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Maternal and Infant Bone Mineral Density 1 Year After Delivery in a Randomized, Controlled Trial of Maternal Tenofovir Disoproxil Fumarate to Prevent Mother-to-child Transmission of Hepatitis B Virus

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Abstract

In a randomized, double-blind, placebo-controlled trial of tenofovir disoproxil fumarate (TDF) use from 28 weeks gestational age to 2 months postpartum to prevent mother-to-child transmission of hepatitis B virus, there was no significant effect of maternal TDF use on maternal or infant bone mineral density 1 year after delivery/birth.

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Clinical Trials Registration—NCT01745822.

Keywords

bone mineral density; tenofovir disoproxil fumarate; hepatitis B; pregnancy; growth

Tenofovir disoproxil fumarate (TDF) is increasingly prescribed for the prevention of mother-to-child transmission (PMTCT) of hepatitis B virus (HBV) [1]. Maternal TDF use during pregnancy and lactation may adversely affect both maternal and infant bone mineral density (BMD) as seen in human immunodeficiency virus (HIV)–infected infants [2]. However, concomitant antiretroviral drugs, HIV infection, or related inflammation may also play a role. We report the results of a secondary endpoint analysis of a randomized, controlled trial assessing the effect of maternal TDF use vs placebo on maternal and infant BMD 1 year after delivery/birth in HBV-infected and HIV-uninfected mothers and their infants.

METHODS

Population and Design

The iTAP study was a randomized, double-blind, multicenter clinical trial where women with chronic HBV infection received TDF or a matching placebo from 28 weeks gestational age (GA) to 2 months postpartum in Thailand [3]. The results of the primary efficacy and safety endpoints have been published [4]. Following an amendment to the protocol, starting on 1 July 2015, all mothers and their infants were invited to participate in a BMD assessment 12 months after delivery/birth (±1.5 months).

Settings and Procedures

Consenting women and their infants were referred to 1 of 3 participating sites for dual-energy X-ray absorptiometry (DXA) assessments using Hologic Discovery A (Hologic, Inc., Marlborough, MA). After maternal consent, maternal hip and lumbar spine BMD and infant lumbar spine BMD were measured 12 months after delivery/birth. No more than 3 attempts were made to acquire a valid hip or spine scan. A DXA specialist (B. F.) circulated the phantoms to each of the participating sites for cross-calibration, trained the operators, and performed a precision study on the first 5 mother and infant scans collected at each site. The DXA scans were centrally analyzed using software version APEX 4.0.2 by a second DXA specialist (W. T.). Participants, investigators, operators, and DXA specialists remained blinded to the study treatment arm during the BMD assessment study.

Statistical Considerations

The main outcome measures were the total hip BMD in mothers and the lumbar spine BMD in both mothers and infants, expressed in grams per square centimeter. The total hip BMD was calculated as the sum of the bone mineral content (BMC) measured at the femoral neck, trochanter, and intertrochanter divided by the sum of the area measured at each of these 3 regions. The lumbar spine BMD was calculated as the sum of the BMC measured at L1, L2, L3, and L4 vertebrae divided by the sum of the area measured at each of these 4 vertebrae. Only scans with valid measurements in all areas were included in the analysis. Mean maternal total hip and lumbar spine BMD and infant lumbar spine BMD were compared

between TDF and placebo arms using a 2-sided Student *t* test. Assuming a mean (standard deviation) lumbar spine BMD of 0.312 g/cm^2 (0.070 g/cm^2) [5] in infants in the placebo arm, we calculated that a sample size of at least 45 mother–infant pairs per arm would provide more than 80% power to detect a mean difference of 0.042 g/cm^2 in infant lumbar spine BMD in the TDF arm compared to the placebo arm, that is, a relative mean difference of 13.5% (2-sided Student *t* test, alpha = .05).

Ethical Considerations

The ethics committee of the Institute for the Development of Human Research Protections at the Ministry of Public Health (Thailand) and the ethics committees at the clinic sites approved the protocol.

RESULTS

Participants

Between July 2015 and October 2016, 140 mothers (71 TDF, 69 placebo) and 137 infants (70 TDF, 67 placebo) were included in the BMD assessment: 135 mother–infant pairs (69 TDF, 66 placebo), 5 singleton mothers (2 TDF, 3 placebo), and 2 singleton infants (1 TDF, 1 placebo). Reasons for exclusion among the 322 randomized mothers who delivered and their infants were the following: reached 12 months postpartum before protocol amendment (116 mothers [59 TDF, 57 placebo], 116 infants [59 TDF, 57 placebo]), declined participation (65 mothers [32 TDF, 33 placebo], 64 infants [31 TDF, 33 placebo]), could not come with their mothers (5 infants [2 TDF, 3 placebo]), and became newly pregnant (1 mother [placebo]).

At study treatment initiation (28 weeks GA), median maternal age was 26.7 years (interquartile range, 23.3 to 29.2), weight 62 kg (56 to 71), and HBV DNA 8.0 $\log_{10}$ IU/mL (7.3 to 8.4). At delivery, median GA was 39.1 weeks (38.3 to 40.1). Median breastfeeding duration was 6.1 months (3.8 to 12.0) for the 135 (96%) mothers who breastfed. BMD was assessed at a median 12.2 months (11.9 to 12.5) after delivery/birth. At this time, median maternal weight was 55 kg (50 to 62). Of the 137 infants, 69 (50%) were male. Median infant weight-for-age *z* score was −0.49 (−1.06 to 0.25) and length-for-age *z* score was −0.46 (−1.18 to 0.58) at the time of BMD assessment.

Except for maternal HBV DNA at delivery, participant characteristics in the 2 arms were similar (Supplementary Table 1).

Maternal and Infant BMD

The BMD measurements were valid for the hip in 129 mothers (64 TDF, 65 placebo) and for the lumbar spine in 138 mothers (71 TDF, 67 placebo) and 115 infants (62 TDF, 53 placebo). Invalid measurements were due to movement or improper positioning.

There were no significant differences between TDF and placebo arms in maternal hip BMD (mean difference of +0.008 g/cm^2 [95% confidence interval, −0.028 to +0.044 g/cm^2]; $P = .67$), maternal lumbar spine BMD (+0.010 g/cm^2 [− 0.026 to +0.046 g/cm^2]; $P = .59$), or infant lumbar spine BMD (−0.006 g/cm^2 [−0.019 to +0.007 g/cm^2]; $P = .38$) (Table 1).

Similar results were found in a sensitivity analysis excluding 2 HBV-infected infants from the placebo arm.

DISCUSSION

In this randomized trial for PMTCT of HBV where women received TDF or placebo from 28 weeks GA to 2 months postpartum and breastfed their infants, we did not find significant evidence for an effect of maternal TDF use on maternal or infant BMD 1 year after delivery/birth.

Postpartum maternal mean total hip and mean lumbar spine BMD in this Asian population seemed similar to that in white populations [6–8] taking into account the specificity of the previous studies in terms of proportion of breastfeeding mothers, duration of breastfeeding, and time of measurement after weaning [6, 9]. Infant mean lumbar spine BMD was similar to that reported in white and African American infants [5, 10].

There were no significant differences in BMD between arms, but it is possible that a deficit in bone mineralization might have occurred earlier in mothers on TDF and/or in infants during breastfeeding, although previous studies have reported conflicting results [2, 11]. All women of our population received TDF for the same duration (5 months) and, in contrast with these studies, were chronically infected with HBV and uninfected with HIV and therefore unexposed to any other antiretrovirals.

A strength of our study was that it provided information on the potential effect of TDF on BMD 1 year after delivery/birth in HBV monoinfected women and their infants. Indeed, the results of studies conducted in an HIV-monoinfected, HIV–HBV-coinfected or HBV-monoinfected population should not be extrapolated to other populations.

A limitation of our study is that BMD was only measured at 1 year after delivery/birth. Earlier measurement time points would have provided information on the evolution of BMD in the 2 arms. Indeed, a progressive decrease in maternal BMD during breastfeeding with spontaneous compensation after weaning has been observed without TDF [6], and the role of TDF during this period remains unknown. Another limitation is that BMD assessment was performed in a subset of all women randomized to receive TDF or placebo. However, the double-blind aspect was maintained during the BMD assessment, and most participant characteristics were found to be similar between the 2 arms, suggesting a limited impact.

In conclusion, together with the absence of significant differences in infant growth parameters [12], TDF prophylaxis to prevent mother-to-child transmission of HBV in HBV-monoinfected women in Asia appeared safe with regard to bone mineralization for both mothers and infants. This information will contribute to our knowledge regarding the safety of this approach [1].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Bone Mineral Density Valid Measurements by Treatment Arm: Maternal Hip and Lumbar Spine and Infant Lumbar Spine

	Tenofovir Disoproxil		Fumarate Placebo			
Bone Mineral Density (g/cm^2)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**Mean Difference (95% Confidence Interval)**	***P* Value[a]**
Maternal total hip	64	0.893 (0.096)	65	0.885 (0.109)	+0.008 (−0.028 to +0.044)	.67
Maternal lumbar spine	71	0.964 (0.100)	67	0.954 (0.113)	+0.010 (−0.026 to +0.046)	.59
Infant lumbar spine	62	0.324 (0.036)	53	0.330 (0.036)	−0.006 (−0.019 to +0.007)	.38

Abbreviation: SD, standard deviation.

[a]From a 2-sided student *t* test.