Effect of Pregnancy and Concomitant Antiretrovirals on the Pharmacokinetics of Tenofovir in Women With HIV Receiving Tenofovir Disoproxil Fumarate-Based Antiretroviral Therapy Versus Women With HBV Receiving Tenofovir Disoproxil Fumarate Monotherapy

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Abstract
Tenofovir disoproxil fumarate (TDF) is recommended as part of antiretroviral therapy (ART) for pregnant women with HIV and as monotherapy for pregnant women with hepatitis B virus (HBV) monoinfection at high risk of transmitting infection to their infants. Tenofovir (TFV) plasma exposures are reduced during pregnancy; however, concomitant antiretrovirals and the viral infection itself can also influence TFV pharmacokinetics. Our aim was to compare TFV pharmacokinetics in pregnant women receiving TDF-based ART, with or without a ritonavir-boosted protease inhibitor (r/PI), to pregnant women with HBV receiving TDF monotherapy. Non-r/PI regimens were primarily integrase strand transfer inhibitors or nonnucleoside reverse transcriptase inhibitor–based regimens. Data were combined from a pharmacokinetic study of pregnant women with HIV on ART (PANNA), and a study assessing TFV pharmacokinetics in pregnant women with HBV (iTAP). A total of 196 pregnant women, 59 with HIV (32 receiving r/PIs) and 137 with HBV monoinfection were included. Intraindividual TFV area under the plasma concentration–time curve from time 0 to 24 hours was 25%, 26%, and 21% lower during the third trimester compared to 1 month postpartum in women with HIV using TDF and an r/PI or TDF and non-r/PI and women with HBV receiving TDF monotherapy, respectively. TFV area under the plasma concentration–time curve from time 0 to 24 hours was similar in pregnant women receiving non-r/PI to pregnant women with HBV receiving TDF monotherapy (1.84 vs 1.86 μg • h/mL); however, pregnant women receiving TDF with an r/PI had higher exposures (2.41 μg • h/mL; *P < .01). Pregnancy reduces TFV exposure and the relative size was not impacted by concomitant antiretroviral drugs or viral infection, but a drug-drug interaction between TDF and r/PI remains during pregnancy, leading to higher exposures than those on TDF and non-r/PI or TDF monotherapy.

Keywords
antiretroviral therapy, hepatitis, HIV, pregnancy, tenofovir disoproxil fumarate

HIV and hepatitis B virus (HBV) can be transmitted from mother to child, and tenofovir disoproxil fumarate (TDF) is recommended as part of antiretroviral therapy (ART) to prevent mother-to-child transmission of HIV and as monotherapy to prevent mother-to-child transmission of HBV in women at high risk of transmission.1,2 Physiological changes during pregnancy can impact the efficacy of antiretroviral drugs (ARVs) by lowering drug exposures due to changes in absorption, distribution, metabolism, and/or elimination.3,4 TDF is a prodrug of tenofovir (TFV), and a mild decrease of TFV plasma exposures was observed in pregnant women living with HIV on ART as well as in pregnant women receiving TDF alone for HBV monoinfection.5–7

Concomitant ARVs can also influence TFV pharmacokinetics (PK). Higher TFV plasma exposures are observed when TDF is coadministered with ritonavir-boosted HIV protease inhibitors (r/PIs) due to inhibition of P-glycoprotein in the intestinal tract.5,8–10 It is unclear if this drug-drug interaction (DDI) persists in the context of pregnancy, as...
previously published PK studies in pregnancy with TDF included low numbers of women without ritonavir-boosted PIs for comparison or did not evaluate the interaction.\textsuperscript{5,6,11} Moreover, while comparison of DDIs between different TDF-based ARV regimens is reasonable the ideal comparison would be to pregnant women using TDF in the absence of other ARVs.

It is also possible that the different viral infections themselves could affect TFV drug exposure by altering hepatic metabolism, kidney function, protein binding, and regulation of drug transporters.\textsuperscript{12,13} For example, studies indicate that protease inhibitor concentrations are altered in individuals with HIV compared to healthy subjects.\textsuperscript{13} Protease inhibitor PK may be altered in individuals with HIV as result of a greater variability in cytochrome P450 3A4 activity, a higher gastric pH, and an increased plasma $\alpha_1$-acid glycoprotein concentration.\textsuperscript{13} The effect of HBV infection on TFV drug exposure has not been investigated.

Assessing TFV exposure across pregnant women with different viral infections and/or concomitant medications will provide valuable information about variability and generalizability of drug exposure in this vulnerable population. Our aim was to compare the effect of pregnancy on TFV exposure in women with HIV receiving TDF-based ART, subdivided into $r$/$PI$-based regimens, and regimens without $r$/$PI$s (eg, integrase strand transfer inhibitor– or nonnucleoside reverse transcriptase inhibitor–based treatment) with the effect of pregnancy on TFV exposure in women with HBV receiving TDF monotherapy for the prevention of mother-to-child transmission.

**Methods**

Data from 2 clinical trials, PANNA (Pharmacokinetics of Antiretroviral Agents in HIV-Infected Pregnant Women; ClinicalTrials.gov NCT00825929) and iTAP (Maternal Antiviral Prophylaxis to Prevent Perinatal Transmission of Hepatitis B Virus in Thailand; ClinicalTrials.gov NCT01745822), were used to assess the pregnancy effect and concomitant treatments on TFV exposure among women with HIV or HBV. Both studies were approved by the ethical committees of the participating centers and by national authorities, if applicable. Signed informed consent was obtained from all participants before participation.

PANNA is an ongoing European multicenter study examining the PK of ARVs in pregnant women living with HIV.\textsuperscript{14} All women undergo intensive PK sampling during the third trimester and postpartum. For this analysis, women with HIV on ART containing TDF were selected and then subdivided into 2 groups: (1) women receiving ART with a once- or twice-daily $r$/$PI$ and (2) women receiving ART containing either a nonnucleoside reverse transcriptase inhibitor, integrase strand transfer inhibitor, or maraviroc (non-$r$/$PI$). TDF data collected within PANNA have been previously published,\textsuperscript{5} but for this new analysis an additional 30 women with ante- and postpartum sampling have been included to the original data set, to enable the comparison of TFV PK parameters between $r$/$PI$- and non–$r$/$PI$-based regimens. Women with HBV coinfection were excluded ($n = 4$) along with women receiving cobicistat-boosted ART regimens, as these regimens are no longer recommended in pregnancy.\textsuperscript{15} TFV plasma concentrations were analyzed using a validated liquid chromatography–based assay (lower limit of quantification, 0.015 mg/L), and the laboratory at Radboud University Medical Center participates in external quality assurance programs for ARV drug quantification.\textsuperscript{5,16,17} TFV area under the plasma concentration–time curve from time 0 to 24 hours (AUC\textsubscript{0–24h}) and trough concentration (C\textsubscript{trough}) were determined using noncompartmental analysis (Phoenix 64, Certara, Princeton, New Jersey).

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.\textsuperscript{18} Sparse blood samples for PK analysis were collected at 32 and 36 weeks’ gestation and 1 and 2 months postpartum.\textsuperscript{7} TFV plasma concentrations were measured using a validated liquid chromatography–triple quadrupole mass spectrometry assay (lower limit of quantification, 0.020 mg/L) and the PHPT-AMS laboratory at Chiang Mai University participates in the same external quality assurance programs as the laboratory analyzing PANNA samples.\textsuperscript{16,17} Data at 32 weeks of pregnancy and 1 month postpartum were selected for this analysis to match the PK visits in PANNA. Individual TFV AUC\textsubscript{0–24h} and C\textsubscript{trough} during pregnancy and postpartum were estimated using the previously reported population PK model.\textsuperscript{7}

Geometric mean (GM) TFV AUC\textsubscript{0–24h} and C\textsubscript{trough} were reported for women with HIV ($r$/$PI$-based regimens and non–$r$/$PI$-based regimens) and women with HBV monoinfection during the third trimester of pregnancy and 1 month postpartum. To assess the pregnancy effect on exposure, intrindividually TFV AUC\textsubscript{0–24h} and C\textsubscript{trough} during the third trimester of pregnancy were compared to postpartum using a GM ratio with 90% confidence interval (90%CI). A
Mann-Whitney U test was used to evaluate statistical differences in PK parameters during pregnancy and postpartum, as well as the pregnancy effect on PK parameters between women with HIV and HBV. Furthermore, women with HIV on r/PIs were compared statistically to women with HIV without r/PIs to evaluate the DDI during pregnancy. A P value of <.01 was considered statistically significant.

Results

Data from 59 pregnant women with HIV enrolled in the PANNA study and 137 women with HBV monoinfection from the iTAP study were included. The characteristics of the women and pregnancy outcomes are reported in Table 1. Among the women with HIV, 32 (54%) received TDF concomitantly with an r/PI. The estimated glomerular filtration rate postpartum was similar between both studies: 116 (106–130) versus 116 (100–128) mL/min/1.73m² in women with HIV and HBV, respectively.

A summary of the GM of the TFV PK parameters is shown in Table 2. Between the third trimester of pregnancy and 1 month postpartum, no significant difference was observed in TFV AUC₀–₂₄h and Cₜᵣᵻₒᵤₜ₉ when comparing women with HIV without r/PIs and women with HBV. However, the GM (95% CI) TFV AUC₀–₂₄h was significantly different in women with HIV treated with r/PIs compared to women with HBV: 2.41 (2.20–2.65) vs 1.84 (1.77–1.92) μg · h/mL (P < .01). The GM TFV Cₜᵣᵻₒᵤ₉ was also significantly different in pregnant women with HIV on r/PIs compared to pregnant women with HBV: 0.048 (0.043–0.054) vs 0.039 (0.038–0.042) μg/mL (P < .01).

Boxplots of TFV AUC₀–₂₄h and Cₜᵣᵻₒᵤ₉ in pregnant and postpartum HBV- and HIV-infected patients are shown in Figure 1; a summary of the GM ratio of these PK parameters is shown in Table 2. The relative impact of pregnancy on TFV PK parameters was comparable between women with HIV and HBV. Tenofovir AUC₀–₂₄h was 25%, 26%, and 21% lower during the third trimester of pregnancy compared to 1 month postpartum in women with HIV on r/PI-based regimens, women with HIV on non–r/PI-based regimens and women with HBV, respectively. Pregnancy decreased the TFV Cₜᵣᵻₒᵤ₉ on average by 19%, 32%, and 31% in women with HIV on r/PI-based regimens, women with HIV on non–r/PI-based regimens, and women with HBV, respectively. Large variability was observed in the pregnancy effect on TFV Cₜᵣᵻₒᵤ₉, and statistical analysis showed no significant effect in both
Table 1. Patient Characteristics

|                                | PANNA (n = 59) | iTAP (n = 137) |
|--------------------------------|----------------|----------------|
| Maternal age, y median (IQR)   | 32 (26–36)     | 26 (23–29)     |
| Ethnicity, n (%)               |                |                |
| White                           | 19 (32)        | Asian: 137 (100) |
| Black                           | 36 (61)        |                |
| Asian                           | 2 (3)          |                |
| Other                           | 2 (3)          |                |
| Concomitant antiretrovirals, n (%) |                |                |
| PI:                             | 32 (54)        | NA             |
| - Atazanavir:                   | 16 (27)        |                |
| - Darunavir:                    | 11 (19)        |                |
| - Fosamprenavir:                | 1 (2)          |                |
| - Lopinavir:                    | 2 (3)          |                |
| - Saquinavir:                   | 2 (3)          |                |
| - Ritonavir:                    | 32 (54)        |                |
| INSTI: 9 (15); NNRTI:           | 20 (34); Other: 2 (3) |
| Duration of TDF treatment at moment of first curve, mo, median (IQR) | 13 (5–34) | 1 (1–1) |
| Third trimester                 | n = 58         | n = 124        |
| Gestational age, weeks (median [IQR range]) | 34 (33–35) | 32 (32–32) |
| Body weight, kg (median [IQR range]) | 75 (67–82) | 64 (58–73) |
| HIV-RNA undetectable,<50 copies / mL (n [%]) | 48 (83%) | 1 unknown |
| Postpartum                      | n = 53         | n = 115        |
| Time after delivery, wk, median (IQR) | 5 (5–7) | 4 (4–5) |
| Body weight, kg, median (IQR)   | 70 (61–77)     | 56 (51–63)     |
| Estimated glomerular filtration rate, mL/min/1.73 m², median (IQR) | 116 (106–130) | 116 (100–128) |
| HIV-RNA undetectable,<50 copies/mL, n (%) | 46 (87%) | 1 unknown |
| Pregnancy outcomes              |                |                |
| Gestational age at delivery, wk, median (IQR) | 39 (38–40) | 39 (38–40) |
| Birth weight, g, median (IQR)   | 3160 (2750–3520) | 3050 (2766–3310) |
| Infant VL HIV RNA load undetectable, n (%) | 52 (100) | 7 unknown |

IQR, interquartile range; INSTI, integrase strand transfer inhibitor; NA, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TDF, tenofovir disoproxil fumarate; VL, viral load.

Discussion

The observed relative effect of pregnancy on TFV exposure was similar in women with HIV on TDF with r/PIs, TDF without r/PIs, and women with HBV monoinfection receiving TDF alone. TFV exposure was decreased by approximately 25% during the third trimester of pregnancy in all groups of women, probably driven by increased renal clearance. Thus, reduced TFV exposure during the third trimester of pregnancy seems independent of HIV or HBV infection and of r/PI coadministration. This demonstrates that, despite the physiological alterations in pregnancy, the interaction between r/PIs and TFV is similar in pregnant and nonpregnant women.

When comparing women with HIV on a non–r/PI-based regimen with women with HBV, a similar absolute TFV exposure was observed. This indicates that HIV and/or HBV viral infection has limited impact on TFV exposure. In healthy subjects in the fed state, a mean TFV AUC0–24h of 2.46 ± 0.83 μg · h/mL is reported in the registration package. This TFV AUC0–24h is similar to that observed in the women with HBV monoinfection postpartum (GM [95%CI]: 2.35 [2.24–2.47] μg·h/mL) and women with HIV postpartum without r/PIs (GM [95%CI]: 2.51 [2.32–2.83] μg · h/mL). Known physiological changes in hepatic metabolism, gastric pH, and plasma related to HIV or HBV may affect drug exposure in these groups compared to healthy individuals.13,19,20 The low plasma protein binding and renal elimination of TFV could explain the limited impact of HIV and HBV infection on TFV exposure. Although adults living with HIV are at higher risk for acute and chronic kidney disease, this is not expected to impact the TFV PK in our relatively young pregnant population.21 Concentrations of the active anabolite of TFV, tenofovir diposphlate (TFV-DP), have been reported to be 27% to 37% lower in dried blood spot samples in pregnant women receiving preexposure prophylaxis compared to nonpregnant women or women postpartum,22,23 but unfortunately no data on TFV-DP in peripheral blood mononuclear cells or dried blood spots samples were available in the PANNA or iTAP studies to compare the effect of HIV and HBV infection on intracellular TFV-DP drug concentrations.

r/PI use in women with HIV significantly increased the TFV GM AUC0–24h and Ctrough during pregnancy compared to women with HIV on non–r/PI-based regimens and women with HBV receiving TDF alone. The magnitude of the DDI between TDF and r/PI does not seem to be influenced by the physiological changes during pregnancy, as a similar relative decreased exposure was observed across all groups. Due to the lowering effect of pregnancy on TFV PK, and the increased exposure due to the DDI between r/PI and TDF,
Table 2. The AUC\textsubscript{0–24} and \( C_{\text{trough}} \) in Pregnant, Postpartum, and Pregnant Compared With Postpartum HIV- and HBV-Infected Patients

| Subgroup | Third Trimester GM (95%CI) | Postpartum GM (95%CI) | Ratio Third Trimester/Postpartum GMR (90%CI)\textsuperscript{a} |
|----------|-----------------------------|------------------------|--------------------------------------------------|
| AUC\textsubscript{0–24}, µg · h/mL | | | |
| HIV | All patients (n = 59) 2.14 (1.97–2.33) 2.84 (2.59–3.10) 0.75 (0.70–0.80) |
| - r/PI (n = 32) 2.41 (2.20–2.65) \textsuperscript{b,c} 3.21 (2.83–3.64) \textsuperscript{b,c} 0.76 (0.69–0.83) |
| - Non r/PI (n = 27) 1.86 (1.64–2.11) 2.51 (2.24–2.83) 0.74 (0.68–0.82) |
| HBV | All patients (n = 137) 1.84 (1.77–1.92) 2.35 (2.24–2.47) 0.79 (0.78–0.80) |
| \( C_{\text{trough}}, \mu g/mL \) | | | |
| HIV | All patients (n = 59) 0.043 (0.039–0.047) 0.059 (0.053–0.066) 0.74 (0.67–0.81) |
| - r/PI (n = 32) 0.048 (0.043–0.054) \textsuperscript{b,c} 0.063 (0.053–0.075) 0.81 (0.69–0.94) |
| - Non-r/PI (n = 27) 0.038 (0.033–0.043) 0.056 (0.050–0.064) 0.68 (0.62–0.75) |
| HBV | All patients (n = 137) 0.039 (0.038–0.042) 0.058 (0.055–0.061) 0.69 (0.68–0.71) |

AUC\textsubscript{0–24}, area under the plasma concentration–time curve from time 0 to 24 hours; \( C_{\text{trough}}, \) trough concentration; CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio; HIV, hepatitis B virus; r/PI, ritonavir-boosted protease inhibitor.

\textsuperscript{a}Only women with paired third trimester and postpartum data were included: 102 women with HBV and 51 women with HIV.

\textsuperscript{b}Statistically significant compared to women with HBV (\( P < .01 \)), tested for the 2 groups of women with HIV stratified by antiretroviral regimen: r/PI and non-r/PI.

\textsuperscript{c}Statistically significant compared to women with HIV without r/PI use (\( P < .01 \)).

The TFV exposure in pregnant women receiving r/PI remained within the expected range for nonpregnant women; therefore, this combination is expected to be safe and efficacious in pregnancy.

The main limitation of our study was the different PK study designs of the iTAP and PANNA trials. The PANNA study estimates PK parameters using noncompartmental analysis, while the iTAP study used a population PK approach. Nevertheless, we believe estimations of individual ante- and postpartum PK parameters to be accurate for both studies. It is also important to note that the women with HBV monoinfection were generally younger, Asian, and had a lower body weight. While oral clearance of tenofovir decreases slightly with age, it is unlikely that the small age different led to major differences in TFV oral clearance.\textsuperscript{11} Glomerular filtration rate (estimate using creatinine clearance) has been reported to be a factor influencing TFV exposure in pregnancy, and estimated glomerular filtration rate was similar in the women between studies.\textsuperscript{6,24} High body weight (>90 kg) has also been shown to be inversely correlated with TFV exposure, but women with such high weights were not included in this analysis.\textsuperscript{6} Also, the lower body weight of the women with HBV did not seem to lead to higher exposures as we found no statistical difference between the postpartum AUC\textsubscript{0–24} between women with HBV or HIV without r/PI use. Finally, race has been shown to influence PK through alterations in plasma protein binding and hepatic metabolism, but this is not likely applicable for TFV disposition due to its low protein binding and renal clearance.\textsuperscript{19,25} Finally, host genetic polymorphisms can influence antiretrovirals but in a study assessing multiple renal drug transporters polymorphisms were not found to be associated with TFV plasma concentrations.\textsuperscript{26}

Conclusions

Pregnancy had a similar effect on TFV PK following TDF administration regardless of HIV or HBV infection. Also, TFV exposure was similar in pregnant women with HBV monoinfection receiving TDF alone compared to pregnant women with HIV receiving ART without an r/PI, but lower when compared to women with HIV receiving TDF with an r/PI.

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Conflicts of Interest

D.B. has received research grants to his institution from Merck, BMS, Janssen/Tibotec, ViiV Healthcare, and Gilead and has received educational grants from Merck, was a speaker at a symposia for Merck, and is a member of the advisory board of ViiV Healthcare and Merck. G.J. has received a grant from Gilead. V.B., E.S, A.C., and T.C. declare no conflicts of interest.

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**Author Contributions**

All authors take responsibility for the integrity of the data and the accuracy of the data analysis and have approved the final version of the article. T.C., A.C., D.B., and E.S. conceived the study. V.B. analyzed the data and drafted the article. A.C., E.S., and V.B. critically reviewed the study design and interpretation of the data. D.B., G.J., and T.C. reviewed the article and its scientific contents.

**Data Sharing Statement**

The authors cannot share the individual data used in this article.

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