The Journal of Clinical Pharmacology
2021, 61(3) 388–393

DOI: 10.1002/jcph.1746

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

Vera E. Bukkems, PharmD[1†], Elise J. Smolders, PhD[1,2†], Gonzague Jourdain, MD, PhD[3,4], David M. Burger[1], Angela P. Colbers, PhD[1], Tim R. Cressey, PhD[3,4,5], on behalf of the PANNA Network and iTAP Study Group[1]

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

[1]Department of Pharmacy, Radboud Institute of Health Sciences (RIHS), Radboud University Medical Center, Nijmegen, The Netherlands
[2]Department of Pharmacy, Isala Hospital, Zwolle, The Netherlands
[3]French National Research Institute for Sustainable Development (IRD), Marseille, France
[4]PHPT/IRD UMI 174, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand
[5]Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK

Submitted for publication 14 July 2020; accepted 28 August 2020.

Corresponding Author:
Vera E. Bukkems, PharmD, Department of Pharmacy, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands
Email: Vera.Bukkems@radboudumc.nl

[†]Drs. Bukkems and Smolders contributed equally to this work

[Correction added on 28 September 2020, after first online publication: "Temofovir" is replaced with "Tenofovir" in the title.]

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.[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.[12,13] For example, studies indicate that protease inhibitor concentrations are altered in individuals with HIV compared to healthy subjects.[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 α_1-acid glycoprotein concentration.[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/PIs (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.[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,[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.[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.[5,16,17] TFV area under the plasma concentration–time curve from time 0 to 24 hours ($AUC_{0–24h}$) and trough concentration (C_{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.[18] Sparse blood samples for PK analysis were collected at 32 and 36 weeks' gestation and 1 and 2 months postpartum.[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.[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 $AUC_{0–24h}$ and C_{trough} during pregnancy and postpartum were estimated using the previously reported population PK model.[7]

Geometric mean (GM) TFV $AUC_{0–24h}$ and C_{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, intraindividually TFV $AUC_{0–24h}$ and C_{trough} during the third trimester of pregnancy were compared to postpartum using a GM ratio with 90% confidence interval (90%CI). A

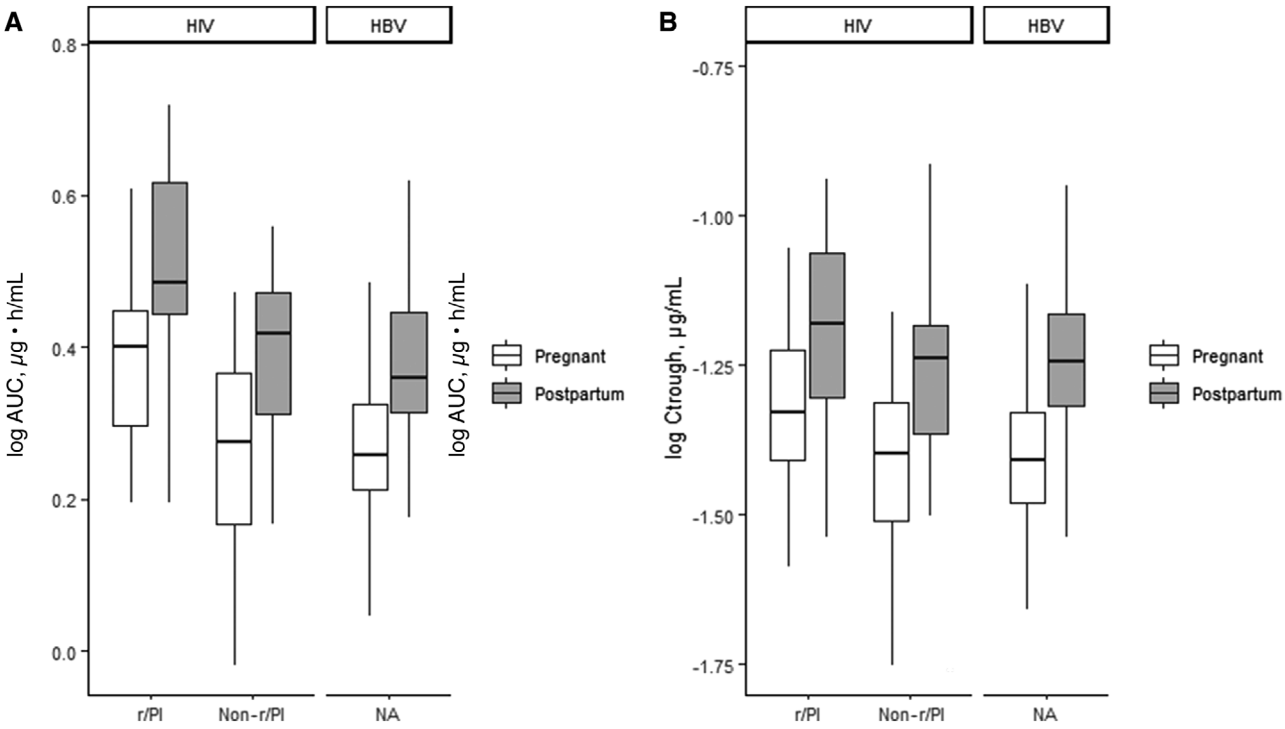

Figure 1. Boxplots of tenofovir pharmacokinetic parameters in pregnant and postpartum women with HIV or HBV. A, log $AUC_{0–24}$; B, log C_{trough}. Boxplots show median (line in the box), interquartile range (box), and minimum and maximum (vertical lines). $AUC_{0–24}$, area under the plasma concentration–time curve from time 0 to 24 hours; C_{trough}, trough concentration; HBV, hepatitis B virus; NA, not applicable; r/PI, concomitant use of ritonavir-boosted protease inhibitors.

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/1.73m^2 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 $AUC_{0–24h}$ and C_{trough} when comparing women with HIV without r/PIs and women with HBV. However, the GM (95%CI) TFV $AUC_{0–24h}$ 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 C_{trough} 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 $AUC_{0–24h}$ and C_{trough} 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 $AUC_{0–24h}$ 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 C_{trough} 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 C_{trough}, 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) Black: 36 (61) Asian: 2 (3) Other: 2 (3)	Asian: 137 (100)
Concomitant antiretrovirals, n (%)	PI: 32 (54) - 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)	NA
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 [IQ range])	34 (33–35)	32 (32–32)
Body weight, kg (median [IQ range])	75 (67–82)	64 (58–73)
HIV-RNA undetectable <50 copies / mL (n [%])	48 (83%): 1 unknown	NA
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 m^2, median (IQR)[a]	116 (106–130)	116 (100–128)
HIV-RNA undetectable <50 copies/mL, n (%)	46 (87): 1 unknown	NA
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	NA

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.
[a]Estimated with Chronic Kidney Disease Epidemiology Collaboration equation.[27,28]

groups of women with HIV compared to women with HBV.

Tenofovir PK parameters of pregnant women living with HIV on r/PI-based regimens were significantly different from pregnant women living with HIV on non–r/PI-based regimens ($P < .01$). A GM $AUC_{0–24h}$ of 2.41 and 1.86 μg · h/mL was observed in HIV-infected women with r/PI and non-r/PI, respectively. Similarly, the C_{trough} of women with HIV on r/PI was significantly different from women on non–r/PI-based regimens ($P < .01$).

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 $AUC_{0–24h}$ of 2.46 ± 0.83 μg · h/mL is reported in the registration package. This TFV $AUC_{0–24h}$ 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 diphosphate (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 $AUC_{0–24h}$ and C_{trough} 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 $AUC_{0–24}$ and C_{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)[a]
$AUC_{0–24h}$, 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) [b,c]	3.21 (2.83–3.64)[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_{trough}, μg/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)[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)

$AUC_{0–24}$, area under the plasma concentration–time curve from time 0 to 24 hours; C_{trough}, trough concentration; CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio; HBV, hepatitis B virus; r/PI, ritonavir-boosted protease inhibitor.

[a] Only women with paired third trimester and postpartum data were included: 102 women with HBV and 51 women with HIV.

[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.

[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.[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.[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.[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 $AUC_{0–24h}$ 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.[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.[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.

Acknowledgments

We thank all patients and all investigators of both the iTAP study and the PANNA study. In addition, we thank Lizzy van Gaalen for the sample analysis and the employees of the Radboud University Medical Center laboratory, PHPT clinical trial unit, and PHPT-AMS laboratory.

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.

Funding

No specific funding was received for this retrospective analysis.

The PANNA network is financially supported by the by the European AIDS Treatment Network/European Commission/DG Research, Sixth Framework program (contract LSHP-CT-2006–037570), Merck Sharp & Dohme Corp., Bristol-Myers Squibb, Gilead, Janssen Research, and ViiV Healthcare.

The iTAP study was supported by a grant from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (U01HD071889) under a cooperative agreement between the National Institute of Child Health & Human Development; the US Centers for Disease Control and Prevention; and the Institut de recherche pour le développement, France. Study drugs (tenofovir disoproxil fumarate and matching placebo) were donated by Gilead Sciences Inc.. The study was conducted under an agreement between the Thailand International Cooperation Agency and the French Embassy to Thailand. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institutes of Health or the Centers for Disease Control and Prevention.

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.

References

1. WHO. Hepatitis B. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Published July 2018. Accessed May 1, 2019.
2. WHO. HIV/AIDS. https://www.who.int/en/news-room/fact-sheets/detail/hiv-aids. Published July 2018. Accessed May 1, 2019.
3. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. *Clin Pharmacokinet*. 2005;44(10):989-1008.
4. Dawes M, Chowienczyk PJ. Drugs in pregnancy. Pharmacokinetics in pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2001;15(6):819-826.
5. Colbers AP, Hawkins DA, Gingelmaier A, et al. The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women. *AIDS*. 2013;27(5):739-748.
6. Best BM, Burchett S, Li H, et al. Pharmacokinetics of tenofovir during pregnancy and postpartum. *HIV Med*. 2015;16(8):502-511.
7. Cressey TR, Harrison L, Achalapong J, et al. Tenofovir exposure during pregnancy and postpartum in women receiving tenofovir disoproxil fumarate for the prevention of mother-to-child transmission of Hepatitis B virus. *Antimicrob Agents Chemother*. 2018;62(12).
8. Chittick GE, Zong J, Blum MR, et al. Pharmacokinetics of tenofovir disoproxil fumarate and ritonavir-boosted saquinavir mesylate administered alone or in combination at steady state. *Antimicrob Agents Chemother*. 2006;50(4):1304-1310.
9. Hoetelmans RM, Marien K, De Pauw M, et al. Pharmacokinetic interaction between TMC114/ritonavir and tenofovir disoproxil fumarate in healthy volunteers. *Br J Clin Pharmacol*. 2007;64(5):655-661.
10. EMA. Prezista; summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/prezista-epar-product-information_en.pdf. Published 2019. Accessed November 18, 2020.
11. Benaboud S, Hirt D, Launay O, et al. Pregnancy-related effects on tenofovir pharmacokinetics: a population study with 186 women. *Antimicrob Agents Chemother*. 2012;56(2):857-862.
12. Petrovic V, Teng S, Piquette-Miller M. Regulation of drug transporters during infection and inflammation. *Mol Interv*. 2007;7(2):99-111.
13. Dickinson L, Khoo S, Back D. Differences in the pharmacokinetics of protease inhibitors between healthy volunteers and HIV-infected persons. *Curr Opin HIV AIDS*. 2008;3(3):296-305.
14. PANNA Network. http://www.pannastudy.com/. Accessed September 6, 2019.
15. Boyd SD, Sampson MR, Viswanathan P, Struble KA, Arya V, Sherwat AI. Cobicistat-containing antiretroviral regimens are not recommended during pregnancy: viewpoint. *AIDS*. 2019;33(6):1089-1093.
16. Clinical Pharmacology Quality Assurance Program. http://www.buffalo.edu/tprc/section-2/CPQA.html. Accessed August 2, 2019.
17. DiFrancesco R, Tooley K, Rosenkranz SL, et al. Clinical pharmacology quality assurance for HIV and related infectious diseases research. *Clin Pharmacol Ther*. 2013;93(6): 479-482.
18. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med*. 2018;378(10):911-923.
19. Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet*. 2004;43(9):595-612.
20. Reesink HW, Fanning GC, Farha KA, et al. Rapid HCV-RNA decline with once daily TMC435: a phase I study in healthy volunteers and Hepatitis C patients. *Gastroenterology*. 2010;138(3):913-921.
21. Wyatt CM. Kidney disease and HIV infection. *Top Antivir Med*. 2017;25(1):13-16.
22. Pyra M, Anderson PL, Hendrix CW, et al. Tenofovir and tenofovir-diphosphate concentrations during pregnancy among HIV-uninfected women using oral preexposure prophylaxis. *AIDS*. 2018;32(13):1891-1898.
23. Anderson PL, Stranix-Chibanda LS, Huang S, et al. TFV-DP in DBS for pregnant/postpartum adolescent and young women on PrEP in Africa, abstract #0980. Conference on Retroviruses and Opportunistic Infections March 8-11 2020, Boston, Massachusetts.
24. Hirt D, Urien S, Ekouevi DK, et al. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). *Clin Pharmacol Ther*. 2009;85(2):182-189.
25. Johnson JA. Predictability of the effects of race or ethnicity on pharmacokinetics of drugs. *Int J Clin Pharmacol Ther*. 2000;38(2):53-60.
26. Sirirungsi W, Urien S, Harrison L, et al. No relationship between drug transporter genetic variants and tenofovir plasma concentrations or changes in glomerular filtration rate in HIV-infected adults. *J Acquir Immune Defic Syndr*. 2015;68(4):e56-e59.
27. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
28. Wang J, Xie P, Huang JM, et al. The new Asian modified CKD-EPI equation leads to more accurate GFR estimation in Chinese patients with CKD. *Int Urol Nephrol*. 2016;48(12):2077-2081.