alanine aminotransferase level (ALT) ≤ 2.5 times the upper limit of the normal range, an estimated creatinine clearance ≥ 60 ml per minute, and no current evidence of serious congenital malformation. Women with HIV and HBV had complete blood count, ALT, aspartate aminotransferase (AST), serum creatinine, alkaline phosphatase, total bilirubin, and albumin collected at entry; antepartum weeks 4, 8, and q8 weeks until delivery, post pregnancy at entry into subsequent step and at weeks 6, 14, 26, 38, 50 and q24 weeks thereafter. Sites were instructed to provide infants born to women with HBV with hepatitis B vaccine within 24 hours after birth. Infants completed the primary series through the study or local immunization programs. If Hepatitis B immunoglobulin (HBIG) was standard of care, administration was recommended at birth.

Pregnant women could enroll at any gestational age after 14 weeks. The primary virology comparison population was women with HBV viremia (>=20 IU/ml) at 14 weeks or older gestation who remained pregnant 8 weeks later. The primary outcome measure was HBV VL (log10 IU/ml) change from baseline (enrolment) to 8 weeks. Safety assessments included ALT, AST, and anemia (Hgb <10g/dl). The DAIDS toxicity table was used for adverse events.[27] Perinatal HBV transmission was defined as either HBsAg or HBV VL positivity at six months of age (visit week 26). If week 26 aliquots were not available, then week 38 aliquots were used.

Serological testing for HBsAg was performed in real time with GS HBsAg EIA 3.0 (ref 32591, Bio-Rad, Hercules, CA) at local sites. All specimens were stored at –80°C. HBeAg was performed using ETI-EBK PLUS (DiaSorin, Stillwater, Minnesota) (UCLA) and using Ortho-Clinical Diagnostics VITROS (Rochester, NY) at Quest. Anti-HBe was performed using Liaison XL (Diasorin) at UCLA and Ortho-Clinical Diagnostics VITROS (Rochester, NY) at Quest. Maternal HBV VL levels were measured at Quest Laboratories with the 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.

For randomized group comparisons, all eligible HBsAg positive randomized women/infants from the antepartum period were included and were analyzed as initially randomized. The HBV viral load (VL) primary efficacy analysis was additionally limited to women who had HBV viremia at baseline and who remained pregnant at week 8 after enrollment. For analyses that used the continuous HBV VL, results below the LLQ were imputed as the LLQ value which was (20 or 10 IU/ml, depending on the assay). We analyzed data until July 7th, 2015, at which time all participants were counseled to initiate ART based on the findings from the Strategic Timing of Antiretroviral Therapy Trial.[28]

Three pairwise comparisons were performed. For HBV related outcomes, the primary focus was on the pairwise comparison between two arms with anti-HBV containing therapy. The two pairwise comparisons with the no anti-HBV arm were considered secondary. Cross-sectional continuous outcome measures were assessed with two-sided two sample t-test, with unequal variances (Satterthwaite method). Binary outcome measures were summarized by estimating within-group proportions and associated 95% Wilson score confidence intervals (CI), and groups compared with Fisher's exact test, and odds ratios with 95% exact CI. Time-to-event distributions were summarized via Kaplan-Meier plots, compared with a log rank test, with ties in failure times handled by the approximate likelihood of Efron and randomized group effects summarized with hazard ratios from Cox proportional hazards pairwise models using profile likelihood-based confidence limits. Analyses were carried out with SAS 9.4. P-values from hypothesis tests were reported without adjustment for multiple comparisons. The sample size for this substudy was dependent on the number of women living with HBV enrolled in the parent study. For the comparison of primary interest, the two HBV-active groups, a total of 96 (48 in each arm) women were randomized and included in analysis. Assuming 20% with undetectable DNA at baseline, and adjusting by 5% for delivery before 8 weeks and attrition, a sample size of approximately 36 women per arm (72 total) was anticipated for this analysis. With an assumed standard deviation of 1.50 or 2.50 there would be 80% power to detect a mean difference of at least 1.0 or 1.7 log10 IU/ml at a 5% type I error level.

Results:

PROMISE participants were randomized between April 2011 and October 1, 2014 and median (Q1–Q3) follow-up was 133 (77–165) weeks. One hundred thirty-nine (3.9%) were positive for HBsAg (Figure 1). Women were followed until the results of the START study, at which time sites were instructed to initiate ART on all women.[28] Infants were followed up to 110 weeks, median infant follow up was 103 weeks. (Table 1)

One woman assigned to Group 3 (HBV active therapy with FTC-TDF) was hospitalized on the day of enrollment before treatment and was excluded. Forty-two, 48, and 48 were randomized to Groups 1, 2, and 3, respectively. The median age was 27 years, 74.0% were HBeAg negative, and 23.9% of all women had HBV VL <20 IU/ml. The median HBV viral load was 2.58 $\log_{10}$ IU/ml. The median ALT was 15 IU/L, median CD4 was 505 cells/mm^3, and median HIV VL was 4.0 $\log_{10}$ copies/ml. Entry characteristics were balanced across groups except for a higher proportion of HBV VL <20 IU/ml in Group 2 vs Group 3 arms, 25.0% vs 17.4%. In the antepartum period, the median duration on HBV-active therapy to delivery was 9 and 12 weeks for Group 2 and Group 3.

Among women who were viremic (HBV VL ≥20 IU/ml), the mean change from baseline in HBV VL was greater in the HBV active arms, −1.86, and −1.89 in group 2 and group 3, respectively vs −0.26 $\log_{10}$ IU/ml in group 1 (no HBV treatment) (Table 2). However, the mean change between the HBV active arms, groups 2 and 3, was not statistically significantly different (mean difference 0.03; 95% CI: −0.89, 0.96, primary comparison group, p=0.94).

In this analysis, 25 HBV VL results at antepartum week 8 were below the assay's lower limit of quantitation. In order to examine whether this was associated with our results, sensitivity analyses were performed which set results below LLQ to the lower limit of quantitation in one group and a low value of 1 IU/ml in the other group, and vice versa, and these did not change conclusions for the 3 comparisons.

Among women who were HBV viremic at baseline, women in Group 1 (no HBV treatment) were less likely to suppress their HBV VL to <20 IU/ml compared to Groups 2 (10.5% vs 54.5%, p=0.004) and 3 (10.5% vs 59.1% p=0.003), but suppression was not significantly different between groups 2 and 3 (54.5% vs 59.1%, p>0.99).

At baseline, 74.0% of 131 women were HBeAg negative. At delivery, 87.1% (27/31), 80.5% (33/41), and 82.9% (34/41) in Groups 1, 2, and 3, respectively, were HBeAg negative, with no differences between each of the arms (p ≥0.54). At delivery, of 27 women who were HBeAg positive at baseline, 44.4% (12/27) had HBeAg loss, with 50.0% (4/8), 40.0% (4/10), 44.4% (4/9) in Groups 1, 2, and 3, respectively. Overall, of 39 women who were anti-HBe negative at baseline, 28.2% (11/39) women gained anti-HBe, with 36.4% (4/11), 23.1% (3/13), and 26.7% (4/15) in Groups 1, 2, and 3, respectively (p ≥0.66). (Table 2)

As hepatotoxicity can sometimes accompany HBeAg serologic changes, we evaluated this association. Of 6 women with grade 3 or 4 ALT elevation in the antepartum period with HBeAg and anti-HBe data, two women, one in Group 1 (no HBV therapy) and one in Group 2 experienced HBeAg loss and anti-HBe gain at delivery. The remaining 4 women with grade 3 or 4 ALT elevations were not associated with HBeAg loss or anti-HBe gain.

Among 128 infants, 84.4% had their first HBV vaccination within their first week of life and 62.9% (78/124) received 3 or more doses. Four infants received HBIG at birth. The overall HBV perinatal transmission incidence was 1.9% (2/105), with 0.0 (0/31), 5.0% (2/40), and 0.0 (0/34) in Groups 1, 2, and 3, respectively. For the two transmissions, maternal HBV VL at delivery were 170 million IU/ml and 556 IU/ml. At delivery, time on antiretroviral therapy was 8.85 and 14.57 weeks. Neither infant received HBIG but both received three doses of HBV vaccine. The first infant received birth dose vaccine while the second received the first dose of vaccine at 45 days of age. More women in the HBV-active arms experienced grade 2 or greater AEs (70.8% in group 2, and 79.2% in group 3 compared to 57.1% in group 1 (no HBV therapy). The majority of AEs were grade 2 events. (Table 3) More women in the HBV-active arms experienced a grade 3 or 4 ALT or AST elevation, 5 (10.4%) each in Groups 2 and 3 vs 2 (4.8%) in Group 1. Only one woman had symptoms; she reported abdominal pain. In each arm, grade 3 or 4 ALT or AST events occurred early on in follow-up (Figure 2).

Compared to Group 1, the hazard of a Grade 3/4 ALT/AST elevation in Group 2 (HR: 2.1; 95% CI: 0.4, 14.3) and Group 3 (HR: 2.2; 95% CI: 0.5, 15.0) was twice as high (Table 4). There was no significant difference in the hazard of Grade 3/4 ALT/AST elevation Group 2 relative to Group 3 (HR: 1.1; 95%CI: 0.3, 3.8).

In the antepartum period, more women in the HBV-active ART arms also had > grade 3/4 ALT/AST elevations; 2 (4.2%) and 3 (6.3%) in Group 2 and Group 3 vs one (2.3%)

in Group 1 (no HBV therapy) although the HR CIs include no difference (ratio of 1.0). (Table 4) At delivery 28.6%, 31.1%, and 15.6% of women with data in Groups 1, 2, and 3, respectively, had anemia with no significant differences between the arms (p>=0.13). Both Groups 1 and 2 contained ZDV, a drug that causes anemia.[23] (Table 2) There were no maternal deaths in the antepartum period. There were two maternal deaths in the post-pregnancy period; one at 155 weeks (Group 2) due to chronic renal insufficiency, and one (Group 3) at 92 weeks due to sepsis.

Discussion:

In this study in pregnant women with HIV and HBV, when comparing ART containing lamivudine (single HBV active therapy in Group 2) vs combination tenofovir and emtricitabine (dual HBV active therapy in Group 3) we did not detect a difference in mean HBV VL change at 8 weeks antepartum, but sample sizes were small. There was a high proportion of HBeAg loss and anti-HBe gain across all arms. The overall incidence of HBV perinatal transmission was 1.9%. Antiretroviral therapy was safe and well tolerated with few grade 3 or 4 ALT elevations. Anemia occurred more often in women receiving ZDV-containing therapy.

We estimated a small difference in mean antepartum HBV VL decline between the 3TC (Group 2) and FTC-TDF (Group 3) arms after eight weeks in HBV-viremic pregnant women living with HIV and HBV. However, the confidence interval was wide and could not rule out a difference of up to 1 log10 IU/ml. Another study which compared HBV monotherapy (3TC) to dual therapy (TDF-3TC) in non-pregnant women with HIV and HBV similarly found little difference in HBV VL decline[29] nor first or second-phase decay of HBV viral load kinetics.[30] Our study adds data from Sub-Saharan African cohorts where HBV genotypes, duration of infection and prevalence of HBeAg are different than Southeast Asian settings yet confirming similar HBV virologic responses. The mean HBV VL decline in HBV-viremic women in the two HBV-active arms of 1.86 and 1.89 $\log_{10}$IU/ml is lower compared to other antepartum HBV monoinfection studies, but this might be due to the overall lower baseline HBV VLs (median $\log_{10}$HBV VL 2.58 $\log_{10}$IU/ml in all, 3.18 $\log_{10}$ IU/ml among HBV viremic women). Our results corroborate those of others indicating no difference in virologic decline between short term 3TC-monotherapy and FTC-TDF or 3TC; useful information for counseling in the event of short-term 3TC monotherapy receipt in settings where HBsAg is inadvertently not evaluated or where TDF is contraindicated. Longer term therapy with 3TC monotherapy for HBV, however, should be avoided given the risk of HBV drug resistance.[31]

We found a low incidence of HBV perinatal transmission (1.9%) with no transmissions in the LPV/r+FTC-TDF and no HBV active ART arm but 2 transmissions in the LPV/r+3TC+ZDV arm. Both infants received HBV vaccination. In the two perinatal HBV transmissions, delivery HBV DNA, gestational age at enrollment, and time on therapy at date of delivery of participant A was 17 million IU/ml, 26.14 weeks gestational age, and 8.9 weeks of therapy and for participant B was 556 IU/ml, 22.49 weeks gestational age, and 14.6 weeks of therapy. Overall, this report reiterates the fact that HBV perinatal transmission can occur when 3TC is the single HBV-active agent, as others have reported.[32, 33] and

raises the question of whether earlier initiation of HBV antiviral therapy could have further reduced the risk of transmission.

In pregnant women with HIV/HBV coinfection initiating HBV-active ART in the antepartum period, the incidence of grade 3 or 4 ALT or AST elevations was 4–6%. This is notable given the absence of grade 3 or 4 ALT/AST elevations in other studies during antiviral therapy in pregnant women living with HBV, but without HIV coinfection.[11, 12] This raises the question of whether these antepartum ALT elevations are markers for immune reconstitution in persons living with HIV PLWH. Immune reconstitution, which results in immunologic restoration of CD4 T cells, is defined as the paradoxical worsening of infectious diseases processes and markers congruent with initiation of antiretroviral therapy.[34, 35, 36] In HBV infection, a similar process is thought to be associated with immunologic control of chronic HBV infection.

Consistent with a possibility of immune reconstitution, we observed a high rate of HBeAg loss (44.4%) and anti-HBe gain (28.2%) at delivery, including with non-HBV ART. Elevated rates of HBeAg loss, compared to matched non-pregnant controls, have been observed in peripartum women; in one study from China, 14.3% of women experienced HBeAg loss, but this was across the antepartum and post- pregnancy periods.[37] Although these are small numbers, these elevated rates of HBeAg loss are noteworthy and raise the question of accelerated immune restoration, as has been seen with higher rates of HBsAg loss in larger HIV/HBV coinfected cohorts.[38–43]

Our small sample size of PROMISE participants identified with HBV/HIV co-infection limits our ability to fully evaluate the effect of 3TC vs FTC-TDF HBV active regimens on antiviral efficacy and transmission. In addition, this study was performed in sub-Saharan Africa where specific HBV phenotypes differ from other regions and limit its generalizability to other populations. However, this study addresses an important knowledge gap as it is one of the few randomized studies in pregnant women with HIV and HBV in Sub-Saharan Africa. Finally, we cannot exclude the possibility that there was an alternative etiology of transaminase elevations, namely lopinavir/ritonavir, as has been associated in persons living with HIV and hepatitis C.[44]

In conclusion, we found that HBV-active therapy was well tolerated in pregnant women with HIV. There was no difference between HBV viral load declines between short course FTC-TDF and 3TC-based ART, although longer term therapy with a TDF-containing regimen is preferred to prevent HBV drug resistance. Perinatal transmission was rare but did occur when 3TC was the only HBV agent. Notably, there was a high probability of HBeAg seroconversion across all arms, raising the question of whether the peripartum period in HIV/HBV coinfection is an opportune time to examine immunologic responses to HBV therapy.

Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No*.

What data in particular will be shared? *Not available*.

What other documents will be available? *Not available*.

When will data be available (start and end dates)? *Not applicable*.

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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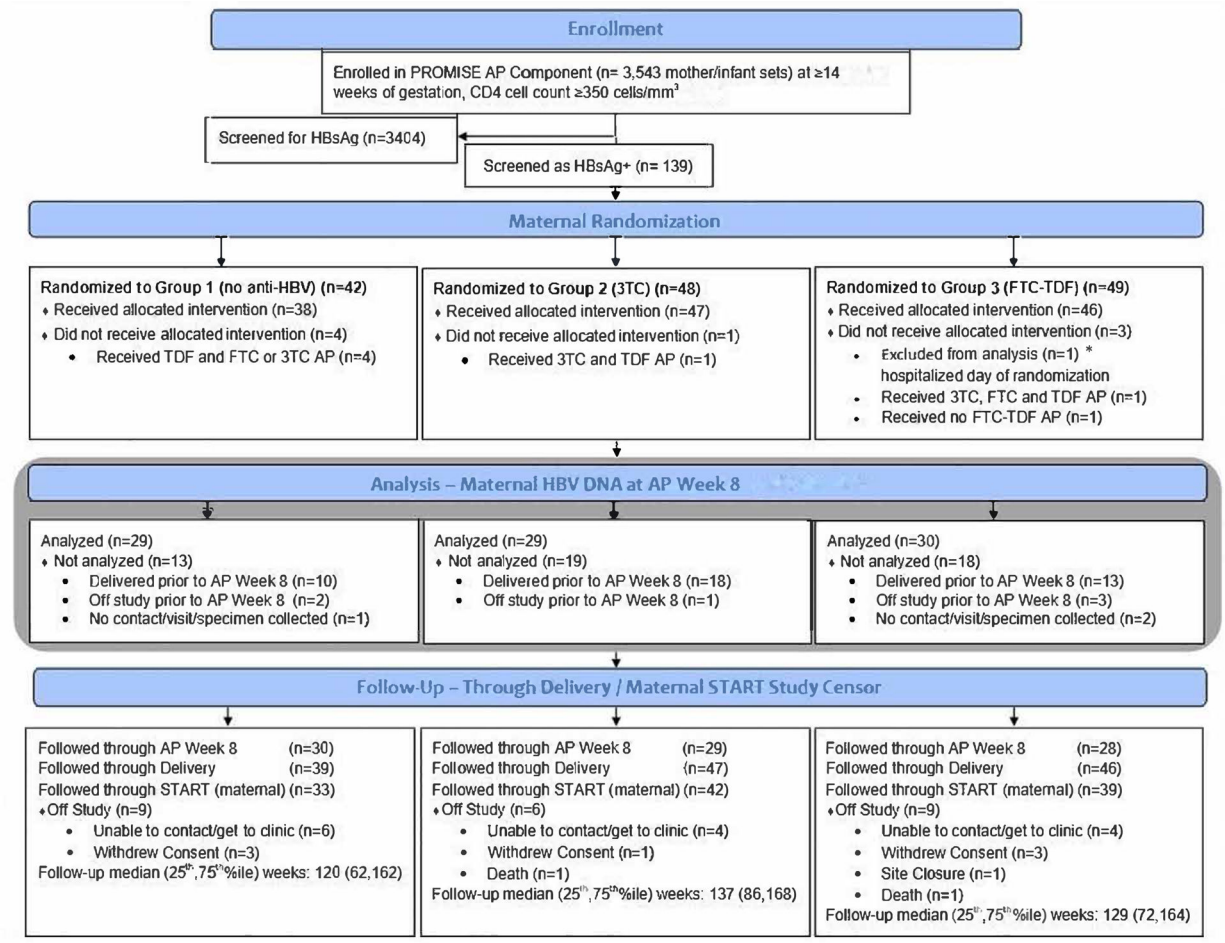
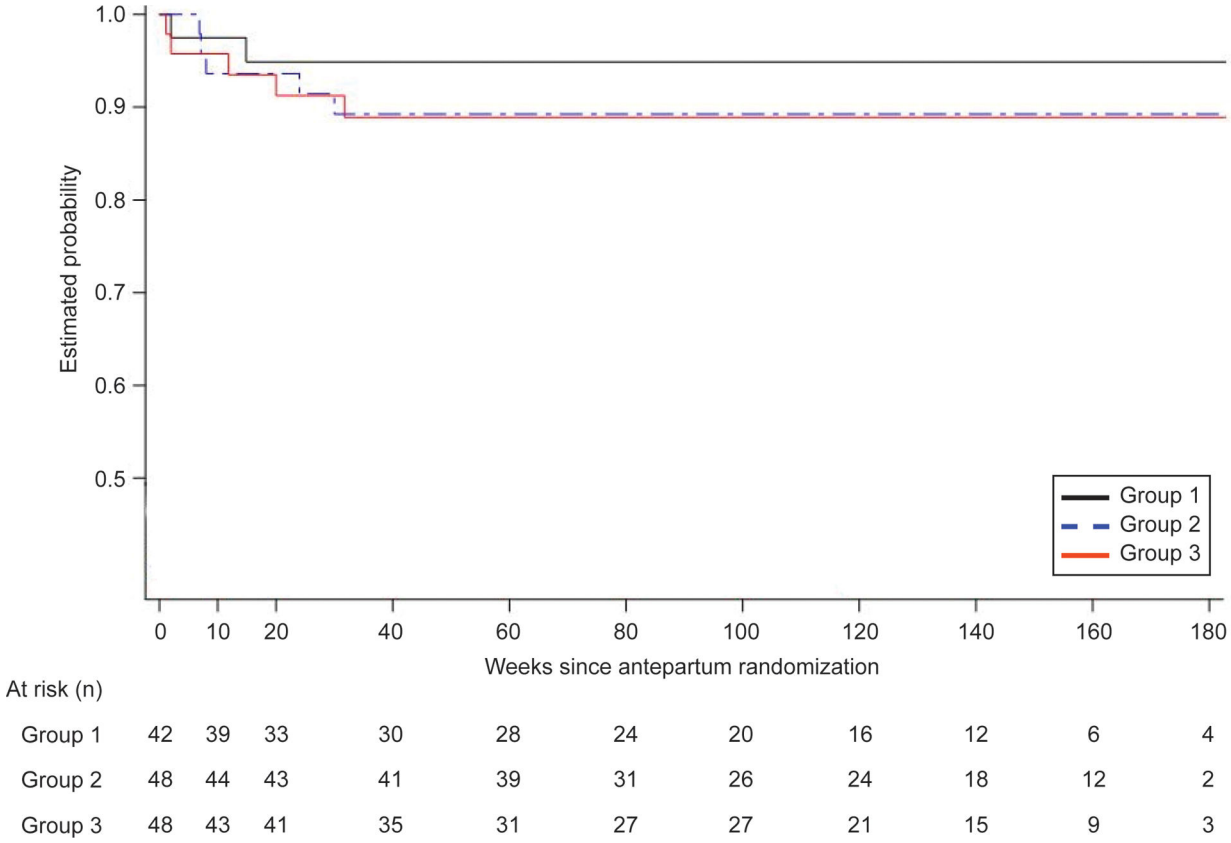


Figure 1:

Flowchart. *Excluded from all subsequent analyses. PROMISE, Promoting Maternal and Infant Survival Everywhere; AP, antepartum; HBsAg, surface antigen of the hepatitis B virus; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; 3TC, lamivudine; AP Week 8, antepartum study week 8; START, Strategic Timing of Antiretroviral Therapy.



At risk (n)											
Group 1	42	39	33	30	28	24	20	16	12	6	4
Group 2	48	44	43	41	39	31	26	24	18	12	2
Group 3	48	43	41	35	31	27	27	21	15	9	3

Figure 2:

Time to first maternal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) grade 3 or 4. Time to event censored at earlier of off study date and July 6, 2015. Group 1: no anti-hepatitis B virus; Group 2: 3TC (lamivudine); Group 3: FTC (emtricitabine)–TDF (tenofovir disoproxil fumarate).

Table 1.

Baseline Maternal Demographic and Clinical Factors

		Antepartum (AP) Randomization Arm			
		Group 1 no anti-HBV (N=42)	**Group 2 LPV/r+ 3TC+ZDV (N=48)**	**Group 3 LPV/r + FTC-TDF (N=48)**	**Total (N=138)**
Country	South Africa	9 (21.4%)	14 (29.2%)	12 (25.0%)	35 (25.4%)
	Malawi	19 (45.2%)	20 (41.7%)	22 (45.8%)	61 (44.2%)
	Zambia	1 (2.4%)	2 (4.2%)	1 (2.1%)	4 (2.9%)
	Uganda	4 (9.5%)	4 (8.3%)	5 (10.4%)	13 (9.4%)
	Zimbabwe	7 (16.7%)	6 (12.5%)	8 (16.7%)	21 (15.2%)
	Tanzania	2 (4.8%)	2 (4.2%)	0 (0.0%)	4 (2.9%)
Age (years)	Median (Q1–Q3)	24 (21–29)	28 (24–31)	28 (25–30)	27 (23–30)
Gestational age at AP Entry (Weeks)	Median (Q1–Q3)	28 (23–32)	25 (22–31)	26 (21–31)	27 (22–31)
	< 14	0 (0.0%)	1 (2.1%)	0 (0%)	1 (0.7%)
	14 - < 28	21 (50.0%)	27 (57.4%)	27 (56%)	75 (54.7%)
	28 - <34	14 (33.3%)	13 (27.7%)	11 (23%)	38 (27.7%)
	34 - <37	4 (9.5%)	4 (8.5%)	7 (15%)	15 (10.9%)
	≥ 37	3 (7.1%)	2 (4.3%)	3 (6%)	8 (5.8%)
CD4+ Cell Count (cells/mm3)	Median (Q1–Q3)	506 (420–695)	507 (433–620)	496 (420–607)	505 (420–634)
Log_{10}HIV RNA (copies/mL)	Median (Q1–Q3)	3.8 (3.2–4.6)	4.1 (3.3–4.5)	4.0 (3.3–4.6)	4.0 (3.2–4.5)
Log_{10}HBV DNA VL (IU/mL)	Median (Q1–Q3)	2.47 (1.30–7.61) (N=40)	2.62 (1.45–5.79) (N=48)	2.55 (1.89–4.15) (N=46)	2.58 (1.38–5.34) (n=134)
Log_{10}HBV VL<20 IU/ml >200,000 IU/ml		12 (30.0%) 11 (27.5%)	12 (25.0%) 12 (25.0%)	8 (17.4%) 11 (23.9%)	32 (23.9%) 34 (25.4%)
HBeAg status	Negative	28/41 (68.3%)	33/44 (75.0%)	36/46 (78.2%)	97/131 (74.0%)
Anti-HBe status	Positive	21/36 (58.3%)	23/38 (60.5%)	25/41 (61.0%)	69/115 (60.0%)
TB Medications	Yes	3 (7.1%)	5 (10.4%)	5 (10.4%)	13 (9.4%)
ALT (IU/L)	Median (Q1–Q3)	14.5 (12–26)	14.5 (12–20.5)	15 (10.5–18.5)	15 (11–21)
AST to Platelet Ratio Index (APRI)	Median (Q1–Q3)	0.32 (0.16–0.45)	0.30 (0.24–0.36)	0.30 (0.20–0.41)	0.30 (0.21–0.41)
Fibrosis-4 (FIB-4)	Median (Q1–Q3)	0.72 (0.44–0.89)	0.72 (0.58–0.80)	0.72 (0.56–0.94)	0.72 (0.56–0.89)

ART in Group 1 comprised no HBV active therapy and was comprised of zidovudine (ZDV) and intrapartum nevirapine. All women in Group 1 also received one week of daily emtricitabine (FTC) and tenofovir diisoproxyl fumarate (TDF). ART in Group 2 comprised single active HBV therapy and was comprised of 3TC, ZDV, and Lopinavir/ritonavir (LPV/r); 3TC is the single HBV active agent. ART in Group 3 comprised dual active HBV therapy and was comprised of 3TC, FTC, and LPV/r; 3TC and FTC are the two HBV active agents. HBV active agents are underlined in the table. One participant in Group 2 had missing data for gestational age at entry.

Table 2.

Maternal Clinical Outcomes During the Antepartum Period.

		Antepartum Randomization Arm			Mean Difference (95% CI), P-value*/ Estimated Odds Ratio (95% CI), P-value*		
Timepoint		**Group 1 No anti-HBV (N=42)**	**Group 2 LPV/r+ 3TC+ZDV (N=48)**	**Group 3 LPV/r + FTC-TDF (N=48)**	**Group 2 vs Group 1 (ref)**	**Group 3 vs Group 1 (Ref).**	**(Primary) Group 3 vs Group 2 (Ref)**
				ALT			
	Mean ALT (IU/L)						
AP Week 8 (all)		18.92 [13.00, 24.84]† N=29	23.77 [11.75, 35.80]† N=28	25.34 [17.30, 33.39]† N=29	−4.85 (−18.06, 8.36) 0.46	−6.42 (−16.21, 3.36) 0.19	−1.57 (−15.76, 12.62) 0.82
Delivery (all)		21.97 [17.93, 26.02]† N=35	37.95 [20.18, 55.71]† N=44	36.91 [21.54, 52.28]† N=45	−15.97 (−34.14, 2.19) 0.083	−14.94 (−30.77, 0.90) 0.064	1.04 (−22.13, 24.20) 0.93
	Mean change from BL ALT (IU/L)						
AP Week 8 (all)		0.00 [−5.22, 5.22]† N=29	3.89 [−6.51, 14.28]† N=28	9.10 [2.86, 15.35]† N=29	−3.89 (−15.35, 7.58) 0.50	−9.10 (−17.07, −1.14) 0.026	−5.22 (−17.13, 6.70) 0.38
Delivery (all)		4.00 [−1.11, 9.12]† N=35	21.14 [4.34, 37.94]† N=44	20.16 [5.19, 35.12]† N=45	−17.14 (−34.61, 0.34) 0.054	−16.15 (−31.87, −0.43) 0.044	0.98 (−21.20, 23.17) 0.93
				AST			
	Mean AST (IU/L)						
AP Week 8 (all)		30.88 [19.91, 41.84]† N=17	33.10 [17.51, 48.68]† N=22	34.80 [22.77, 46.83]† N=20	−2.22 (−20.70, 16.26) 0.81	−3.92 (−19.62, 11.77) 0.61	−1.70 (−20.82, 17.41) 0.86
Delivery (all)		34.41 [27.31, 41.51]† N=28	45.14 [28.66, 61.62]† N=37	47.17 [30.82, 63.51]† N=42	−10.73 (−28.48, 7.03) 0.23	−12.76 (−30.40, 4.89) 0.15	−2.03 (−24.87, 20.81) 0.86
	Mean change from BL AST (IU/L)						
AP Week 8 (all)		−0.94 [−8.61, 6.73]† N=13	5.31 [−11.98, 22.60]† N=17	12.00 [1.12, 22.88]† N=19	−6.25 (−24.69, 12.19) 0.49	−12.94 (−25.74, −0.14) 0.048	−6.69 (−26.49, 13.12) 0.49
Delivery (all)		11.59 [0.19, 22.99]† N=21	20.38 [−2.60, 43.37]† N=27	23.41 [4.88, 41.93]† N=37	−8.79 (−34.00, 16.42) 0.48	−11.81 (−33.16, 9.53) 0.27	−3.02 (−31.96, 25.91) 0.83
				Anemia			
Delivery (all)		28.6% (10/35) [16.3, 45.1]†	31.1% (14/45) [19.5, 45.7]†	15.6% (7/45) [7.7, 28.8]†	1.13 (0.39, 3.37) >0.99	0.46 (0.13, 1.56) 0.18	0.41 (0.12, 1.25) 0.13
				HBV VL			
	Mean change from BL in HBV VL						

		Antepartum Randomization Arm			Mean Difference (95% CI), P-value*/ Estimated Odds Ratio (95% CI), P-value*		
Timepoint		**Group 1 No anti-HBV (N=42)**	**Group 2 LPV/r+ 3TC+ZDV (N=48)**	**Group 3 LPV/r + FTC-TDF (N=48)**	**Group 2 vs Group 1 (ref)**	**Group 3 vs Group 1 (Ref).**	**(Primary) Group 3 vs Group 2 (Ref)**
	Log_{10}(IU/ml)**						
AP Week 8*		−0.26 [−0.54, 0.02]† N=19	−1.86 [−2.49, 1.23]† N=22	−1.89 [−2.61, 1.18]† N=22	1.60 (0.92, 2.28) <0.001	1.64 (0.88, 2.39) <0.001	0.03 (−0.89, 0.96) 0.94
	Proportion <20 IU/ml						
AP Week 8*		10.5% (2/19) [2.9%, 31.4%]†	54.5% (12/22) [34.7%, 73.1%]†	59.1% (13/22) [38.7%, 76.7%]†	10.20 (1.64, 105.73) 0.004	12.28 (1.96, 126.89) 0.003	1.20 (0.31, 4.68) >0.99
Delivery*		9.5% (2/21) [2.7%, 28.9%]	43.8% (14/32) [28.2%, 60.7%]	55.9% (19/34) [39.5%, 71.1%]	7.39 (1.34, 73.46) 0.013	12.03 (2.22, 117.37) <0.001	1.63 (0.55, 4.82) 0.46
Delivery (all)		26.7% (8/30) [14.2%, 44.4%]†	48.8% (20/41) [34.3%, 63.5%]†	60.0% (24/40) [44.6%, 73.7%]†	2.62 (0.86, 8.36) 0.086	4.13 (1.33, 13.30) 0.008	1.58 (0.60, 4.17) 0.37
		HBeAg loss and anti-HBe gain					
Delivery $	HBeAg loss	50.0% (4/8)	40.0% (4/10)	44.4% (4/9)	0.67 (0.07, 6.23) >0.99	0.80 (0.08, 7.80) >0.99	1.20 (0.14, 10.54) >0.99
Delivery	anti-HBe gain	36.4% (4/11)	23.1% (3/13)	26.7% (4/15)	0.53 (0.06, 4.35) 0.66	0.64 (0.09, 4.75) 0.68	1.21 (0.16, 10.34) >0.99
		HIV RNA and CD4					
Delivery (all)	Proportion with HIV RNA <400 copies/ml	47.1% [31.5, 63.3]† N=34	61.7% [47.4, 74.2]† N=47	68.9% [54.3, 80.5]† N=45	1.81 (0.68, 4.87) 0.26	2.49 (0.90, 6.94) 0.065	1.37 (0.53, 3.57) 0.52
Delivery (all)	Mean CD4 count change from BL (cells/mm^3)	163 [103, 223]† N=36	219 [154, 284]† N=41	214 [127, 302]† N=43	−56 (−143, 31) 0.20	−52 (−156, 53) 0.33	5 (−103, 112) 0.93

ART in Group 1 comprised no HBV active therapy and was comprised of zidovudine (ZDV) and intrapartum nevirapine. All women in Group 1 also received one week of daily emtricitabine (FTC) and tenofovir diisoproxyl fumarate (TDF). ART in Group 2 comprised single active HBV therapy and was comprised of 3TC, ZDV, and Lopinavir/ritonavir (LPV/r); 3TC is the single HBV active agent. ART in Group 3 comprised dual active HBV therapy and was comprised of 3TC, FTC, and LPV/r; 3TC and FTC are the two HBV active agents. HBV active agents are underlined in the table.

† 95% confidence interval

* Among those with HBV VL ≥20 at baseline,

** values below assay quantification limit set to 20 IU/ml;

$ Among those with HBeAg and anti-HBe data at baseline

Table 3.

Maternal Adverse Events Grade ≥ 2 Across Antepartum and Post- Pregnancy.

	Antepartum Randomization Arm		
	Group 1 No anti-HBV (N=42)	**Group 2 LPV/r+ 3TC+ZDV (N=48)**	**Group 3 LPV/r + FTC-TDF (N=48)**
Any grade ≥ 2 adverse event	24 (57.1%)	34 (70.8%)	38 (79.2%)
Hematology-Hemoglobin	5 (11.9%)	9 (18.8%)	4 (8.3%)
Hematology-Absolute Neutrophil Count	5 (11.9%)	9 (18.8%)	9 (18.8%)
Liver/Hepatic			
ALT (SGPT)	4 (9.5%)	7 (14.6%)	13 (27.1%)
AST (SGOT)	6 (14.3%)	6 (12.5%)	10 (20.8%)
Total Bilirubin	0 (0.0%)	2 (4.2%)	0 (0.0%)
Renal-Creatinine	0 (0.0%)	2 (4.2%)	1 (2.1%)
Chemistry-Albumin	19 (45.2%)	25 (52.1%)	24 (50.0%)

ART in Group 1 comprised no HBV active therapy and was comprised of zidovudine (ZDV) and intrapartum nevirapine. All women in Group 1 also received one week of daily emtricitabine (FTC) and tenofovir diisoproxyl fumarate (TDF). ART in Group 2 comprised single active HBV therapy and was comprised of 3TC, ZDV, and Lopinavir/ritonavir (LPV/r); 3TC is the single HBV active agent. ART in Group 3 comprised dual active HBV therapy and was comprised of 3TC, FTC, and LPV/r; 3TC and FTC are the two HBV active agents. HBV active agents are underlined in the table.

Table 4.

Maternal Grade 3 or 4 ALT or AST Elevations Antepartum (AP) and Post- Pregnancy

				Hazard Ratio (95% CI), Logrank P-value		
AP Randomization arm	Cumulative Events	Total Person Years (PY)	Incidence Rate (95% CI) per 100 PY	. Group 2 (LPV/r+3TC+ZDV)) vsGroup 1 (no anti-HBV) (Ref)	Group 3 (LPV/r + FTC-TDF) vs Group 1 (no-anti HBV) (Ref)	(Primary) Group 3 (LPV/r + FTC-TDF) vs. Group 2 (LPV/r+3TC+ZDV) (Ref)
Group 1 No anti-HBV	2	74.96	2.7 (0.7, 9.8)	2.05 (0.44, 14.31), 0.38	2.15 (0.46, 15.01), 0.35	1.05 (0.29, 3.77), 0.94
Group 2 3TC	5	99.09	5.1 (2.2, 11.5)			
Group 3 FTC-TDF	5	89.30	5.6 (2.5, 12.8)			
Maternal Grade 3 or 4 ALT or AST Elevations in Antepartum Alone						
Group 1 No anti-HBV	1	8.96	11.2 (3.5, 36.0)	1.52 (0.14, 33.06), 0.73	2.45 (0.31, 49.41), 0.42	2.80 (0.36, 56.68), 0.35
Group 2 3TC	2	9.85	20.3 (8.9, 46.5)			
Group 3 FTC-TDF	3	10.41	28.8 (14.7, 56.7)			

ART in Group 1 comprised no HBV active therapy and was comprised of zidovudine (ZDV) and intrapartum nevirapine. All women in Group 1 also received one week of daily emtricitabine (FTC) and tenofovir diisoproxyl fumarate (TDF). ART in Group 2 comprised single active HBV therapy and was comprised of 3TC, ZDV, and Lopinavir/ritonavir (LPV/r); 3TC is the single HBV active agent. ART in Group 3 comprised dual active HBV therapy and was comprised of 3TC, FTC, and LPV/r; 3TC and FTC are the two HBV active agents. HBV active agents are underlined in the table.