Pharmacokinetics of Tenofovir During Pregnancy and Postpartum

Brookie M. Best, PharmD, MAS[1], **Sandra Burchett, MD, MS**[2], **Hong Li, PhD**[3], **Alice Stek, MD**[4], **Chengcheng Hu, PhD**[5], **Jiajia Wang, MS**[6], **Elizabeth Hawkins, MA**[7], **Mark Byroads, BA**[8], **D. Heather Watts, MD**[9], **Elizabeth Smith, MD**[10], **Courtney V. Fletcher, PharmD**[11], **Edmund V. Capparelli, PharmD**[1], and **Mark Mirochnick, MD**[12] **for the IMPAACT P1026s Team**

[1]University of California San Diego, School of Medicine-Rady Children's Hospital and Skaggs School of Pharmacy & Pharmaceutical Sciences, San Diego, CA, USA

[2]Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

[3]Rush University Medical Center, Department of Preventive Medicine, Chicago, IL

[4]University of Southern California School of Medicine, Department of Obstetrics and Gynecology, Los Angeles, CA, USA

[5]University of Arizona Mel & Enid Zuckerman College of Public Health, Division of Epidemiology and Biostatistics, Tucson, AZ, USA

[6]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, USA

[7]Social and Scientific Systems, Silver Springs, Maryland, USA

[8]Frontier Science & Technology Research Foundation, Amherst, NY, USA

[9]*Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD), Bethesda, MD, USA

[10]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, USA

[11]College of Pharmacy, University of Nebraska Medical Center, Omaha, NE, USA

[12]Boston University School of Medicine, Boston, MA, USA

Abstract

Objectives—Tenofovir disoproxol fumarate (TDF) is increasingly used in HAART regimens of pregnant women, but limited data exist on pregnancy pharmacokinetics of chronically-dosed TDF. This study described tenofovir pharmacokinetics during pregnancy and postpartum.

Methods—IMPAACT P1026s is a prospective, non-blinded pharmacokinetic study of HIV-infected pregnant women that included a cohort receiving 300 mg TDF once daily. Steady-state

Corresponding Author: Brookie M. Best, PharmD, MAS, University of California, San Diego, 9500 Gilman Drive MC 0719, La Jolla, CA 92093-0719, 858-822-5550, 858-246-0007, FAX 858-822-5624, brookie@ucsd.edu.

24-hour pharmacokinetic profiles were measured at 2nd and 3rd trimester and postpartum, with maternal and umbilical cord samples at delivery. Tenofovir was measured by LC-MS. The target AUC was 1.99 mcg•hr/mL (non-pregnant historical control 10th percentile).

Results—Median tenofovir AUC was decreased during the 2nd (1.9 mcg•hr/mL) and 3rd (2.4 mcg•hr/mL, p=0.005) trimesters versus postpartum (3.0 mcg•hr/mL). Tenofovir AUC exceeded the target for 2/4 (50%) 2nd trimester; 27/37 (73%; 95% CI: 56%, 86%) 3rd trimester; and 27/32 (84%; 95% CI: 67%, 95%) postpartum women (p>0.05). Median 2nd/3rd trimester troughs were lower (39/54 ng/mL) than postpartum (61 ng/mL). Median 3rd trimester weight was heavier for subjects below target AUC versus those above target (97.9 vs. 74.2 kg, p = 0.006). Median ratio of cord blood to maternal concentrations was 0.88. No infants were HIV infected.

Conclusions—This study found lower tenofovir AUC and troughs during pregnancy. Transplacental passage with chronic TDF use during pregnancy was high. Standard TDF doses appear appropriate for most HIV-infected pregnant women but therapeutic drug monitoring with dose adjustment should be considered in pregnant women with high weight (> 90kg) or inadequate HIV RNA response.

INTRODUCTION

HIV-1-infected pregnant women are prescribed antiretroviral regimens to quickly and fully suppress maternal HIV RNA levels in order to prevent perinatal transmission of HIV to the fetus/newborn as well as to optimize maternal health and maintain treatment susceptibility. Common antiretroviral combinations prescribed include nucleoside/tide analogs (NRTIs) with either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. While treatment guidelines for HIV in pregnancy are similar to those for non-pregnant adults, treatment success is most commonly achieved with agents that are dosed infrequently and perhaps more importantly have few side effects even in pregnancy[1]. These attributes make tenofovir disoproxil fumarate (TDF or PMPA, trade name Viread®; Gilead Sciences, Inc., Foster City, CA) an increasingly prescribed component of antepartum regimens.

Physiologic changes in pregnancy can result in lower drug exposure of essentially all classes of antiretroviral agents compared to exposure in non-pregnant persons[2]. Use of standard adult antiretroviral doses in pregnant women may not be adequate to ensure full suppression of viral load in plasma, which is needed to minimize the risk of fetal HIV exposure and antiretroviral drug resistance. Additionally, agents may have different side effects on the growing fetus compared to infants or children. Therefore, understanding maternal and fetal antiretroviral drug exposure and safety is important to optimize treatment or prevention pregnancy regimens.

TDF is a once daily nucleotide analogue reverse transcriptase inhibitor and is an appealing agent for use as a component of antenatal and peripartum antiretroviral regimens. TDF, the prodrug of tenofovir, is formulated alone as Viread® or in combination with emtricitabine

(Truvada®; Gilead Sciences, Inc., Foster City, CA); efavirenz and emtricitabine (Atripla®; Bristol Myers Squibb, New York City, NY and Gilead Sciences, Inc., Foster City, CA); rilpivirine and emtricitabine (Complera®; Gilead Sciences, Inc., Foster City, CA); and elvitagravir, cobicistat and emtricitabine (Stribild®; Gilead Sciences, Inc., Foster City, CA) for treatment of HIV and/or hepatitis B. Adverse events reported have included bone and renal toxicities[3, 4].

The primary objectives of this study were to describe tenofovir pharmacokinetics in HIV-infected pregnant and postpartum women and to determine if the standard TDF dose produces equivalent tenofovir exposure during pregnancy to that seen in: 1) historical data from non-pregnant adults; and 2) the same women in the study cohort during the postpartum period. We also evaluated the transplacental passage of tenofovir by comparing concentrations in cord and maternal blood.

METHODS

Study population and design

P1026s (Pharmacokinetic (PK) Properties of Antiretroviral Drugs (ARVs) During Pregnancy) is a multicenter, ongoing, prospective, non-blinded study of the International Maternal Pediatric and Adolescent AIDS Clinical Trials (IMPAACT) group. P1026s subjects were also enrolled in P1025, the Perinatal Core Protocol, a prospective cohort study of HIV-infected pregnant women and their infants receiving care at IMPAACT sites in the U.S. All subjects signed appropriate institutional informed consent prior to participation in P1025 and P1026s. All study procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000. This cohort's P1026s eligibility included receipt of 300 mg TDF daily, either as Viread® or co-formulated with emtricitabine (Truvada®), as part of clinical care for at least two weeks prior to pharmacokinetic sampling and with intent to continue at least 6 weeks postpartum. Exclusion criteria were: multiple gestation or clinical or laboratory toxicity that, in the opinion of the site investigator, might result in a required change to the chosen antiretroviral regimen during the study. Renal dysfunction was not an explicit exclusion criterion. Subjects received medications that were prescribed by their clinical care providers, and remained on study unless a change to a different antiretroviral regimen was desired due to toxicity, lack of viral load suppression or for inability to achieve desired pharmacokinetic targets. Pharmacokinetic sampling of tenofovir was performed between November 2004 and September 2008.

Clinical and laboratory monitoring

Maternal and infant clinical, laboratory, demographic and historical data were accessed from the P1025 and P1026s databases. On each pharmacokinetic sampling visit and at delivery, subjects had an interval medical history, physical examination and laboratory studies [complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine, blood urea nitrogen (BUN), and albumin]. The P1026s study team reviewed toxicity reports on monthly conference calls and assigned causality and grade for all toxicities according to the Division of AIDS (DAIDS) standardized Toxicity Table for Grading Severity of Adult Adverse Experiences (August 1992); http://rcc.tech-res-intl.com).

All toxicities were followed through resolution; and the subject's clinical care provider was responsible for subject toxicity management.

Sample collection and measurement

Pharmacokinetic sampling was performed during the second trimester (20–28 weeks gestation), the third trimester (30–38 weeks gestation) and postpartum (6–12 weeks after delivery). Subjects were asked to take TDF at the same time for three days prior to and on the day of assessment when plasma samples were collected immediately before the witnessed dose (C_0) and 1, 2, 4, 6, 8, 12 and 24 hours post-dose. Single umbilical cord blood and maternal plasma samples were collected at delivery. Tenofovir concentrations were measured by a previously described validated, liquid chromatography-mass spectrometry (LC-MS) method[5,6]. The linear range was 10 ng/mL to 1500 ng/mL, with a lower limit of detection for tenofovir of 10 ng/mL. Accuracy and precision were within ± 20% at 10 ng/mL and ± 15% at other quality control concentrations[6].

Pharmacokinetic analyses

The pre-dose concentration (C_0), the maximum plasma concentration (C_{max}), the corresponding time (T_{max}), and the last measurable concentration (C_{24}) were identified by direct inspection. The area under the concentration versus time curve from time 0 to 24 hours post dose (AUC) for tenofovir was estimated using the trapezoidal rule up to the last measurable concentration.

Apparent oral clearance (CL/F) from plasma was calculated as the dose (135.6 mg of tenofovir contained in a 300 TDF mg tablet) divided by AUC. The apparent volume of distribution (V_d/F) was determined as CL/F divided by λ_z, where λ_z was the terminal slope of the log concentration versus time curve. The half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Because the log concentration versus time curve of the observed data shows two distinct slopes, CL/F, distribution volumes and elimination rate constants were also computed using a two-compartment model in WinNonlin, Version 6.2.1 (Pharsight Corp., St Louis, MO).

Statistical analyses

The study design incorporated a two-stage analysis approach. Each individual woman's tenofovir exposure during pregnancy was determined in real time, compared with the average and estimated 10th percentile target (1.99 mcg•hr/mL) AUCs for non-pregnant, adult HIV-1-infected historical controls, and reported to each subject and her care provider. The control population included HIV-infected and healthy subjects reported in the 2003 Viread Package Insert; co-administered medications including other antiretrovirals in these subjects were not described at that time[7].Based on the subject's pharmacokinetics, clinical and laboratory status, and the study pharmacologist's recommendations (if any), the subject and care provider could decide whether or not to modify dosing. If the latter option was chosen, pharmacokinetic assessment after at least one week on the new dose was offered. A study stopping criterion to trigger an evaluation of the adequacy of drug exposure was predefined as six of 25 women (24%; exact 80% confidence limits: 13%, 38%) falling below the target AUC. The goal was to prevent excess accrual to a cohort with known inadequate anti-retroviral exposure.

After all pharmacokinetic sampling was complete for all subjects, a repeated measures design was used to assess antepartum and postpartum tenofovir exposure for each woman. Third-trimester tenofovir exposure was compared at the within-subject level to postpartum exposure, using 90% confidence limits for the geometric mean ratios of antepartum to postpartum pharmacokinetic parameters. When the true geometric mean of the ratio (the antilog of the true mean of the log ratios) of the pharmacokinetic parameters for pregnant and non-pregnant conditions has a value of 1, this indicates equal geometric mean pharmacokinetic parameters for the pregnant and non-pregnant conditions. If the 90% confidence intervals (CIs) are entirely outside the limits (0.8 and 1.25), the pharmacokinetic exposure parameters for the pregnant and non-pregnant conditions are considered different. If the 90% CIs are entirely within the limits, the drug exposures are considered equivalent. If, however, the 90% CIs overlap the 0.8 or 1.25 limits, these data alone do not support any conclusions. The magnitudes of the differences in the median values of pharmacokinetic parameters antepartum and postpartum were assessed with the Wilcoxon signed-rank test. Differences in weight and serum creatinine between groups meeting and not meeting AUC targets were explored with univariate Wilcoxon rank-sum tests and Spearman's correlation.

RESULTS

Subject characteristics

Thirty-seven women enrolled and completed third trimester pharmacokinetic sampling. Of these, 4 also completed second trimester sampling and 32 completed postpartum sampling. Table 1 summarizes the clinical characteristics of the subjects. Women received TDF as part of a combination antiretroviral regimen, which most commonly included emtricitabine, atazanavir, fosamprenavir and/or ritonavir. Four women were taking non-nucleoside based regimens, and 33 were on protease inhibitor containing regimens. Median gestational age at delivery was 38 weeks. All infants had birth weights that were appropriate for gestational age. Median CD4+ cell count at delivery was 469 cells/mm^3. Viral load at delivery was available for 34 subjects, and was   400 copies/mL for 33 subjects and 9733 copies/mL for the remaining subject.

Six women had Grade 3 elevated total bilirubin. Six infants had anomalies as follows, 1) bilateral hip clicks, 2) lacrimal duct stenosis, 3) Mongolian spots on shoulder and buttocks, 4) vesicoureteral reflux, 5) parvovirus positive, and 6) bilateral preauricular skin tags. Investigators were unable to judge whether the parvovirus result and the vesicoureteral reflex were related to maternal use of tenofovir. The other four anomalies were deemed unrelated to maternal use of tenofovir. None of the infants were HIV infected.

Tenofovir exposure

The target tenofovir exposure was AUC   1.99 mcg•hr/mL, the 10th percentile of the average exposure for non-pregnant historical controls. This target was met for 27/37 (73%) in 3rd trimester and 2/4 (50%) in 2nd trimester. The 10 subjects with AUC's below the 1.99 mcg•hr/mL target remained on the standard dose of 300 mg TDF once daily. Figure 1 shows the antepartum concentration versus time curves for each subject. Figure 2 shows the

postpartum concentration versus time curves for each subject, of whom 27/32 (84%) met or surpassed the tenofovir target AUC.

Table 2 summarizes the tenofovir pharmacokinetic parameters from the noncompartmental analysis, and Figure 3 outlines the median antepartum and postpartum concentration-time curves. The median AUC was significantly higher postpartum compared to 3rd trimester; and was lowest in the 2nd trimester. For the four women with 2nd trimester data, their corresponding median 2nd trimester, 3rd trimester and postpartum AUCs were 1.9, 2.1 and 2.6 mcg•hr/mL. For the entire population, CL/F, Vd/F, and half-life were significantly higher in the 3rd trimester compared to postpartum. C_{24} and C_0 were significantly lower in the 3rd trimester compared to postpartum, but C_{max} was not different antepartum compared to postpartum. Only one pharmacokinetic parameter was deemed different by the pre-specified geometric mean ratio and 90% CI criterion; V_d/F was higher in the 3rd trimester than postpartum. For all other parameters, the geometric mean ratios and 90% CI were inconclusive (the 90% CI all crossed one of the limits, 0.8 or 1.25).

At the 3rd trimester visit, the median (range) weight for the 10 women who did not meet the target AUC was 97.9 (68.1 – 121.9) kg. In contrast, the median (range) weight for the 27 women who met the AUC target was 74.2 (50.8 – 93.5) kg (p=0.006). Third trimester weight and tenofovir AUC were inversely correlated (spearman's rho = −0.48, p=0.004). Three of these 10 women were also below the AUC target at their postpartum visit; all three weighed > 90 kg both ante- and postpartum. For the five women who did not meet the AUC target at the postpartum visit (the three mentioned above plus two who had met the target during their 3rd trimester visit), their median (range) postpartum weight was 83.7 (59.8 – 101.4) kg. The women who met the AUC target at the postpartum visit weighed 71.2 (45.2 – 108.4) kg, which was not significantly different (p=0.282). Again, however, the postpartum tenofovir AUC and subject weights were inversely correlated (spearman's rho = −0.51, p = 0.005).

Serum creatinine was a median (range) 20% (−38% to 60%) higher postpartum than during the 3rd trimester (p=0.002 for within-subject comparison). At the 3rd trimester visit, the median (range) serum creatinine for the 10 women who did not meet the target AUC was 0.5 (0.4 – 0.8) mg/dL. The median (range) serum creatinine for the 27 women who met the AUC target was 0.6 (0.4 – 0.8) mg/dL (p=0.209). Third trimester serum creatinine and tenofovir AUC were directly correlated (spearman's rho = 0.39, p=0.024). For the five women who did not meet the AUC target at the postpartum visit, their median (range) postpartum serum creatinine was 0.6 (0.6 – 0.8) mg/dL. The women who met the AUC target at the postpartum visit had a median serum creatinine of 0.7 (0.5 – 1.1) mg/dL, which was also not significantly different (p=0.612). Again, however, the postpartum tenofovir AUC and subjects' serum creatinine were positively correlated (spearman's rho = 0.41, p = 0.025).

For the two-compartment analysis, the model successfully estimated the pharmacokinetic parameters for all four subjects (100%) in the 2nd trimester, for 22 (63%) of the 3rd trimester subjects, and for 18 (69%) of the postpartum subjects. The median (interquartile range; IQR) CL/F for the 2nd trimester, 3rd trimester, and postpartum were 35 (25, 45) L/hr, 35 (16, 44) L/hr, and 28 (18, 32) L/hr. The central compartment apparent volumes were 260 (178, 339) L, 256 (191, 321) L and 211 (149, 278) L and the peripheral compartment apparent volumes

were 750 (567, 1315) L, 705 (549, 1045) L, and 433 (304, 738) L in the 2nd trimester, 3rd trimester and postpartum, respectively. The terminal half-lives in the three study periods were 17 (15, 40) hours, 20 (16, 35) hours and 18 (15, 28) hours.

The median (IQR) concentration of tenofovir in 31 maternal plasma samples collected at delivery was 62.4 (44.1, 73.4) ng/mL, and in 32 umbilical cord blood samples was 56.7 (37.0, 76.5) ng/mL. Cord blood to maternal plasma concentration ratio was 0.88 (0.76, 1.03) for 28 mother/infant pairs.

DISCUSSION

In this study of 37 pregnant women with 584 plasma tenofovir samples, tenofovir overall exposure was 20% lower in the 3rd trimester compared to postpartum in the same women. Similarly, CL/F was 25% higher and C_{24} and C_0 were about 20% lower during pregnancy. Apparent volume of distribution was nearly 60% larger in the 3rd trimester compared to postpartum. Even though CL/F was faster during pregnancy, the terminal half-life was actually longer in pregnancy compared to postpartum, presumably due to a larger magnitude increase in distribution volume compared to CL/F (half-life is directly proportional to volume of distribution, but inversely proportional to clearance). The time of maximum concentration post dose was 1 hour and was not influenced by pregnancy, nor was maximum concentration significantly different between pregnancy and postpartum. The plasma concentration just before an observed dose did not differ from the plasma concentration 24 hours after the observed dose, suggesting that women had been consistently taking prescribed TDF.

The postpartum tenofovir AUC found in this study of 3.0 mcg•hr/mL is similar to the average AUC in non-pregnant adults, 3.3 mcg•hr/mL. The 10th percentile target was met for 2/4 (50%) women in 2nd trimester, for 27/37 (73%) in 3rd trimester and 27/32 (84%) postpartum. Ninety-four percent of subjects had an HIV RNA 400 copies/mL in the 3rd trimester and none discontinued their regimen or altered their TDF dose based on their reported lower-than-target AUC. At delivery, 97% of women were virally suppressed under 400 copies/mL. In a study of tenofovir pharmacokinetics in Caucasian and Black European pregnant women from the PANNA network, 27 of 34 (79%) women had HIV RNA 50 copies/mL at delivery[8].

The PANNA study found 3rd trimester and postpartum AUCs of 2.5 and 3.2 mcg•hr/mL[8], comparable to the values found in the current study, a US cohort, of 2.4 and 3.0 mcg•hr/mL. The PANNA study also reported approximately 20% reductions in maximum and trough concentrations in the 3rd trimester compared to postpartum. The current study found similar reductions of about 17% in maximum and trough concentrations during pregnancy, though the findings were not statistically different from postpartum for C_{max}. CL/F was significantly increased by 30% during the 3rd trimester in the PANNA study, similar to our observed 25% increase. One potential explanation for the increased clearance during pregnancy is that tenofovir is being more rapidly eliminated by the kidney. The subjects in this study did have lower serum creatinine values during 3rd trimester compared to postpartum, and serum creatinine was positively correlated with tenofovir AUC at both time

points. Women who met AUC targets had a serum creatinine that was a median of 0.1 mg/dL higher than the value in those who did not meet AUC targets both in the 3rd trimester and postpartum. However, these differences were not statistically significant, possibly due to lack of power with small numbers of subjects not meeting AUC targets. Pregnancy causes an increase in renal plasma flow by 25 – 50% due to increased cardiac output[9], and tenofovir undergoes renal elimination. In contrast to this study, the PANNA study reported identical terminal half-lives during third trimester and postpartum, 15 hours, while this study found significantly longer half-lives (16 hours versus 12 hours) and larger distribution volumes during pregnancy compared to postpartum. However, as the women in this study were assessed at steady-state with multiple dosing, a half-life associated with the terminal elimination phase may not have been reliably estimated. Because intravenous tenofovir formulations have not been studied during pregnancy, possible alterations in oral absorption during pregnancy cannot be teased apart from changes in clearance and distribution volume. The European study did not have 2nd trimester data for comparison.

In this study, the subject's weight was inversely significantly correlated with tenofovir AUC during the 3rd trimester and postpartum. During the 3rd trimester, the 10 women who were below the target AUC were significantly heavier, by about 23 kg, than the 27 women who met the AUC target. One potential explanation for the lower tenofovir concentrations is that the larger subjects have a larger distribution volume of tenofovir. Tenofovir is distributed to most tissues, with highest concentrations in kidney, liver and intestinal contents[7]. Obese women may have higher distribution volumes and lower tenofovir exposure in general, which can then be compounded by the ~20–25% decrease in tenofovir exposure seen during pregnancy.

Benaboud et al. reported a population pharmacokinetic study of tenofovir chronic use in French pregnant and non-pregnant women[10]. The retrospective study dataset included 52 samples collected clinically from 46 pregnant women (6 in the 1st trimester, 18 in the 2nd trimester and 28 in the 3rd trimester) for therapeutic drug monitoring; doses were not observed. The data were best described by a two-compartment model with linear absorption and elimination. Pregnancy significantly increased oral clearance of tenofovir, by 39% at delivery specifically. The model was not able to discriminate changes in clearance by gestational age due to the small number of samples, especially early in pregnancy. The estimated AUC and C_{min} during pregnancy from this population analysis were 1.6 mcg•hr/mL and 39 ng/mL, similar to the values reported in this study in the 2nd trimester of pregnancy, 1.9 mcg•hr/mL and 38 ng/mL. Age also had a significant impact on the overall population pharmacokinetic model, while weight did not. A measure of renal function was not included.

The pharmacokinetics, including intracellular concentrations of tenofovir metabolites have been described by Hirt et al. at delivery and 1 week postpartum[11,12], and by Flynn et al.[13] for single dose maternal and neonatal or 7 days of maternal peripartum dosing. With single doses at delivery, tenofovir appears to cross the placenta well, achieving 73% of the maternal level in the cord blood[13]. With chronic TDF dosing during pregnancy, the ratio of cord to maternal blood concentrations was 0.82 in the PANNA study[8] and 0.88 in this study. Even so, infants must be dosed almost immediately after birth to maintain appropriate levels[11].

This study was not powered for a full safety analysis, or to understand the single contribution of tenofovir exposure to the antiretroviral regimen in prevention of perinatal HIV transmission. However, adverse effects and transmission data were collected. The maternal subjects appeared to tolerate TDF well during pregnancy. None of the infants was small for gestational age or infected. Measurements of bone toxicities, kidney function or long-term growth of the infants were not available in this study.

One limitation of this study is that the active moiety, intracellular tenofovir diphosphate, was not collected or measured. While plasma tenofovir concentrations are being used as a surrogate marker for active drug exposure at the site of action, the intracellular active metabolite pharmacokinetics may or may not be affected by and altered to the same extent during pregnancy as plasma pharmacokinetics. Another limitation is that measurements were not collected in the early stages of pregnancy in these women, so the timing of the pregnancy-induced changes cannot be well characterized.

This is the largest study to date of tenofovir pharmacokinetics in pregnant women, and provides the first published data available on intensive 2nd trimester pharmacokinetic profiles and the potential impact of higher weight in pregnancy on tenofovir exposure. This and prior studies have shown that tenofovir exposure is decreased during pregnancy compared to postpartum[8] and non-pregnant adults[10]. CL/F is increased by 25 – 30% during pregnancy, with corresponding 15 – 25% decreases in AUC and minimum concentrations. The clinical impact of these exposure changes remains unclear. Colbers et al. (the PANNA study) concluded that the 25% lower exposure was not associated with virologic failure or infant transmission. Other nucleoside reverse transcriptase inhibitors have also shown decreased exposure during pregnancy, but with small enough magnitudes that the standard dose is still thought to be therapeutic[14–16]. On the other hand, Benaboud et al. suggested that women should consider taking increased tenofovir doses in the second and third trimesters to achieve exposure similar to those of non-pregnant women. The population pharmacokinetic model predicted an AUC of 3.4 mcg•hr/mL and a C_{min} of 78 ng/mL with two tablets of TDF (600 mg dose of TDF = 272 mg of tenofovir). In our study, the majority of women achieved an AUC greater than the 10th percentile of expected in non-pregnant adults. HIV RNA was   400 copies/mL in all but one subject taking the standard dose, and no infants were infected. However, more sensitive viral load measurements (between 20 – 400 copies/mL) were not available for all study subjects, and high weight was associated with lower than expected tenofovir exposure. Given the currently available evidence, standard doses appear appropriate for a majority of HIV-infected pregnant women. HIV RNA should be closely monitored in pregnant women taking TDF. Therapeutic drug monitoring with TDF dose adjustment should be considered in women with high weight (> 90kg), or in those with detectable HIV RNA during pregnancy or with a less than expected decline in HIV RNA if initiating therapy during pregnancy.

Acknowledgments

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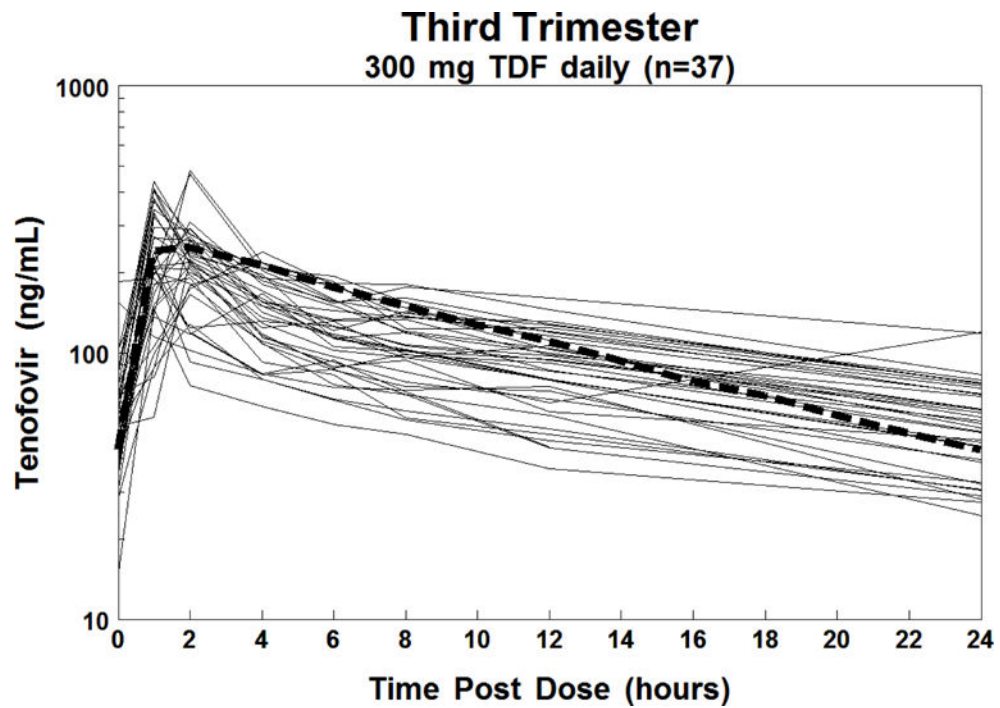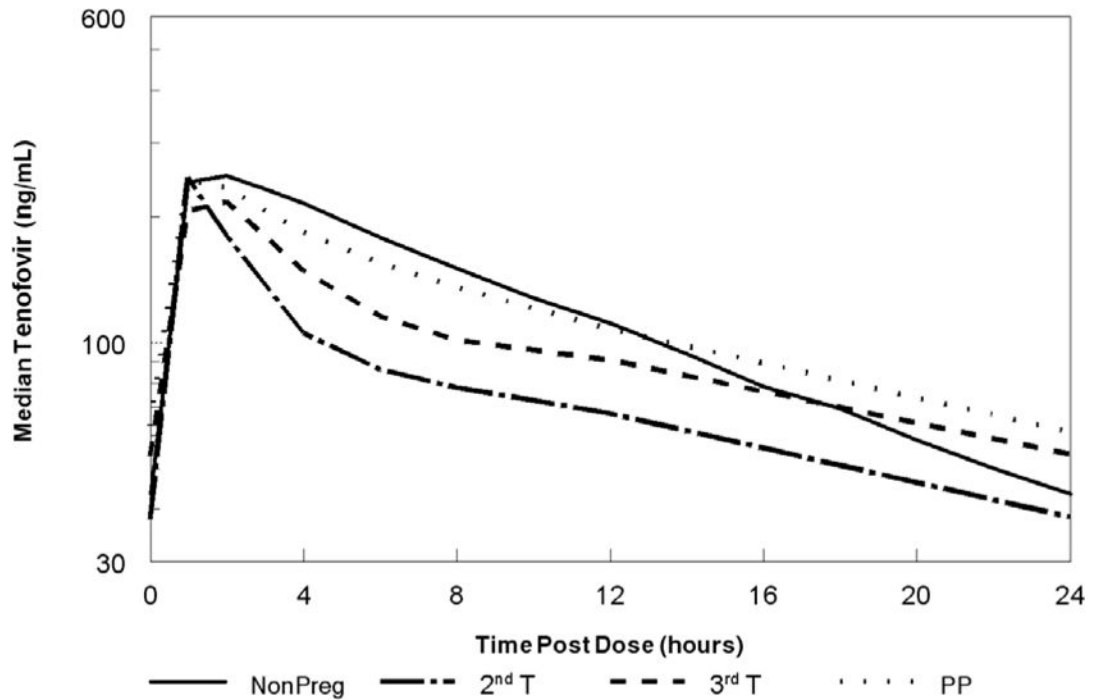
Figure 1.
Individual plasma concentration-time curves of tenofovir in 37 HIV-1 infected pregnant women in the 3rd trimester (solid lines) and the estimated 50th percentile concentration-time curve for non-pregnant HIV-infected historical adult controls (thick dashed line).
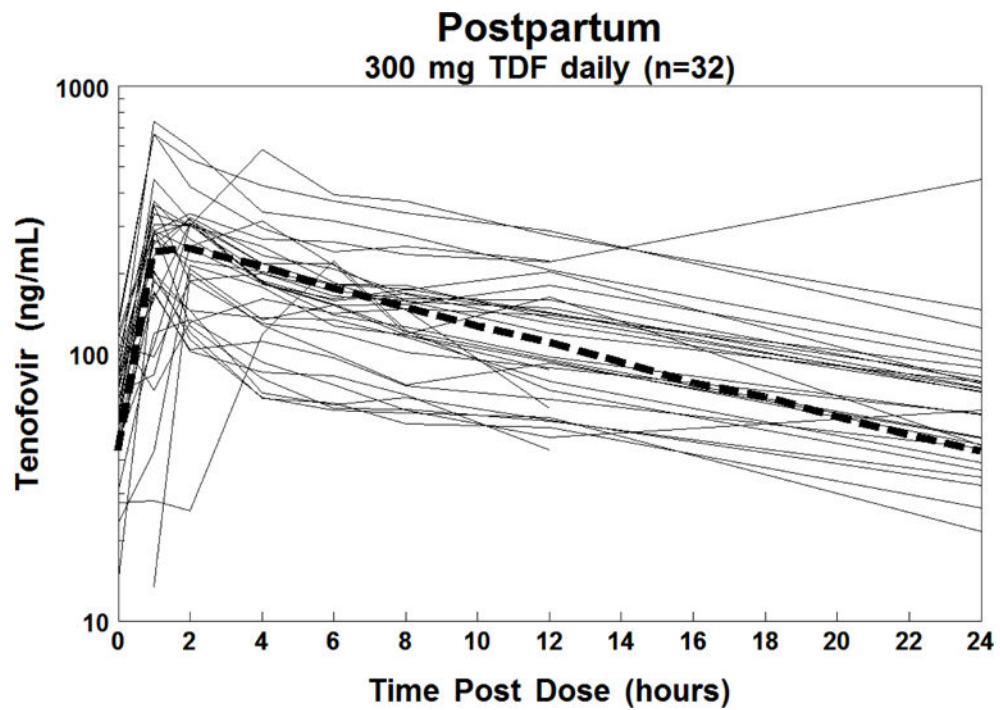
Figure 2.
Individual plasma concentration-time curves of tenofovir in 32 HIV-1-infected women postpartum (solid lines) and the estimated 50th percentile concentration-time curve for non-pregnant HIV-infected historical adult controls (thick dashed line).

Median Tenofovir Concentrations

Figure 3.
Median tenofovir concentration-time curves during the second trimester (dash/dot line; n = 4); third trimester (dashed line; n = 37) and postpartum (dotted line; n = 32), and the estimated 50th percentile concentration-time curve for non-pregnant HIV-infected historical adult controls (solid line). IQR, interquartile range.

Table 1

Characteristics of the Study Population and Pregnancy Outcomes

	Median (Range)[a] or Number of Subjects (%)[b]
Maternal Demographics	
Age (years) at 3rd trimester[a]	30.8 (13.5 – 39.2)
Weight (kilograms) at 3rd trimester[a]	80.6 (50.8 – 121.9)
Race/Ethnicity[b]	
Hispanic, Latina	15 (41)
Black, non-Hispanic	10 (27)
White, non-Hispanic	9 (24)
Asian, Pacific Islander	1 (3)
More than one race	1 (3)
Unknown/missing	1 (3)
CD4+ count (cells/mm^3) at delivery[a]	469 (9 – 1494)
Women with plasma HIV RNA at:[b]	
2nd Trimester	
Undetectable (< 400 copies/mL) *	4/4 (100)
Detectable (400 copies/mL)	0/4 (0)
3rd Trimester	
Undetectable (< 400 copies/mL) †	33/35 (94)
Detectable (400 copies/mL)	2/35 (6)
Delivery	
Undetectable (< 400 copies/mL) ‡	33/34 (97)
Detectable (400 copies/mL)	1/34 (3)
Postpartum	
Undetectable (< 400 copies/mL) §	22/26 (85)
Detectable (400 copies/mL)	11/26 (15)
Concomitant antiretrovirals	
Emtricitabine	25
Atazanavir (with rtv)	16
Lopinavir/ritonavir	12
Lamivudine	10
Zidovudine	7
Nelfinavir	4
Abacavir	3
Saquinavir (with rtv)	2
Didanosine, efavirenz, fosamprenavir (with rtv), nevirapine	1 each

	Median (Range)[a] or Number of Subjects (%)[b]
Pregnancy Outcomes	
Gestational age at delivery (weeks)[a]	38.1 (34.7 – 41.7)
Infant birth weight (kilograms)	2.93 (2.23 – 4.05)

[a] Median (range)

[b] Number of subjects (percent)

[*] 3/4 (75%) subjects were < 50 copies per milliliter.

[†] 22/35 (63%) subjects were < 50 copies per milliliter.

[‡] 20/34 (59%) subjects were < 50 copies per milliliter.

[§] 11/26 (42%) subjects were < 50 copies per milliliter.

Table 2

Pharmacokinetic Parameters by Gestational Age

PK Parameter Median (Interquartile Range)	Second trimester (20–28 weeks gestation) (n=4)	Third Trimester (30–38 weeks gestation) (n=37)	Postpartum (6–12 weeks after delivery) (n=32)	3rd Trimester/Postpartum Ratio Geometric Mean (90% CI)	P Value*
AUC (mg·h/L)	1.9 (1.7, 2.5)	2.4 (1.9, 3.1)	3.0 (2.2, 3.7)	0.80 (0.72, 0.89)	0.0046
CL/F (L/hr)	72 (58, 82)	57 (44, 71)	46 (36, 62)	1.25 (1.12, 1.40)	0.0122
V_d/F (L)	1570 (941, 2501)	1155 (1027, 1613)	899 (652, 1236)	1.59 (1.29, 1.97)	0.0014
C_{max} (mcg/L)	250 (202, 355)	245 (207, 334)	298 (200, 341)	0.89 (0.79, 1.01)	0.1636
T_{max} (hours)	1 (1, 1.25)	1 (1, 2)	1 (1, 2)	–	0.3302
$T_{1/2}$ (hours)	16.9 (15.2, 20)	16.1 (14.4, 18.2)	12.4 (11.7, 15.9)	1.28 (1.07, 1.53)	0.0213
C_0 (mcg/L)	38 (35, 50)	54 (44, 69)	64 (42, 86)	0.83 (0.70, 0.98)	0.01
C_{24} (mcg/L)	39 (34, 49)	54 (40, 70)	61 (45, 79)	0.82 (0.71, 0.96)	0.0325

*
3rd trimester compared to postpartum