Tenofovir Exposure during Pregnancy and Postpartum in Women Receiving Tenofovir Disoproxil Fumarate for the Prevention of Mother-to-Child Transmission of Hepatitis B Virus

Tim R. Cressey,^{a,b,c} Linda Harrison,^d Jullapong Achalapong,^e Prateep Kanjanavikai,^f Orada Patamasingh Na Ayudhaya,^g Prateung Liamongsabuddhi,^h Thitiporn Siriwachirachai,ⁱ Chaiwat Putiyanun,^j Pornnapa Suriyachai,^k Camlin Tierney,^d Nicolas Salvadori,^a Dujrudee Chinwong,^l Luc Decker,^m Yardpiroon Tawon,^a Trudy V. Murphy,ⁿ Nicole Ngo-Giang-Huong,^{a,b,m} George K. Siberry,^o Gonzague Jourdain,^{a,b,l} for the iTAP Study Team

^aPHPT/IRD, Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand

^bDepartment of Immunology & Infectious Diseases, Boston, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

^cDepartment of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom

^dCenter for Biostatistics in AIDS Research (CBAR), Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

^eChiangrai Prachanukroh Hospital, Chiang Rai, Thailand

^fBanglamung Hospital, Chonburi, Thailand

^gNopparat Rajathane Hospital, Bangkok, Thailand

^hLampang Hospital, Lampang, Thailand

ⁱKhon Kaen Hospital, Khon Kaen, Thailand

^jChiang Kham Hospital, Phayao, Thailand

^kPhayao Provincial Hospital, Phayao, Thailand

^lDepartment of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand

^mInstitut de Recherche pour le Développement (IRD), Unité Mixte Internationale 174-PHPT, Chiang Mai, Thailand

ⁿCenters for Disease Control and Prevention, Atlanta, Georgia, USA

^oEunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA

ABSTRACT We assessed tenofovir exposure during pregnancy and postpartum in hepatitis B virus (HBV)-infected HIV-uninfected women receiving tenofovir disoproxil fumarate (TDF) to prevent mother-to-child transmission of HBV. Data from 154 women who received TDF within a randomized controlled trial were included. Individual plasma tenofovir exposures (area under the concentration-time curve from 0 to 24 h [AUC_{0-24}]) were estimated using a population pharmacokinetic approach. The estimated geometric mean tenofovir AUC_{0-24} was 20% (95% confidence interval [95% CI], 19 to 21%) lower during pregnancy than during postpartum; this modest reduction in the absence of HBV transmission suggests that no dose adjustment is needed.

KEYWORDS pregnancy, tenofovir, hepatitis B virus, pharmacokinetics

An estimated 257 million people (approximately 3.5% of the global population) were living with chronic hepatitis B virus (HBV) infection in 2015, with the highest burden occurring in the Asia-Pacific region (1). Today, the majority of new cases of chronic HBV infection occur through mother-to-child transmission (MTCT) (2). The risk of MTCT transmission of HBV remains highest among infants born to women with a

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Address correspondence to Tim R. Cressey, tim.cressey@phpt.org.

high HBV DNA load or who are HBeAg positive (3). Antiviral therapy starting at 28 to 32 weeks of pregnancy and continuing through the early postpartum period is recommended for HBsAg-positive pregnant women, with an HBV DNA level of $>200,000$ IU/ml to prevent mother-to-child HBV transmission, in addition to standard infant immunoprophylaxis (4). Tenofovir disoproxil fumarate (TDF) is a potent antiviral against HBV and is the preferred anti-HBV drug to use during pregnancy (5). TDF has also been widely used as part of combination antiretroviral therapy (ART) to prevent MTCT of HIV, as per World Health Organization guidelines (6). TDF is an oral prodrug that is converted to tenofovir (TFV) following absorption; intracellularly, TFV is phosphorylated to its active anabolite TFV-diphosphate (7). In HIV-infected women, plasma TFV exposure is lower during pregnancy when TDF is administered as part of combination ART (8, 9); however, there are no pharmacokinetic data on TFV in the absence of concomitant antiretrovirals. We assessed TFV exposure during pregnancy and postpartum in HBV-infected HIV-uninfected women receiving TDF alone to prevent MTCT of HBV within the context of a large clinical trial.

The iTAP study was a phase III randomized double-blind placebo-controlled trial in Thailand assessing the safety and efficacy of TDF to prevent HBV perinatal transmission (ClinicalTrials.gov identifier NCT01745822) (10). HIV-uninfected women ≥ 18 years old testing positive for HBsAg and HBeAg and with an alanine aminotransferase (ALT) level of ≤ 60 IU/liter were randomized to receive TDF (300 mg once daily) or placebo from 28 weeks of pregnancy to 2 months postpartum. The safety and efficacy results of the main trial have been reported (10). This analysis focused on the assessment of TFV plasma concentrations in mothers who received TDF. The iTAP study was approved by the ethics committees at the Ministry of Public Health, Thailand, the Faculty of Associated Medical Sciences, Chiang Mai University, and local hospitals.

Single random maternal blood samples (i.e., at a nonpredefined time) were collected at 32 and 36 weeks of pregnancy, at delivery, and at 1 and 2 months postpartum to measure TFV plasma concentrations. The exact times of last drug intake and blood draw were recorded, and the plasma samples were frozen at -20°C . A subset of women who consented to additional blood draws had prespecified samples drawn at predose, between 0.5 and 3 h postdose, and the third sample at least 1 h later. Food intake with TDF administration was not controlled at study visits. TFV plasma concentrations were quantified using a validated liquid chromatography-triple quadrupole mass spectrometry assay over the range of 0.02 to 2.5 mg/liter. The average accuracy of the assay was 99% to 102%, and the precision was at $<5\%$ coefficient of variation. The laboratory participates in an external quality control program (11).

Population means and variances of TFV pharmacokinetic parameters were estimated using a nonlinear mixed-effects regression model (NONMEM VII). Maternal demographic data, including body weight, body surface area, the number of weeks of pregnancy, serum creatinine (sCr) level, creatinine clearance (CrCL) (estimated using Cockcroft-Gault equation), and pregnancy status (as a binary covariate), were evaluated for their inclusion in the model using a stepwise forward-selection/backward-elimination procedure (12). The validity of the final model was evaluated using a visual predictive check (VPC) by simulating 500 data sets (13). Bayesian *post hoc* estimates of subject-specific pharmacokinetic parameters (e.g., oral clearance [CL/F] and volume of distribution [Vd/F]) were used to calculate individual TFV trough concentrations (C_{24}) and the area under the concentration-time curve ($\text{AUC} = \text{dose}/\text{CL}$) at each time point. Estimates of the $\log_{10}$ AUC from 0 to 24 h (AUC_{0-24}) and C_{24} during pregnancy were compared to postpartum values using a linear mixed-effects model with a random effect of subject.

A total of 594 plasma samples (441 during pregnancy/delivery and 153 postpartum) from 154 women were used to build the TFV population pharmacokinetic model. Prenatal samples were collected at a median (interquartile range [IQR]) of 36.0 weeks of pregnancy (IQR, 35.1 to 36.4 weeks), with a median patient age of 26 years (IQR, 22 to 29 years), weight of 65.3 kg (IQR, 59.0 to 73.0 kg), sCr level of 0.57 mg/dl (IQR, 0.51 to

FIG 1 Tenofovir plasma concentration-time curves for the average woman during pregnancy (closed diamonds) and postpartum (open diamonds), derived using the final population pharmacokinetic model. Conc., concentration.

0.63 mg/dl), and CrCL of 156 ml/min (IQR, 131 to 179 ml/min). Samples were collected from women at 1 and 2 months postpartum when their median weight was 56.0 kg (IQR, 50.5 to 62.9 kg), sCr was 0.73 mg/dl (IQR, 0.65 to 0.83 mg/dl), and CrCL was 105 ml/min (IQR, 91 to 119 ml/min).

A 2-compartment pharmacokinetic model with first-order absorption and elimination best described the TFV concentrations during pregnancy/postpartum. Residual variability was described using a proportional error model. In the univariate analysis of covariates, body weight, pregnancy status, and CrCL each influenced TFV oral clearance (CL/F), but CrCL led to the largest decrease in objective function. After the inclusion of CrCL in the model, the addition of the other covariates no longer improved the model fit; thus, the TFV CL/F was estimated using the equation $CL/F = TVCL \times (CrCL/143)^{0.57}$ (TVCL was the population CL/F value, and 143 was the median CrCL). Final estimates of TFV population pharmacokinetic parameters are shown in Table S1, and the VPC data are shown in Fig. S1 in the supplemental material.

Using the final model, the estimated geometric mean TFV AUC_{0-24} values at 32 and 36 weeks of pregnancy and at delivery were similar (1.85, 1.88, and 1.87 $\mu\text{g h/ml}$, respectively). The estimated AUC_{0-24} values were also similar at the two postpartum time points, at 2.35 and 2.25 $\mu\text{g h/ml}$ at 1 and 2 months, respectively. The estimated AUC_{0-24} was significantly lower during pregnancy (geometric mean ratio, 0.80 [95% CI, 0.79 to 0.81]; $P < 0.0005$). The tenofovir C_{24} was also significantly lower during pregnancy than during postpartum, with a geometric mean ratio of 0.71 (95% CI, 0.70 to 0.73; $P < 0.0005$). Tenofovir concentration time curves during pregnancy and postpartum derived using the model are shown in Fig. 1.

The pharmacokinetic model describing TFV concentrations in these women was similar to that used for nonpregnant HIV-infected adults receiving TDF-based ART (14). Due to the study design, a higher number of samples were collected during pregnancy versus postpartum, but this was not considered to bias the pharmacokinetic (PK) model. The 20% reduction in TFV exposure during pregnancy compared to postpartum is similar to historical data in HIV-infected pregnant women on ART (8, 9) and is driven in our study by higher CrCL during pregnancy. Interestingly, compared to a study with intrasubject PK data of HIV-infected women on TDF-based ART during pregnancy and postpartum, the TFV exposures in these HBV-infected women were lower during both periods (9), while a population PK analysis of TFV using pooled data from unrelated pregnant and nonpregnant HIV-infected women found exposures comparable to those in our study (15). No mothers randomized to receive TDF in the iTAP trial transmitted

HBV to their infant (10). The *in vitro* 50% effective concentration (EC_{50}) of TFV is lower for the treatment of HBV than for the treatment of HIV, and the TFV C_{24} concentrations observed in our study were within the EC_{50} range reported for HBV (0.14 to 1.5 μ M) (16). However, direct comparisons to *in vitro* EC_{50} of TFV is not ideal, as antiviral activity is dependent on intracellular activation to TFV diphosphate.

This is the first report on the pharmacokinetics of TFV in pregnant women receiving TDF to prevent MTCT of HBV. The modest reduction in TFV exposures observed during pregnancy does not suggest that a dose adjustment is necessary.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.01686-18>.

SUPPLEMENTAL FILE 1, PDF file, 0.7 MB.

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