Safety And HBV Efficacy Of Antiretroviral Therapy In Women With HIV And HBV In The Promoting Maternal And Infant Survival Everywhere Study (PROMISE)

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Background

- HBV coinfection occurs in 3-12% of pregnant women living with HIV in Sub-Saharan Africa[1-5]
- WHO recommends antiretroviral therapy (ART) in pregnant women infected with HIV and HBV[6] and ART in women with HBV monoinfection[7]
- ART generally considered safe in pregnancy
- There is little data regarding efficacy of antepartum therapy in HIV/HBV coinfection, particularly for shorter courses of therapy
- Objectives
  - Assess HBV viral load change between 3 different antepartum (AP) strategies at week 8 (efficacy)
    - No HBV active ART (no anti-HBV), ART with 3TC alone as HBV active agent (3TC), and ART with TDF-FTC (TDF-FTC)
  - Assess safety between these strategies: hepatotoxicity and anemia

Methods

- PROMISE: multicenter randomized trial of ART strategies in women living with HIV (Figure 1). Pregnant women living with HIV and who were ART naïve with CD4>350 and ALT< 2.5 ULN were assigned to AP and postpartum (PP) ART strategies to assess HIV vertical transmission, safety, and maternal disease progression. Sites participated between 4/2011-9/2016
- In a substudy, women with HIV and HBV were randomized to receive: ZDV only (no anti-HBV), ZDV+3TC+LPV/r (3TC-ZDV), or FTC+TDF+LPVr (TDF-FTC)
- Primary Outcome: HBV VL change from baseline (BL) at 8 weeks AP among HBV viremic (>20 IU/ml) women
- Primary Comparison Analysis: for the HBV active arms; women who entered the study with HBV DNA ≥20 IU/ml and who had not delivered by AP week 8
- Safety Assessments: alanine transaminase (ALT), aspartate aminotransferase (AST), and anemia (Hgb <10 g/dl)
- Pairwise comparisons applied t-tests and Fisher's exact tests
- Time-to-event analyses were censored at the earlier of last clinic visit, last relevant laboratory measurement with data available, or end follow-up period for the specific analysis (e.g. through labor/delivery (visit))
- DAIDS Toxicity Scale v2.0 was used to grade adverse events

Results

- Between April 2011-October 2014, 3543 women were randomized in the parent trial, 3.9% (138) were HBsAg+ (Table 1)
- Among 138 women, 42 received ZDV only, 48 received 3TC-ZDV, and 48 received TDF-FTC
- Median BL age was 27 years, 74% (97/138) of women were HBeAg (-), Median HBV VL was 2.58 $\log_{10}$ IU/ml, 24% (32/138) of women had HBV VL <20 IU/ml

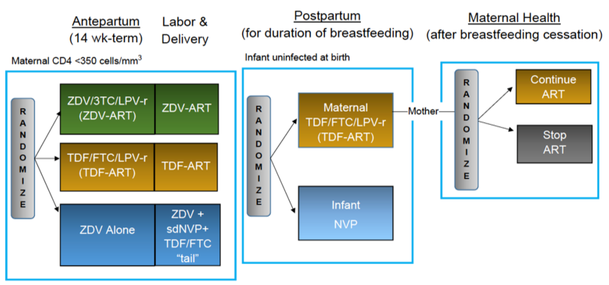


Figure 1. Study Method Arms. AP randomization: HIV+ women enrolled at 14 weeks gestation or later to one of 3 regimens: ZDV plus intrapartum single-dose NVP with 6 to 14 days of TDF and FTC PP (no anti-HBV); ZDV, 3TC, and LPV/r (3TC-ZDV); or TDF, FTC, and LPV/r (TDF-FTC). All regimens continued through 6 to 14 days PP. All infants received NVP through 6 weeks PP per WHO. PP randomization differed by breast-feeding status; breastfeeding women randomized to daily maternal ART or daily infant NVP prophylaxis. At cessation of breastfeeding, mothers on ART in the PP component enrolled into "maternal health" component and randomized to either continue ART or stop ART. Formula-feeding women: randomized to stop or continue ART at delivery. Breast- feeding and formula-feeding settings began enrollment in April and July 2011, respectively.

Results

HBV VL Reduction

- Among 63 (60%) of 105 women with BL HBV >20 IU/ml and measured at AP week 8, the mean change from BL HBV VL was -0.26 , and -1.86 and -1.89 log (IU/ml) in the ZDV (n=19), 3TC-ZDV (n=22) and FTC-TDF (n=22) arms (Table 2)
- Mean HBV VL decline was significantly smaller in the ZDV vs. each of 3TC-ZDV and FTC-TDF arms (mean difference 1.60 and 1.64 ($\log_{10}$ (IU/ml), p<0.001 each), and did not differ between 3TC-ZDV and FTC-TDF arms (0.03, p=0.94)
- At AP week 8, HBV VL was < 20 IU/ml in 2 (11%) women in the ZDV arm, and 12 (55%) and 13 (59%) women in 3TC-ZDV and FTC-TDF arms (p=0.004, p=0.003, p>0.99) (Table 2)

Table 1. Baseline Maternal Demographic and Clinical Factors

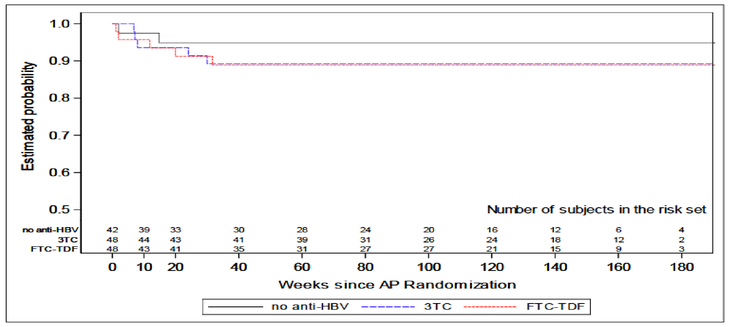
		AP Randomization Arm			
		no anti-HBV (N=42)	3TC (N=48)	TDF-FTC (N=48)	Total (N=138)
Country	South Africa	9 (21%)	14 (29%)	12 (25%)	35 (25%)
	Malawi	19 (45%)	20 (42%)	22 (46%)	61 (44%)
	Zambia	1 (2%)	2 (4%)	1 (2%)	4 (3%)
	Uganda	4 (10%)	4 (8%)	5 (10%)	13 (9%)
	Zimbabwe	7 (17%)	6 (13%)	8 (17%)	21 (15%)
	Tanzania	2 (5%)	2 (4%)	0 (0%)	4 (3%)
Race	Asian (from Indian subcontinent)	1 (2%)	0 (0%)	0 (0%)	1 (1%)
	Black African	41 (98%)	48 (100%)	48 (100%)	137 (99%)
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%)	1 (2%)	0 (0%)	1 (1%)
	14 - < 28	21 (50%)	27 (57%)	27 (56%)	75 (55%)
	34 - <37	4 (10%)	4 (9%)	7 (15%)	15 (11%)
	≥ 37	0 (0%)	1 (2%)	0 (0%)	1 (1%)
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)
TB Medications	Yes	3 (7%)	5 (10%)	5 (10%)	13 (9%)
ALT (IU/L)	Median (Q1-Q3)	14.50 (12.00-26.00)	14.50 (12.00-20.50)	15.00 (10.50-18.50)	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)

Table 2. Maternal HBV Viral Load Decline

Timepoint (Population)	HBV DNA $\log_{10}$(IU/ml)	no anti-HBV (N=42)	3TC (N=48)	TDF-FTC (N=48)
AP Week 8 (women with BL >20 IU/ml)	Mean change from BL in HBV DNA	-0.26	-1.86	-1.89
	Proportion <20 IU/ml	11% (2/19)	55% (12/22)	59% (13/22)
Delivery (randomized women)	Proportion <20 IU/ml	27% (8/30)	49% (20/41)	60% (24/40)

Results

Figure 2. Time to First Maternal AL or AST Grade 3 or 4



Hepatotoxicity

- Grade 3 or 4 ALT/AST elevations were reported on 12 of 138 women
  - 2 (5%) in the ZDV
  - 5 (10%) each in the 3TC-ZDV and FTC-TDF arms (p>=0.35)
  - Events occurred between 1 and 32 weeks post AP Entry date

Table 3. Maternal Hepatotoxic Events

AP Randomization arm	Cumulative Events	Incidence Rate (95% CI) per 100 PY
No anti-HBV	2	2.7 (0.7, 9.8)
3TC	5	5.1 (2.2, 11.5)
FTC-TDF	5	5.6 (2.5, 12.8)

Table 4. Time to ALT or AST Grade 3 or 4 Comparisons

Hazard Ratio (95%) CI, Log rank P-value		
No anti-HBV (Ref) vs. 3TC	No anti-HBV (Ref) vs. FTC-TDF	(Primary) 3TC (Ref) vs. FTC-TDF
2.05 (0.44, 14.31), 0.38	2.15 (0.46, 15.01), 0.35	1.05 (0.29, 3.77), 0.94

Table 5. Comparisons of Maternal Anemia

No anti-HBV	3TC	FTC-TDF
10 (29%)	14 (31%)	7 (16%)

Conclusions

- Antepartum ART with HBV activity was superior for HBV VL reduction to no-HBV active ART
- No statistically sig difference between 3TC and FTC-TDF ART in HBV VL decline at 8 weeks or proportion undetectable HBV VL at delivery
- Numerically higher proportion of ALT/AST elevations in HBV-active ART arms, but not statistically significant
- HBV-ART was well tolerated in pregnancy with ZDV-containing therapy resulting in a higher incidence of anemia

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