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Hepatitis B Virus (HBV) Load Response to 2 Antiviral Regimens, Tenofovir/Lamivudine and Lamivudine, in HIV/ HBV-Coinfected Pregnant Women in Guangxi, China: The Tenofovir in Pregnancy (TiP) Study

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Abstract

Background.—There is limited information on antiviral therapy for hepatitis B virus (HBV) infection among pregnant women coinfected with human immunodeficiency virus (HIV) and HBV.

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Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

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Methods.—A phase 2 randomized, controlled trial of a regimen containing tenofovir (TDF)/lamivudine (3TC) and a regimen containing 3TC in HIV/HBV-coinfected pregnant women in China. The HBV virological response was compared in study arms.

Results.—The median decline in the HBV DNA level was 2.60 $\log_{10}$ copies/mL in the TDF/3TC arm and 2.24 $\log_{10}$ copies/mL in the 3TC arm ($P = .41$). All women achieved HBV DNA levels of <6 $\log_{10}$ copies/mL at delivery.

Conclusions.—Initiation of either regimen led to achievement of HBV DNA levels below the threshold associated with perinatal HBV transmission.

Clinical Trials Registration.—NCT01125696.

Keywords

tenofovir; HIV/HBV coinfection; pregnancy; HBV suppression; lamivudine; HBV DNV viral load

Hepatitis B virus (HBV) infection is an important cause of morbidity and mortality worldwide [1]. Up to 90% of infants who acquire their HBV infection perinatally will develop chronic infection. The risk of HBV transmission to the infant is higher for mothers who are positive for HBV e antigen (HBeAg) and have a higher HBV load [2]. Despite active and passive immunization, the rate of breakthrough transmission to the infant remains 5%–15% in such women [2].

Human immunodeficiency virus type 1 (HIV) shares similar transmission routes with HBV. Coinfection with HIV results in higher rates of chronic infection and higher levels of HBV replication [3]. It is thus likely that coinfected women have an even higher risk of HBV transmission to their infants [1].

China has a high burden of HBV infection, with an estimated 7% of its population chronically infected with HBV [4]. Even though HBV vaccination has been available free of charge for all newborns since 2005 [4],the risk of mother-to-child transmission (MTCT) of HBV remains, particularly for mothers with a higher HBV load [5].There is limited information on the effects of tenofovir disoproxil fumarate (TDF), when initiated during pregnancy, on the HBV load response. Some studies have investigated TDF and/or lamivudine (3TC) in reducing MTCT of HBV in HBV-monoinfected pregnant women [6, 7], but no studies have been performed among HIV/HBV-coinfected women.

The Tenofovir in Pregnancy (TiP) study was designed to test the safety, during pregnancy, of an antiretroviral combination containing TDF in women coinfected with HIV and HBV. The study's objectives were to evaluate the renal, liver, and bone mineral density effects of TDF, administered beginning in the second trimester of pregnancy, to women and their infants through postnatal year 1. We also evaluated the HBV load response to the 2 regimens (TDF/3TC vs 3TC) when initiated during the second trimester of pregnancy.

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METHODS

Study Design and Participants

The TiP study is a phase 2 randomized, controlled trial (clinical trials registration NCT01125696) that recruited participants between 2012 and 2015 in Guangxi Zhuang Autonomous Region (Guangxi Province) in southwestern China. The target sample size for this phase 2 study was 80 women.

Eligible women had to have serologically confirmed HIV and HBV infection; pregnancy between 14–28 weeks' gestation (estimated on the basis of the dates of the last menstruation and ultrasonography findings, if available); an age of ≥20 years; no previous or current use of antiretroviral agents, with the exception of short regimens to prevent MTCT of HBV in any previous pregnancy; a hemoglobin level of >8 g/dL at recruitment; and a creatinine clearance rate of ≥60 mL/minute, estimated by the Cockroft-Gault formula for women [8].

The study was approved by the institutional review boards at the US Centers for Disease Control and Prevention and the Guangxi Provincial Center for Disease Control and Prevention.

Randomization and Study Procedures

All eligible study participants were randomly assigned (ratio, 1:1) to start either tenofovir/lamivudine/lopinavir-ritonavir therapy or the local standard regimen for prevention of MTCT of HIV, zidovudine/lamivudine/lopinavir-ritonavir.

There are 10 visits in the study: the screening and enrollment visit, 2 weeks and 8 weeks after randomization, at 34 weeks of gestation, at delivery, 6 weeks after delivery, and 3, 6, 9, and 12 months after delivery. At each visit, a standardized data collection form was administered by the study coordinator at each study clinic. All mothers were advised to come to the study sites for delivery. All newborn infants were provided free antiretroviral drugs for prevention of MTCT of HIV per local standard of care. Three doses of HBV vaccine and 100 mg of HBV immunoglobulin (HBIG) were given to all infants within 24 hours after birth [4].

Laboratory Testing

Quantification of antibody to HBV surface antigen, HBV surface antigen, antibody to HBV e antigen, HBeAg, and antibody to HBV core antigen was performed on collected sera at the laboratories at the LZ MCH and GX MCH, using standardized China Food and Drug Administration–approved assays (time-resolved fluoroimmunoassay; SYM-BIO LifeScience, China). HBV load was measured at the HIV Reference Laboratory of the Guangxi Center for Disease Control and Prevention, using the m2000 RealTime System (Abbott RealTime HBV Assay, California), with a lower detection limit of 15 IU/mL (51.2 copies/mL).

The $CD4^+$ T-cell counts were determined at the HIV Reference Laboratory of the Guangxi Center for Disease Control and Prevention by an automated bench-top flow cytometry

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system (FACSCalibur system, BD). Plasma HIV RNA was measured using the Abbott assay (Abbott RealTime HIV-1), with a lower limit of detection of 40 copies/mL.

Statistical Analysis

Analyses were restricted to women who had delivered by January 2016. The decline in HBV load from baseline to delivery and the percentage of women with an undetectable HBV load at delivery were compared between treatment arms. The associations between HBV load and duration of antiviral treatment and demographic and pretreatment clinical and laboratory measures were assessed using linear regression, for the decline in HBV load, and Poisson regression with robust error variance, for the percentage with an undetectable HBV load at delivery. All analyses followed the intention-to-treat principle and were conducted using SAS, version 9.3 (Cary, North Carolina).

RESULTS

Between 1 August 2012 and 31 December 2015, 76 HIV/HBV-coinfected pregnant women were screened for study eligibility; 41 (53.9%) were excluded because they did not fulfill inclusion criteria. Thirty-five eligible women were enrolled and randomized in the study (Supplementary Materials).

By January 2016, 31 women had delivered. Treatment for 3 women in the ZDV/3TC/LPV-r arm was switched to TDF/3TC/LPV-r antenatally because of anemia (for 2 women) or liver function abnormalities (for 1 woman).

At baseline, 9 women (29.0%) were positive for HBeAg. Twenty-one women (67.7%) had an HBV load of < 200 000 IU/mL; 2 women (6.5%) had undetectable HBV DNA at baseline.

The 2 arms were balanced in terms of baseline characteristics and laboratory values (Table 1). The median HBV load at baseline was similar between the TDF/3TC and 3TC treatment arms (4.01 $\log_{10}$ copies/mL vs 3.64 $\log_{10}$ copies/mL). The proportion of women with an HBV load of > 200 000 IU/mL at baseline (equivalent to approximately 6 $\log_{10}$ copies/mL) was 37.5% in the TDF/3TC arm versus 26.7% in the 3TC arm ($P = .52$).

The median duration of treatment by delivery was 19 weeks (range, 11–24 weeks). All women achieved an HBV DNA load of < 6 $\log_{10}$ copies/mL at delivery, and 61% reached an undetectable HBV DNA load (50.0% [8 of 16] in the TDF/3TC arm and 73.3% [11 of 15] in the 3TC arm; $P = .27$). The median HBV DNA load at delivery was similar in the 2 arms (1.55 $\log_{10}$ copies/mL in the TDF/3TC arm vs 1.40 $\log_{10}$ copies/mL in the 3TC arm; $P = .25$). There was no difference in the median decline in the HBV DNA load from baseline between the treatment arms (2.60 $\log_{10}$ copies/mL in the TDF/3TC arm vs 2.24 $\log_{10}$ copies/mL in the 3TC arm; $P = .41$).

The proportion reaching an undetectable HBV load at delivery was significantly higher (85.7% [18 of 21]) in mothers with a low baseline HBV viremia level (defined as ≤200 000 IU/mL), compared with only 10% (1 of 10) in those with a high HBV DNA level at baseline ($P < .001$; Table 1). The decline in HBV DNA load with treatment was larger in individuals

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with a high viremia level, compared with those with a lower viral load, at baseline (5.55 $\log_{10}$ copies/mL vs 1.38 $\log_{10}$ copies/mL, respectively; $P < .001$; Figure 1).

Baseline HBV load of > 200 000 IU/mL and HBeAg-positive status were statistically significantly associated with lower proportions of women reaching an undetectable HBV load at delivery (relative risk [RR], 0.12 [95% confidence interval {CI}, .02–.76] and 0.14 [95% CI, .02–.87], respectively), and higher $CD4^+$ T-cell count was associated with higher proportions of women reaching undetectable HBV load at delivery (RR, 1.11 [95% CI, 1.01–1.23]) in unadjusted analyses. High baseline HBV load and positive HBeAg status were also associated with larger declines in $\log_{10}$ HBV load from baseline in unadjusted linear regression analyses ($P < .001$ for both baseline HBV load and HBeAg positivity). Higher baseline serum alanine aminotransferase (ALT) level was also associated with larger declines in $\log_{10}$ HBV load ($P = .001$). However, the associations with baseline HBeAg positivity, $CD4^+$ T-cell count, and ALT level were no longer statistically significant in a multivariable model including baseline HBV load and study arm; only baseline HBV load remained statistically significantly associated with HBV DNA level at delivery (Supplementary Materials). The duration of treatment (range, 11–24 weeks) did not have a significant effect on HBV load at delivery ($P = .70$).

DISCUSSION

Even though the use of HBV vaccine and HBIG has dramatically decreased new infant HBV infections [9], breakthrough transmission still occurs at a rate of 5%–15% or even higher in mothers with high levels of HBV viremia [2]. Studies have suggested that a maternal HBV DNA level of >6 $\log_{10}$ copies/mL at delivery is the most important factor for MTCT of HBV and prophylaxis failure [10]. Use of HBV antiviral agents during pregnancy has been proposed as an adjunct to immunization for such mother/infant pairs [3, 6, 11].

Mostly nonrandomized studies have been published on the use of antiviral agents with activity against HBV during pregnancy to prevent MTCT of HBV; the agent most frequently used was 3TC. A recent meta-analysis showed that HBV antiviral use in late pregnancy can significantly decrease the risk of HBV MTCT by approximately 70% [7]. However, 3TC has a low barrier to resistance [12]. Tenofovir is an agent with high potency against HBV and also a high genetic barrier to resistance. Data on the use of TDF during pregnancy indicate a substantial decline in HBV viral load by the time of delivery [6, 10, 13, 14].

Our findings showed that, over a median of 19 weeks of treatment (range, 11–24 weeks), 61% of study participants reached an undetectable HBV DNA load at delivery. The proportion of patients achieving HBV virologic suppression is similar to that reported in previous studies in HIV/HBV-coinfected nonpregnant adults after 24–48 weeks of treatment [15].

There was no difference in the proportion of women achieving undetectable HBV DNA at delivery by study arm. This may be due to the fact that most women had low baseline HBV DNA levels and was also seen in a study of nonpregnant coinfected individuals [15]. HBV load reduction was faster and of greater magnitude in women with a high baseline viremia

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level, and multivariable analysis showed that a maternal baseline HBV load of > 200 000 IU/mL was the only factor significantly associated with not reaching an undetectable HBV load at delivery.

All women, regardless of treatment assignment or level of baseline HBV viremia, achieved an HBV DNA level of <6 $\log_{10}$ copies/mL at delivery, suggesting that either regimen started during the second trimester has the potential, in combination with active and passive HBV immunoprophylaxis, to interrupt MTCT of HBV.

This study's main limitation is the limited power to detect differences between the 2 arms, as well as to conduct subgroup analyses to explore possible differences in HBV virologic response among patients with high or low baseline HBV load in each study arm. Owing to large numbers of women already receiving highly active antiretroviral therapy or opting to terminate their pregnancies, we were not able to reach the target sample size of 80. A few women switched treatment arms before delivery, because of laboratory abnormalities. Our analysis followed the intention-to-treat principle, but a sensitivity analysis adjusting for the actual duration of treatment in each arm did not yield different results.

Notwithstanding these limitations, this is the first randomized, controlled clinical trial comparing 2 HBV antiviral regimens among HBV/HIV-coinfected pregnant women. The regimens started at the second trimester of pregnancy among drug-naive women and demonstrated the feasibility of reducing HBV DNA to a level that, combined with newborn delivery of HBV vaccine and HBIG, can fully prevent MTCT of HBV.

We would argue that pregnant women identified as HBV infected during their first antenatal visit need to have their HBV DNA level or HBeAg status checked at that time. HBeAg-positive women who have higher baseline HBV DNA levels may need earlier initiation of therapy in the first trimester or even prior to pregnancy, to reach undetectable HBV levels at delivery. However, all women in our study reached levels of <6 $\log_{10}$ copies/mL at delivery, suggesting that initiation of HBV antiviral therapy in the second trimester may prevent HBV transmission to the infant, when combined with active and passive immunoprophylaxis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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L. W., J. W., and A. P. K. had full access to all the data in the study and take responsibility for the integrity of the data, the accuracy of the data analysis, and for the work as a whole, from inception to published article.

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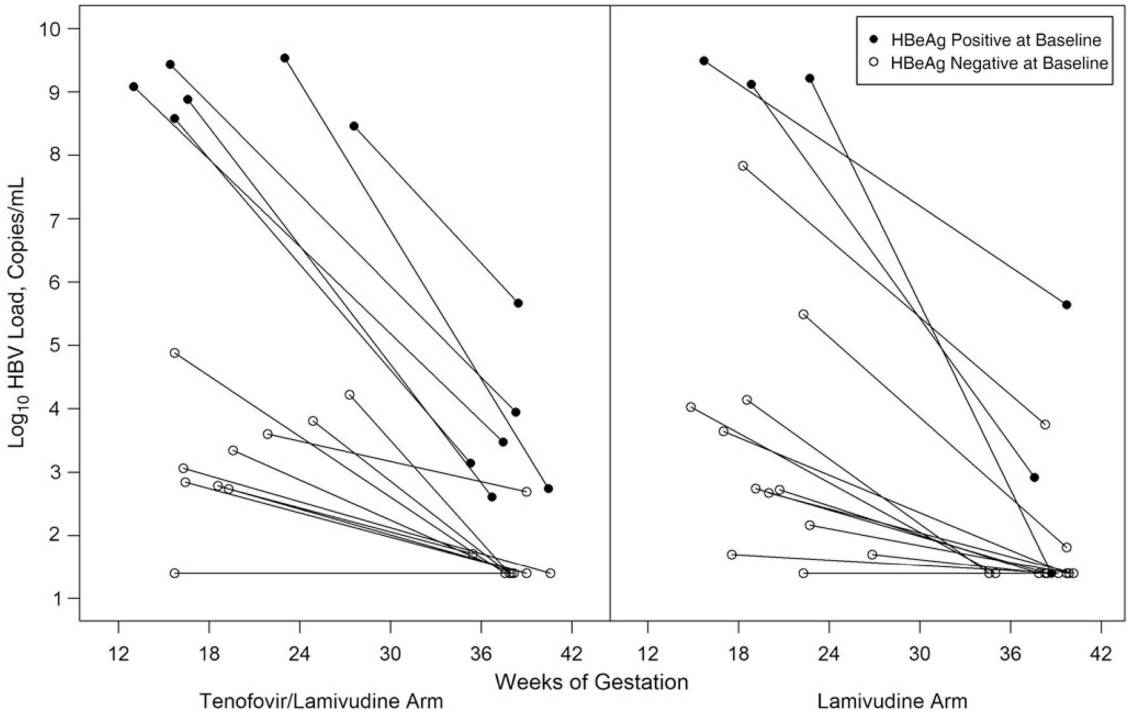

Figure 1.

Hepatitis B virus (HBV) loads from baseline to delivery among pregnant women coinfected with human immunodeficiency virus and HBV, by study arm, in the Tenofovir in Pregnancy study. Abbreviation: HBeAg, HBV e antigen.

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Table 1.

Demographic and Hepatitis B Virus (HBV) Virological Characteristics, by Study Arm, in the Tenofovir in Pregnancy Study

Characteristic	TDF/3TC (n = 16)	3TC (n = 15)	*P* Value
Baseline Demographic			
Nanning study site	8 (50.0)	7 (46.7)	
Education beyond primary school	10 (62.5)	11 (73.3)	
Married	12 (75.0)	11 (73.3)	
Weeks of gestation at enrollment	17.6 (14.0–27.6)	19.1 (14.9–26.9)	
Age, y	29.0 (24.0–36.0)	28.0 (19.0–39.0)	
BMI[a]	20.7 (17.4–24.7)	21.8 (17.8–27.3)	
ALT level, mU/mL	14.0 (8.0–40.0)	17.0 (6.0–141.0)	
Hemoglobin level, g/dL	10.7 (8.6–12.9)	11.1 (9.9–12.4)	
$CD4^+$ T-cell count, cells/mm^3	311.5 (154.0–623.0)	333.0 (147.0–924.0)	
Log_{10} HIV load, copies/mL	4.18 (3.17–6.10)	4.21 (1.76–5.72)	
Log_{10} HBV load, copies/mL	4.01 (1.40–9.53)	3.64 (1.40–9.49)	
HBV load >200 000 IU/mL	6 (37.5)	4 (26.7)	
HBeAg positive	6 (37.5)	3 (20.0)	
HBV Viremia at Delivery			
Log_{10} viral load, copies/mL	1.55 (1.40–5.67)	1.40 (1.40–5.64)	.25
Decline in log_{10} HBV load from baseline, copies/mL	−2.60 (−6.79–0)	−2.24 (−7.81–0)	.41
Decline in log_{10} HBV load per week of treatment, copies/mL	−0.17 (−0.39–0)	−0.10 (−0.49–0)	.34
Undetectable HBV DNA	8 (50.0)	11 (73.3)	.27

Data are median value (range) or no. (%) of women.

Abbreviations: 3TC, lamivudine; ALT, alanine aminotransferase; HBeAg, HBV e antigen; HIV, human immunodeficiency virus; TDF, tenofovir disoproxil fumarate.

[a]Body mass index (BMI) is calculated as the weight in kilograms divided by the height in meters squared.