### Title

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### Journal

Journal of Clinical Pharmacy and Therapeutics, 46(5)

### ISSN

0269-4727



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### Publication Date

2021-10-01

### DOI

10.1111/jcpt.13477

Peer reviewed

HHS Public Access

Author manuscript

*J Clin Pharm Ther*. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

*J Clin Pharm Ther*. 2021 October ; 46(5): 1459–1464. doi:10.1111/jcpt.13477.

# Lopinavir and Tenofovir Interaction Observed in Non-Pregnant Adults Altered During Pregnancy

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## Abstract

**What is Known and Objective:** Tenofovir exposure is increased in non-pregnant adults when tenofovir disoproxil fumarate is co-administered with lopinavir/ritonavir. In pregnant women, tenofovir exposure is decreased. Our objective is to describe the effect of lopinavir/ritonavir on tenofovir pharmacokinetics during pregnancy.

**Methods:** Data were collected through the International Maternal Pediatric and Adolescent AIDS Clinical Trials (IMPAACT) Network P1026s protocol. This was a nonrandomized, open-label, parallel-group, multi-center phase-IV prospective study in pregnant women with HIV.

Intensive steady-state 24-hour pharmacokinetic profiles were collected during the third trimester of pregnancy and postpartum. Tenofovir was measured in plasma using validated liquid chromatography-mass spectrometry method (quantification limit: 10 ng/mL). Statistical tests compared paired and between group pharmacokinetic data.

**Results and Discussion:** In women not receiving lopinavir/ritonavir (n=28), tenofovir $AUC_{0–24}$ was 27% lower (2.2 mcg*hr/mL vs 2.8 mcg*hr/mL, p = 0.002) and oral clearance was 27% higher (61 L/hr vs 48 L/hr, p = 0.001) during the third trimester compared to paired postpartum data. In women receiving lopinavir/ritonavir (n = 10), tenofovir $AUC_{0–24}$ and oral clearance were not different antepartum compared to postpartum. Women with and

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women without concomitant lopinavir/ritonavir displayed no significant differences in postpartum tenofovir pharmacokinetics.

**What is New and Conclusion:** Tenofovir exposure during the third trimester was reduced compared to postpartum in pregnant women not receiving lopinavir/ritonavir, but not in pregnant women also receiving lopinavir/ritonavir. Our findings suggest that pregnancy confounds the expected decrease in tenofovir exposure with concomitant lopinavir/ritonavir in non-pregnant adults. These findings illustrate the need for drug-drug interaction studies in pregnant women as drug disposition differs significantly in pregnant women compared to non-pregnant adults.

### Keywords

tenofovir; Viread ™; Truvada ™; Kaletra; lopinavir; nucleoside reverse transcriptase inhibitor; pregnancy; HIV infection; pharmacokinetics; mother-to-child transmission; perinatal transmission; drug-drug interaction; kidney; drug transporters

## What is Known and Objective

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor (NRTI) prodrug used for the treatment of HIV type 1, HIV type 2, and hepatitis B. The standard oral dose in non-pregnant adults is 300 mg of TDF daily - corresponding to 245 mg of tenofovir - which is converted intracellularly to the active diphosphate metabolite.[1] No dose adjustments are recommended for TDF in pregnant women.[2] Tenofovir is a substrate for several renal drug transporters, including organic anion transporters 1 and 3 (OAT1, OAT3) as well as multidrug resistance proteins 2, 4, and 7 (MRP2, MRP4, MRP7), all of which are potentially affected by pregnancy.[3]

In non-pregnant adults, coadministration of TDF with lopinavir/ritonavir increases tenofovir exposure.[4–6] On the other hand, multiple studies have reported decreased tenofovir exposure during the third trimester of pregnancy.[7–9] However, the pharmacokinetics of tenofovir when coadministered with lopinavir/ritonavir in pregnant women have not been described. The mechanisms by which pregnancy lowers tenofovir exposure or by which lopinavir/ritonavir increases tenofovir exposure are thought to be due to increased renal clearance in pregnancy and increased volume of distribution.[7–9] As such, the effect of concomitant lopinavir/ritonavir on tenofovir pharmacokinetics during pregnancy cannot be predicted. Subtherapeutic concentrations of tenofovir could increase the risk of viral replication while elevated tenofovir exposure is linked to increased kidney dysfunction in non-pregnant adults.[10] A previous review examining drug-drug interactions in pregnancy demonstrated that multiple studies show the clinical relevance of a drug-drug interaction can change during pregnancy.[11] The objective of this analysis was to determine the effect of lopinavir/ritonavir on tenofovir exposure in pregnant women.

## Methods

IMPAACT P1026s was a prospective, non-blinded pharmacokinetic study that enrolled pregnant women with and without HIV at study sites throughout the world (NCT00042289). Each study site received local ethical review board approval and all women were consented.

Intensive steady-state 24-hour profiles for TDF 300 mg daily were collected from pregnant women with HIV in the second trimester (20–28 weeks gestation), third trimester (30–38 weeks gestation), and postpartum (6–12 weeks after delivery) between 2005 and 2009. We included pregnant women receiving TDF 300 mg daily who were then categorized into 2 primary treatment groups: those receiving lopinavir/ritonavir (400 mg/100 mg twice daily) and those not receiving lopinavir/ritonavir. The group not receiving lopinavir/ritonavir was further stratified into those receiving concomitatnt atazanvir/ritonavir (300/100 mg twice daily) or other regimens. The primary study results have been previously reported.[8]

After drawing a pre-dose sample on site, TDF was dosed under observation and blood samples were drawn at 1, 2, 4, 6, 8, 12, and 24 hours post-dose. Plasma concentrations of tenofovir were measured by a validated liquid chromatography with tandem mass spectrometry method (lower limit of quantification: 10 ng/mL). Tenofovir plasma minimum ($C_{min}$), maximum ($C_{max}$), and trough concentrations ($C_{24}$) and corresponding time points were observed directly. Area under the concentration versus time curve from time 0 to 24 hours post-dose ($AUC_{0–24}$) was estimated with the trapezoidal rule. The elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$ where $\lambda_z$ is the elimination rate constant derived from the terminal slope of the log concentration versus time curve. Apparent oral clearance (CL/F) from plasma was calculated as dose divided by $AUC_{0–24}$. Undetectable concentrations of tenofovir were set at half the lower limit of quantification to calculate summary statistics. The Wilcoxon signed rank test compared paired pharmacokinetic data during the third trimester to postpartum for each group, and Kruskal-Wallis tests compared pharmacokinetic parameters between women in the three different groups (lopinavir/ritonavir, atazanavir/ritonavir and other) with a two-sided p-value $< 0.05$.

## Results and Discussion

Tenofovir plasma concentration data were available for 44 pregnant women in the third trimester, 32 women at the time of delivery (cord blood and single maternal samples), and 38 women postpartum. The median (range) maternal age at third trimester was 31.2 years (13.5–44.9) and weight was 80.6 kg (50.8–167.6). Twelve women were taking concomitant lopinavir/ritonavir, 22 were taking concomitant atazanavir/ritonavir, and 10 women were taking other protease inhibitors or non-nucleoside reverse transcriptase inhibitors (efavirenz n=1; fosamprenavir/ritonavir n=2; nelfinavir n=4; nevirapine n=1; saquinavir n=2). Demographic data including race, age, weight and serum creatinine are summarized by treatment group (lopinavir/ritonavir, atazanavir/ritonavir, or other) in Table 1.

The effect of lopinavir/ritonavir on tenofovir pharmacokinetics was evaluated in the third trimester (n = 22 with atazanavir/ritonavir, n = 12 with lopinavir/ritonavir, n = 10 with other regimens) and postpartum (n = 20 with atazanavir/ritonavir, n = 10 with lopinavir/ritonavir, n = 8 with other regimens). No significant differences were observed in tenofovir pharmacokinetic parameters antepartum vs. postpartum among women receiving concomitant lopinavir/ritonavir (Table 2). The median (interquartile range; IQR) $AUC_{0–24}$ was 3.0 mcg*hr/mL (2.4 – 3.4) in the third trimester and 3.0 mcg*hr/mL (1.8 – 3.8) postpartum (Table 2). The half-life ($t_{1/2}$) of tenofovir in women taking lopinavir/ritonavir in

the third trimester was 17.5 h (15.2 – 18.5) and 12.5 h (11.9 – 19.9) postpartum, with no statistically significant difference between the two.

In patients not receiving concomitant lopinavir/ritonavir, the median (IQR) tenofovir $AUC_{0–24}$ was 2.2 mcg*hr/mL (1.8 – 2.6) in the third trimester and 2.8 mcg*hr/mL (2.3 – 3.6) postpartum ($p = 0.002$). The median (IQR) tenofovir CL/F in this group was 61 L/hr (52 – 78) in the third trimester and 48 L/hr (38–59) postpartum ($p < 0.001$). In the atazanavir/ritonavir subgroup, a statistically significant 25% decrease in tenofovir $AUC_{0–24}$ and 33% increase in CL/F was observed during the third trimester as compared to postpartum ($AUC_{0–24}$ $p = 0.006$, CL/F $p = 0.002$). In the subgroup of women who received other regimens, differences in $AUC_{0–24}$ did not reach statistical significance (Figure 1). The tenofovir $t_{1/2}$ of patients receiving atazanavir/ritonavir in the third trimester was 15.6 h (13.9 – 18.3) and in patients receiving other regimens in the third trimester was 15.9 h (14.3 – 19.2); no statistical difference was found in tenofovir $t_{1/2}$ in these groups compared to lopinavir/ritonavir administered in the third trimester (Table 2). Similar trends were seen postpartum with the atazanvir/ritonavir group's tenofovir $t_{1/2}$ at 12.8 h (11.6 – 19.7) and other regimens $t_{1/2}$ at 12.4 h (10.6 – 15.7), also with no significant difference compared to the lopinavir/ritonavir's group tenofovir $t_{1/2}$ of 12.5 h (11.9 – 19.9) postpartum.

No significant differences in tenofovir concentrations were found in cord samples or maternal plasma at time of cord sampling between women taking lopinavir/ritonavir compared to women not taking lopinavir/ritonavir. Similarly, no significant differences were found in tenofovir cord or maternal concentrations between women taking lopinavir/ritonavir, women taking atazanavir/ritonavir, and women taking other antiretrovirals.

Previous studies, including the initial analysis of P1026s study data, found tenofovir exposure was 20–33% lower and clearance was 22–39% higher in the third trimester of pregnancy compared to postpartum.[7–9] This finding illustrates the effect of physiological changes during pregnancy on drug disposition. However, stratification of pregnant women by concomitant lopinavir/ritonavir use displayed two distinct patterns in tenofovir exposure. Among women not receiving lopinavir/ritonavir, tenofovir exposure was 27% lower and clearance was 27% higher in the third trimester compared to postpartum. In contrast, tenofovir exposure was unchanged between pregnancy and postpartum in women receiving lopinavir/ritonavir. Further stratification by concomitant lopinavir/ritonavir, atazanavir/ritonavir, and other antiretroviral regimens found similar trends (Table 2). Tenofovir exposure was comparable between the third trimester of pregnancy and postpartum among women receiving concomitant lopinavir/ritonavir. Both women receiving atazanavir/ritonavir as well as women with other antiretroviral regimens had lower tenofovir exposure in the third trimester compared to postpartum. The tenofovir $AUC_{0–24}$ was significantly lower with atazanavir/ritonavir use and non-significantly lower with other antiretroviral use in the third trimester compared to postpartum.

Tenofovir is eliminated primarily by the kidneys by a combination of glomerular filtration and active tubular secretion. The basolateral uptake into the proximal tubules is mediated by OAT1 and OAT3, whereas apical efflux is mediated by MRP2, MRP4, and MRP7.[3,12–15] Studies in proximal tubule isolates suggest MRP4 (ABCC4) is the key tenofovir efflux

kidney transporter.[3,16] Both ritonavir and lopinavir inhibit hOAT3 *in vitro* and ritonavir also inhibits MRP4 although at concentrations greater than achieved with therapeutic doses.[17] These *in vitro* results suggest that the apparent drug-drug interaction between tenofovir and lopinavir/ritonavir may be at least partially due to inhibition of tenofovir transport into the renal tubule. Uptake experiments also suggest that hOAT1 and hOAT3 are significant tenofovir influx transporters with hOAT1 having greater affinity but hOAT3 having greater expression in the proximal tubule.[3,18] However, the clinical relevance of lopinavir/ritonavir inhibiting OATs and MRP4 *in vitro* is debatable because the concentrations necessary for this effect are higher than those achieved clinically.

The present study indicates that pregnancy unexpectedly alters the drug-drug interaction between tenofovir and lopinavir/ritonavir as seen in the lack of difference in tenofovir levels in the third trimester versus postpartum for women taking concomitant lopinavir/ritonavir. Pregnancy affects all aspects of renal physiology, including increases in renal plasma flow and glomerular filtration rate (GFR) of approximately 80% and 50%, respectively, compared to non-pregnant levels.[19] In this study, a decrease of serum creatinine in the third trimester compared to postpartum was noted in women taking lopinavir/ritonavir and atazanavir/ritonavir; all women had normal renal function (Table 1). Tubular secretion increases during pregnancy as well, though recent physiologically-based pharmacokinetic analyses suggest that increased secretion is related to increased renal plasma flow and not due to pregnancy-related changes in OAT1/3, MATE1, and MRP4 activity. Tubular function is also altered, though this is less well understood at the level of individual transporters.. No data exist on the impact of human pregnancy on activity or drug-drug interactions at these transporters.[20] Another possible explanation for the lack of decreased tenofovir exposure during pregnancy may be that lopinavir/ritonavir increases the bioavailability of F through increased absorption of tenofovir, thus driving the decrease in CL/F seen in the lopinavir/ritonavir group. The observed changes in tenofovir AUC and Cmax may be explained by lopinavir potentially increasing tenofovir's limited absorption in the gut.[21] These differences in renal function and absorption in pregnancy demonstrate the need for evaluating drug pharmacokinetics including drug-drug interactions in pregnant women, as data from non-pregnant adults can differ significantly.

## What is New and Conclusion

Among non-pregnant adults, tenofovir exposure is increased by 32% with concomitant lopinavir/ritonavir.[1] Ritonavir is known to act as a booster for HIV agents metabolized by CYP3A4 by inhibiting CYP3A4 metabolism; however, tenofovir is not a CYP3A4 substrate and is instead eliminated solely through renal clearance. Therefore, inhibition of CYP3A4 inhibition by ritonavir does not account for the increase in tenofovir exposure with lopinavir/ritonavir. Additionally, the lack of decreased tenofovir exposure in pregnancy observed with concomitant lopinavir/ritonavir does not appear to be a class effect with boosted protease inhibitors. However, ritonavir dosing differs between protease inhibitor regimens examined in this analysis. Notably, atazanavir/ritonavir increases tenofovir exposure in non-pregnant adults to a similar degree as lopinavir/ritonavir; however, atazanavir/ritonavir coadministration did not prevent the pregnancy-associated decrease in tenofovir exposure in the third trimester. Ritonavir is dosed at 100 mg once daily with atazanavir and at 200

mg daily or higher with lopinavir, typically as lopinavir/ritonavir 400 mg/100 mg twice daily; increased doses of 600 mg/150 mg twice daily have been studied in pregnancy. Ritonavir is utilized as a CYP3A4 inhibitor to boost concentrations of CYP3A4 substrates including lopinavir or atazanavir. As such, ritonavir exposure is also impacted by protease inhibitors and would not be a simple two-fold difference between the lopinavir and atazanvir regimens. Ritonavir exposure is also decreased in pregnancy, with a previous analysis demonstrating a 68% increase in LPV/r clearance.[22] Various protease inhibitors are also CYP3A4 inhibitors as well, ranging from weak inhibition with saquinavir to very potent inhibition with ritonavir.[23] Administration of ritonavir-boosted protease inhibitors with TDF have been associated with renal function decline[24], thus demonstrating that the concentration of ritonavir may indirectly affect tenfovir pharmacokinetics by increasing exposure through impaired renal function. In women taking higher doses of ritonavir with a lopinavir/ritonavir combination during pregnancy, median tenofovir exposure was within the expected therapeutic range. Importantly, drug-drug-interaction studies performed in non-pregnant adults may not be generalizable to pregnant women, as pregnancy-related changes may modulate or counteract the expected interaction.

## Acknowledgements

We thank the study participants and their families. In addition to the authors, members of the IMPAACT P1026s protocol team include Jullapong, Achalapong, Francesca Aweeka, Emily Barr, Sandra K. Burchett, Tim Cressey, Lisa M. Frenkel, Kathy George, Katelyn Hergott, Benjamin Johnson, Gonzague Jourdain, Regis Kreitchmann, Pooja Mehta, Rita Patel, Kittipong Rungruengthanakit, David Shapiro, Pra-ornsuda Sukrakanchana, Elise Tjaden, and Marije Van Schalkwyk.

**Source of support that requires acknowledgement:**

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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**Study Highlights:**

Non-pregnant adults taking lopinavir/ritonavir with concomitant tenofovir have higher exposure of tenofovir. In contrast, pregnancy is known to decrease tenofovir exposure due to increased glomelular filtration and increased volume of distribution. Our study demonstrates that pregnant women who take lopinavir/ritonavir and tenofovir together do not see a decrease in tenofovir exposure; rather, tenofovir exposure is similar in the third trimester compared to postpartum. This demonstrates that drug interactions observed in non-pregnant adults may not be generalizable to pregnant women and that more dedicated drug-interaction studies should be conducted in pregnancy.

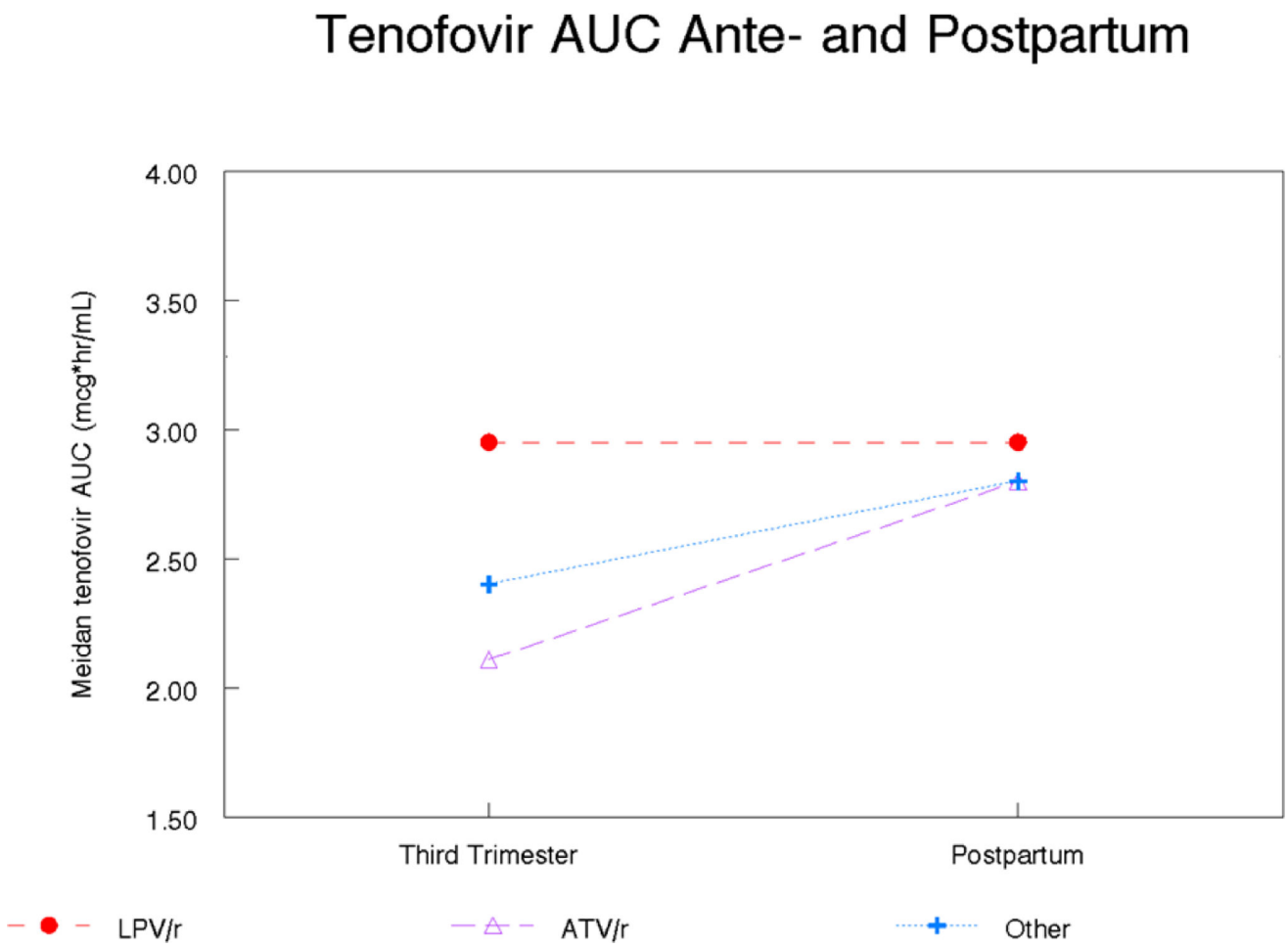


**Figure 1:**

Area under the concentration time curve ($AUC_{0–24}$) is shown among women receiving lopinavir/ritonavir (n = 12 in third trimester, n = 10 postpartum), women receiving atazanavir/ritonavir (n = 22 in third trimester, n = 20 postpartum) and women receiving other antiretroviral regimens not including ritonavir (n = 10 in third trimester, n = 8 postpartum).

**Table 1.**

Demographic Information Stratified by Treatment Regimen, Median (Range)

| | With LPV/r | Without LPV/r | |
|---|---|---|---|
| **Parameter** | | **With ATV/r** | **Other** |
| Race | n = 12 | n = 22 | n = 10 |
| White | 2 | 3 | 4 |
| Black | 5 | 8 | 3 |
| Hispanic | 5 | 10 | 2 |
| Asian/Pacific Islander | 0 | 1 | 0 |
| More than one race | 0 | 0 | 1 |
| Third Trimester | n = 11 | n = 20 | n = 9 |
| Age (years) | 30.8 (26.5 – 37.1) | 32.2 (22.2 – 44.9) | 25.3 (13.5 – 35.2) |
| Weight (kg) | 80.1 (56.7 – 106.2) | 85.8 (56.0 – 167.6) | 72.5 (50.8 – 110.0) |
| SCr (mg/dL) | 0.6 (0.3 – 0.8) | 0.6 (0.5 – 0.8) | 0.7 (0.6 – 0.8) |
| Postpartum | n = 9 | n = 13 | n = 7 |
| SCr (mg/dL) | 0.6 (0.6 – 1.0) | 0.7 (0.5 – 1.1) | 0.7 (0.6 – 0.8) |

LPV/r = lopinavir/ritonavir

**Table 2.**

Median (Interquartile Range) Tenofovir Pharmacokinetics

| Parameter | P Value[a] | With LPV/r | Without LPV/r | |
|---|---|---|---|---|
| | | | With ATV/r | Other |
| Third Trimester | | n = 12 | n = 22 | n = 10 |
| $AUC_{0-24}$ (mcg*hr/mL) | 0.062 | 3.0 (2.4 – 3.4) | 2.1 (1.6 – 2.4) | 2.4 (2.2 – 2.9) |
| $V_d/F$ (L/hr) | 0.311 | 1103 (973 – 1312) | 1284 (1120 – 2181) | 1159 (1037 – 1709) |
| CL/F (L/hr) | 0.062 | 46 (40 – 60) | 64 (57 – 85) | 57 (47 – 62) |
| $C_{min}$ (ng/mL) | 0.039 | 65 (48 – 76) | 43 (29 – 52) | 49 (40 – 61) |
| $C_{max}$ (ng/mL) | 0.053 | 301 (218 – 406) | 210 (191 – 269) | 284 (233 – 344) |
| $C_0$ (ng/mL) | 0.153 | 70 (53 – 85) | 48 (36 – 59) | 54 (42 – 67) |
| $C_{24}$ (ng/mL) | 0.087 | 68 (51 – 78) | 47 (31 – 64) | 55 (44 – 69) |
| $t_{1/2}$ (hr) | 0.783 | 17.5 (15.2 – 18.5) | 15.6 (13.9 – 18.3) | 15.9 (14.3 – 19.2) |
| Postpartum | | n = 10 | n = 20 | n = 8 |
| $AUC_{0-24}$ (mcg*hr/mL) | 0.944 | 3.0 (1.8 – 3.8) | 2.8 (2.2 – 3.6) | 2.8 (2.4 – 4.9) |
| $V_d/F$ (L/hr) | 0.446 | 1224 (643 – 1312) | 949 (676 – 1246) | 757 (514 – 1133) |
| CL/F (L/hr) | 0.944 | 49 (36 – 75) | 48 (38 – 63) | 49 (30 – 58) |
| $C_{min}$ (ng/mL) | 0.670 | 58 (5 – 76) | 53 (31 – 67) | 73 (39 – 83) |
| $C_{max}$ (ng/mL) | 0.852 | 257 (191 – 335) | 295 (219 – 366) | 289 (174 – 453) |
| $C_0$ (ng/mL) | 0.700 | 59.4 (5.0 – 77.8) | 60 (31 – 93) | 74 (50 – 118) |
| $C_{24}$ (ng/mL) | 0.486 | 48.2 (32.1 – 77.2) | 59 (46 – 78) | 81 (39 – 102) |
| $t_{1/2}$ (hr) | 0.781 | 12.5 (11.9 – 19.9) | 12.8 (11.6 – 19.7) | 12.4 (10.6 – 15.7) |

LPV/r = lopinavir/ritonavir; ATV/r = atazanavir/ritonavir

[a]P values for Kruskal-Wallis equality-of-population rank test comparing between LPV/r vs ATV/r vs Other categories for each pharmacokinetic parameter

Tenofovir pharmacokinetic parameters stratified by with or without concomitant use of LPV/r. Women receiving tenofovir without LPV/r are further stratified by comcomitant ATV/r and other regiemsn not including lopinavir or ritonavir. $AUC_{0-24}$ = area under the concentration versus time curve from 0 to 24 hours; $V_d/F$ = apparent volume of distribution; CL/F = oral clearance; $C_{min}$ = minimum observed concentration; $C_{max}$ = maximum concentration; $C_0$ = pre-dose concentration; $C_{24}$ = 24 hour post-dose concentration.