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

Poster Session Presentation: BONE DISEASE - P-N1 on Monday, March 5, 2018, 2:30 PM-3:30 PM Themed Discussion: BONES OF CONTEND (TDF)-1 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) monoinfected pregnant women with high HBV DNA levels to prevent mother-to-child transmission (PMTCT) of HBV
- In HBV 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 28 weeks' pregnancy to 2 months postpartum in hepatitis B chronically infected women on:
  - Maternal total hip and lumbar spine bone mineral density
  - Infant's infant lumbar spine bone mineral density

This is a sub-study of the IATP 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 enrolment, women had: HBeAg+, ALT ≥60 U/L, creatinine clearance ≥ 50 ml/min. Breastfeeding was encouraged.

Design of Parent Study (NCT01745822)

- Infants
  - 818 HBsAg- women randomized
  - Follow-up from pregnancy to 24 months postpartum
  - 28 weeks of gestation
- Postpartum
  - 16 weeks postpartum (22 weeks of lactation)
  - 24 months postpartum (60 weeks of lactation)

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 13.3% 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

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.
- 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.

Table 1: Infant characteristics by treatment arm.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TDF</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>29 (14, 53)</td>
<td>29 (13, 48)</td>
<td>0.65</td>
</tr>
<tr>
<td>Maternal BMI</td>
<td>23.0 (19.4, 26.3)</td>
<td>23.9 (20.7, 26.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Infant age</td>
<td>25.8 (23.9, 27.0)</td>
<td>25.8 (24.0, 27.1)</td>
<td>0.98</td>
</tr>
<tr>
<td>Infant weight</td>
<td>5.8 (0.8, 12.0)</td>
<td>6.2 (4.3, 12.0)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 2: Infant BMD characteristics by maternal treatment arm.

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<tr>
<td>Infant age</td>
<td>29.0 (26.8, 30.1)</td>
<td>29.1 (26.8, 30.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>Infant weight</td>
<td>5.9 (3.0, 12.7)</td>
<td>6.1 (4.0, 12.0)</td>
<td>0.14</td>
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Table 3: Bone Mineral Density Measurements by treatment arm

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Figure: Participant disposition

Items for Discussion

- Mothers were HBV infected, HIV uninfected. They received only TDF and no other antiretrovirals 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 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.