Poster #720

TDF PROPHYLAXIS FOR PMTCT OF HBV: EFFECT ON MATERNAL AND INFANT BONE MINERAL DENSITY

CROI Conference on Retroviruses and Opportunistic Infections

Poster Session Presentation: BONE DISEASE - P-N1 on Monday, March 5, 2018, 2:30 PM-3:30 PM Themed Discussion: BONES OF CONTENTION (TD-09) on Tuesday, March 6, 2018, 1:30 PM-2:30 PM

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Background

- Tenofovir disoproxil fumarate (TDF) is used during pregnancy
- TDF is increasingly used for hepatitis B virus (HBV) mono-infected pregnant women with high HBV DNA levels to prevent mother-to-child transmission (PMTCT) of HBV
- In HIV infected women, TDF may adversely affect maternal and infant bone mineral density (BMD)

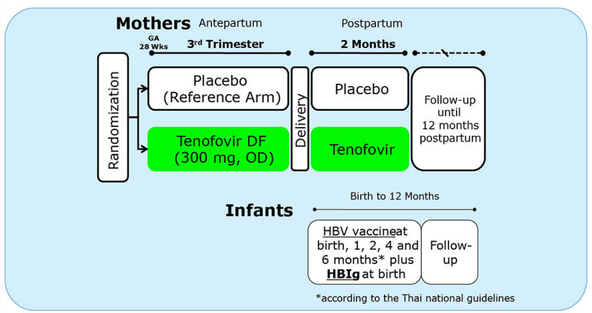
Objective

- Assess one year after delivery/birth the effect of a maternal short course of TDF from 28 weeks' pregnancy to 2 months post partum in hepatitis B chronically infected women on:
  - Maternal total hip and lumbar spine bone mineral density
  - Their infant lumbar spine bone mineral density

Setting

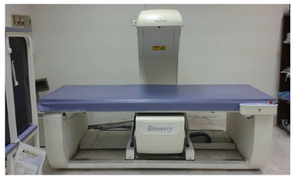
This is a sub-study of the iTAP study, a randomized double-blind, controlled trial of TDF for PMTCT of HBV where HBV chronically infected mothers were randomized to receive TDF or a matching placebo from 28 weeks gestational age (GA) to 2 months postpartum (NCT01745822) in Thailand.
At enrollment, women had: HBeAg+, ALT ≤60 IU/L, creatinine clearance ≥ 50 mL/min.
Breastfeeding was encouraged.

Design of Parent Study (NCT01745822)



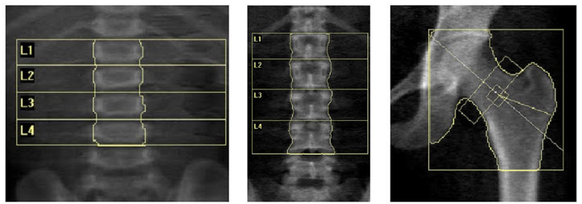
Measurement of Bone Mineral Density (BMD)

- Maternal hip and lumbar spine BMD and infant lumbar spine BMD using dual-energy X-ray absorptiometry (DXA) at three participating institutions.



Picture of one of the DXA machines used (Hologic Discovery A)

- Phantoms were circulated for cross calibration.
- All investigators and operators were blinded to the randomized study treatment
- All DXA scans were centrally reviewed by two experts (BF, WT) for accuracy.



From left to right: DXA scans of infant lumbar spine, maternal lumbar spine and maternal hip

Statistical considerations

- Sample size calculation: at least 45 mother-infant pairs per arm for ≥80% power to detect a 13.5% mean reduction in infant lumbar spine BMD in the TDF arm compared to the placebo (using two-sided Student's t-test at the significance level of 0.05).
- Comparisons of baseline characteristics: Wilcoxon-Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables

Results

- Enrollment (see Figure)
  - 135 mother-infant pairs (69 TDF, 66 placebo)
  - + 5 singleton mothers (2 TDF, 3 placebo) who did not come with their infants
  - + 2 singleton infants (1 mother unavailable, on TDF; 1 mother pregnant, not eligible, on placebo)
- Characteristics: see Tables 1 and 2. Maternal and infant characteristics were balanced between arms.
- BMD measurements: see Table 3.
- There were no significant differences between arm for each of the three measurements.

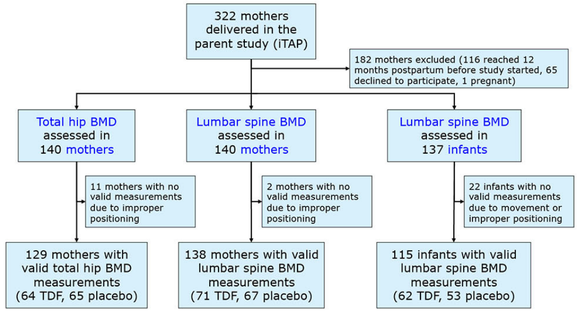


Figure: Participant disposition

Table 1: Maternal characteristics by treatment arm.

Maternal Characteristics	TDF median (IQR)	Placebo median (IQR)	P-value[a]
	N=71	N=69	
At enrollment in parent study:			
Age (years)	25.9 (23.0 to 29.2)	26.7 (23.5 to 29.2)	0.72
Gestational age (weeks)	28.3 (27.9 to 28.6)	28.1 (27.7 to 28.6)	0.12
Height (cm)	158 (153 to 164)	157 (151 to 160)	0.13
Weight (kg)	63 (56 to 72)	62 (54 to 68)	0.21
At delivery:			
Gestational age (weeks)	39.0 (38.4 to 40.1)	39.1 (38.1 to 40.1)	0.97
During postpartum:			
Breastfeeding duration (months)	5.9 (3.0 to 11.7)	6.1 (4.0 to 12.0)	0.14

[a] Wilcoxon-Mann-Whitney test.
Abbreviations: IQR, interquartile range; TDF, tenofovir disoproxil fumarate

Table 2: Infant characteristics by maternal treatment arm.

Infant Characteristics	TDF n (%) or median (IQR)	Placebo n (%) or median (IQR)	P-value[a]
	N=70	N=67	
At birth:			
Male sex	38 (54%)	31 (46%)	0.40
Ballard score	39 (36 to 41) (N=66)	39 (36 to 41) (N=64)	0.84
Preterm	3 (5%) (N=66)	3 (5%) (N=64)	1.00
At BMD assessment:			
Age (weeks)	53.1 (51.5 to 54.8)	52.8 (51.5 to 53.8)	0.08
Weight (kg)	9.0 (8.2 to 9.8)	8.8 (8.2 to 9.8)	0.93
Length (cm)	74 (72 to 76)	74 (72 to 76)	0.78

[a] Wilcoxon-Mann-Whitney test for continuous variables, and Fisher's exact test for categorical variables.
Abbreviations: BMD, bone mineral density; IQR, interquartile range; TDF, tenofovir disoproxil fumarate;

Table 3: Bone Mineral Density Measurements by treatment arm

BMD (g/cm²)	TDF N	TDF Mean (SD)	Placebo N	Placebo Mean (SD)	Mean difference percentage (95% CI)	P-value[a]
Maternal total hip	64	0.893 (0.096)	65	0.885 (0.109)	+0.9% (-3.2% to +5.0%)	0.67
Maternal lumbar spine	71	0.964 (0.100)	67	0.954 (0.113)	+1.0% (-2.7% to +4.8%)	0.59
Infant lumbar spine	62	0.324 (0.036)	53	0.330 (0.036)	-1.8% (-5.8% to +2.2%)	0.38

[a] Student's t-test.
Abbreviations: BMD, bone mineral density; SD, standard deviation; TDF, tenofovir disoproxil fumarate.

Items for Discussion

- Mothers were HBV infected, HIV uninfected. They received only TDF and no other anti(retro)virals in contrast to most previous TDF studies, which were conducted in the setting of HIV infection.
- Comparisons of BMD in mothers and infants exposed versus unexposed to TDF benefited from the randomization, though not all women and infants participated in this sub-study.
- Follow up and assessments were made blindly to treatment assignment.

Conclusions

- We did not find evidence for a persistent effect of short-course TDF on BMD in mothers or infants after TDF discontinuation.
- Temporary reductions in BMD may have occurred during TDF therapy.
- Nevertheless, we can exclude a persistent TDF-mediated reduction in BMD as small as 3% in mothers and 6% in infants.