Infant Outcomes in HIV/Hepatitis B Co-Infected Women Initiating ART in the Promoting Maternal and Infant Survival Everywhere Study Flavia

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Background

- HBV infection affects 3-12% of HIV infected pregnant women in Sub-Saharan Africa[1,2]
- Despite its wide spread use[3], there is limited data on the impact of tenofovir -based antiretroviral treatment (ART) on infant outcomes in HIV/HBV co- infected women
- We compared adverse outcomes through two years post-partum among HIV/HBV co-infected women randomized to a variety of perinatal transmission ART regimens in the PROMISE study.

Methods

- PROMISE enrolled pregnant women living with HIV who were ART-naive from 14 sites in Africa and India who had not met criteria for initiating ART at the time the study was conducted (enrolled 2011 to 2014, follow-up through September 2016).
- Women at ≥14 weeks gestation with high CD4 cell count (>350) and HBV were randomized to either, **Arm A: ZDV alone (no anti-HBV), Arm B: 3TC+ZDV+LPV/r (3TC), or Arm C: FTC+TDF+LPV/r (FTC-TDF).**
- Pairwise group comparisons of pregnancy, delivery, and time-to-event outcome measures were carried out with Fisher's exact, t-tests, and log rank tests.
- The adverse pregnancy outcome was a composite of low birth weight (< 2500g), preterm delivery (< 37 weeks), spontaneous abortion (<20 weeks), stillbirth (≥20 weeks) or a congenital anomaly.
- Adverse outcomes were graded per the DAIDS toxicity table (Grade 3=severe, Grade 4=potentially life threatening) [4]

Results

Table 1: Maternal Baseline Characteristics

Variable (Median, 25th 75th percentile) or proportion	Total (N=138)	No anti-HBV (n=42)	3TC (n=48)	FTC-TDF (n=48)
Age (years)	27 (23,30)	24 (21,29)	28 (24,31)	28 (25,30)
Gestational age at entry (weeks)	27 (22,31)	28 (23,32)	25 (22,31)	26 (21,31)
CD4 (cells/mm3)	505 (420,634)	506 (420,695)	507 (433,620)	496 (420,607)
HIV RNA (10 Log_{10} copies/ml)	4.0 (3.2, 4.5)	3.8 (3.2,4.6)	4.1 (3.3,4.5)	4.0 (3.3,4.6)
HBV DNA (10 Log10 IU/ml)	2.6 (1.4,5.3)	2.5 (1.3,7.6)	2.6(1.5,5.8)	2.6 (1.9,4.2)
Detectable HBV DNA Viral Load (≥20 IU)/ml)	102 (76%)	28 (70%)	36 (75%)	38 (83%)

Results

- Of the 3,543 women randomized in PROMISE, 138 were HBV co-infected (Table 1), and had 128 live births.

Maternal outcomes

- Arms did not significantly differ in the adverse pregnancy outcomes, with 26%, 38%, 35% events in the no anti-HBV, 3TC and FTC-TDF arms, p>=0.25 (Table 2).

Infant outcomes

- Through 2 years, death occurred among 2 (5%) infants in the no anti-HBV, 3 (7%) in 3TC, and 6 (13%) in FTC-TDF arms (Figure 1).
- The risk of a grade 3 or 4 infant events was not significantly different in no anti-HBV vs 3TC arms (hazard ratio (HR) 1.6, 95% CI: (0.8, 3.2), p=0.17)), no anti-HBV vs FTC-TDF (1.2 (0.7, 2.4), p=0.51)), or 3TC vs FTC-TDF arms (0.8 (0.4,1.5), p=0.49)).
- There were no significant differences in time to HIV- free survival, or mean WHO Z-score length-for-age, and head circumference at birth or one year.
- Infants in the 3TC arm had lower mean hemoglobin level at birth vs those in FTC-TDF (-1.3 g/dl, 95% CI: -2.3, -0.4, p<0.05) but not vs no anti- HBV arm (-0.8 g/dl, 95%CI: -1.8, 0.2, p=0.12); or the FTC-TDF vs no anti- HBV arm (0.5 g/dl 95%CI: -0.4,1.5, p=0.25, Figure 2).

Figure 1: Time to infant death

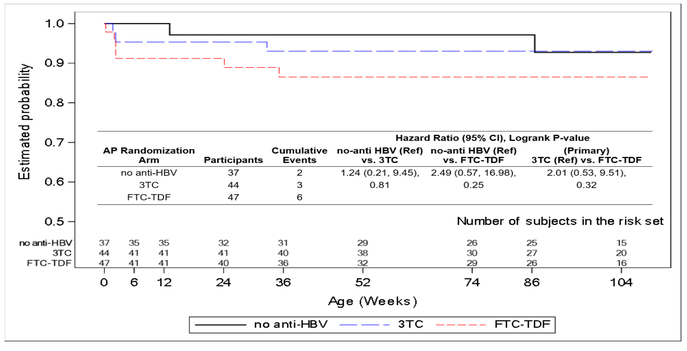
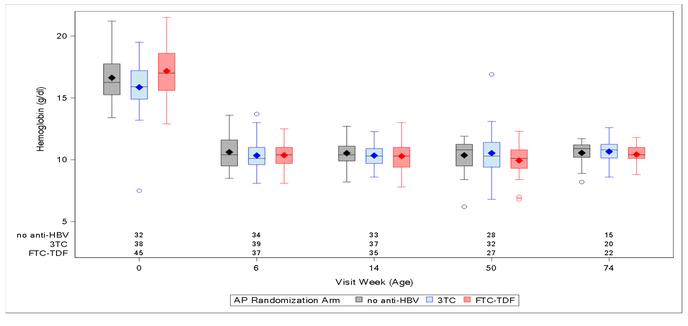


Figure 2: Infant Hemoglobin Distributions from Birth



Results

Table 2: Pregnancy Outcomes among HIV/HBV co-infected Women

Variable		no anti-HBV (N=39)	3TC N=47	FTC-TDF N=46
Number of infants	Singleton	39 (100%)	47 (100%)	45 (98%)
	Twins**	0 (0%)	0(0%)	1 (2%)
Any adverse Pregnancy outcome	No	29 (74%)	29 (62%)	30 (65%)
	Yes	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)
Outcome of delivery	Live Birth	37(95%)	44(94%)	46(100%)
	Stillbirth (IUFD ≥ 20 wks)	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)
Preterm delivery (<37 week)*	No	33 (89%)	35 (80%)	33 (72%)
	Yes	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)
Low birth weight (<2500 grams)*	No	31 (84%)	35 (80%)	38 (83%)
	Yes	6 (16%)	9 (20%)	8 (17%)
	Prob. LBW (95% CI)	(7.7, 31.1)	20.5%(11.2,34.5)	17.4% (9.1, 30.7)
Congenital anomaly	Yes	1 (3%)	1 (2%)	1 (2%)
	No	36 (97%)	43 (98%)	45 (98%)

*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, *Live birth infant only, **Both twins were preterm live births, with low birth weight, ***This was reported as severe congenital anaomaly: congenital cataract.*

Conclusions

- Use of 3TC+ZDV+LPV/r in HIV/HBV co-infected women resulted in lower infant hemoglobin at birth compared to FTC+TDF+LPV/r .
- As was observed in the overall PROMISE study[5], infant mortality was highest with FTC+TDF+LPV/r although the mechanism is still unknown and the HBV substudy sample size was small.
- Future research should evaluate the safety of other ART regimens in pregnant women with HIV/HBV coinfection.

References

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