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MAJOR ARTICLE

Tenofovir Alafenamide Plasma Concentrations Are Reduced in Pregnant Women Living With Human Immunodeficiency Virus (HIV): Data From the PANNA Network

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Background. Tenofovir alafenamide (TAF), a prodrug of tenofovir (TFV), is included in the majority of the recommended first-line antiretroviral regimens for patients living with human immunodeficiency virus (HIV), but there are limited data on TAF use in pregnant women. We aimed to examine the plasma pharmacokinetics of TAF and TFV in pregnant women from Europe.

Methods. Pregnant women living with HIV were included from treatment centers across Europe, and intensive pharmacokinetic sampling in the third trimester and postpartum was performed. Pharmacokinetic parameters of TAF and TFV were determined with noncompartmental analysis. The proportion of women with a TAF area under the curve (AUC_{last}) below the target of 53.1 ng*h/mL was determined. Clinical efficacy and safety outcome parameters were reported.

Results. In total, 20 pregnant women living with HIV were included. At the third trimester, geometric mean TAF AUC_{last} and C_{max} were decreased by 46% and 52%, respectively, compared with postpartum. TFV $AUC_{0\text{-}24h}$, C_{max}, and C_{trough} decreased by 33%, 30%, and 34%, respectively. The proportion of women with a TAF AUC_{last} < 53.1 ng*h/mL was 6% at third trimester and 0% postpartum. One out of 20 women had a viral load > 50 copies/mL at third trimester and no mother-to-child transmission occurred.

Conclusions. TAF plasma concentrations were reduced by about half in women living with HIV during third trimester of pregnancy but remained above the predefined efficacy target in the majority of the pregnant women. TFV concentrations were reduced by approximately 30% during third trimester. Despite the observed exposure decrease, high virologic efficacy was observed in this study.

Clinical Trials Registration. NCT00825929.

Keywords. HIV; tenofovir alafenamide; pharmacokinetics; pregnancy; mother-to-child transmission.

Pregnant women living with human immunodeficiency virus (HIV) need adequate antiretroviral treatment for their own health and to reduce the risk of mother-to-child-transmission [1]. However, the physiology of women changes during pregnancy, possibly impacting the exposure and efficacy of antiretroviral drugs. For example, the volume of distribution of drugs may be altered in pregnant women due to increased plasma volume and decreased plasma protein concentrations. In addition, hepatic metabolism and renal excretion are generally increased in pregnant women [2–4]. A substantial number of pregnant women use antiretroviral agents in the absence of any pregnancy-specific safety or pharmacokinetic data due to the lag time between drug registration and the availability of these data, which places mother and child at potential risk [5].

Tenofovir alafenamide (TAF), a nucleoside reverse transcriptase inhibitor, is a widely used antiretroviral drug that is included in the majority of the recommended first-line antiretroviral regimens for HIV [6, 7]. Generally, TAF is dosed as 25 mg once daily, but fixed-dose combination tablets consisting of both TAF and the boosting agent cobicistat contain 10 mg of TAF because TAF exposure increases around 2-fold as a result of inhibition of the intestinal efflux transporter P-glycoprotein (P-gp) by cobicistat [8, 9]. Similar TAF exposure has been observed with TAF 25 mg and TAF 10 mg co-administered with cobicistat [10].

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Like the earlier marketed tenofovir disoproxil fumarate (TDF), TAF is a pro-drug of tenofovir (TFV). TAF has a short plasma half-life before it passively enters HIV-target cells, where it is quickly hydrolyzed to TFV and subsequently phosphorylated into the active TFV-dp, a potent inhibitor of HIV reverse transcriptase [11]. TFV, the major plasma metabolite, is slowly released from the cells and eliminated renally by passive glomerular filtration and active tubular secretion [12]. Compared to TDF, TAF is more stable in plasma, distributes more selectively to tissues of lymphatic origin, and degrades intracellularly more rapidly creating sink conditions [12]. As a results, TAF is more efficient at concentrating the active TFV-dp in HIV-target cells, requiring a lower daily dosage, and the plasma levels of circulating TFV are lower [13]. Because there is a correlation between TFV plasma concentrations and toxicity, TAF has a more favorable renal and bone safety profile in comparison to TDF, while showing similar efficacy [12, 14–16].

Guidelines about TAF use during pregnancy are conflicting: the US guideline recommends TAF as an alternative drug because of the limited data, whereas the European guideline includes TAF-containing regimens among the preferred treatment regimens for pregnant women [6, 17]. The limited pharmacokinetic data consist of 1 study including 58 pregnant women [18]. This study observed no significant difference between pregnancy and postpartum in women taking TAF 10 mg with cobicistat, whereas a decrease in exposure of approximately 40% was seen during pregnancy in women taking TAF 25 mg [18]. Clinical outcomes were investigated in 1 large clinical trial that compared TAF versus TDF in combination with emtricitabine and dolutegravir or efavirenz. The study arm using TAF/emtricitabine and dolutegravir had the lowest frequency of composite adverse pregnancy outcomes and neonatal deaths [19].

Because there is large variability and uncertainty in the limited TAF pregnancy data as the plasma concentrations are often the below limit of quantification, we believe that additional data are essential to establish the applicability of TAF during pregnancy. Also data on TFV exposure during pregnancy are lacking. Therefore, our study aims to examine the pharmacokinetics of TAF and TFV in pregnant women from Europe.

METHODS

A nonrandomized, open-label, multicenter, phase IV study was performed in pregnant women living with HIV. This study was a part of the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) study, which is an ongoing study established to prospectively collect pharmacokinetic profiles of newly developed antiretroviral drugs in pregnant women from HIV treatment centers across Europe. The primary objective of the current analysis was to compare TAF pharmacokinetic parameters in the third trimester with postpartum. Secondary objectives were to report safety and efficacy outcomes for TAF-based regimens, to determine TFV pharmacokinetic parameters during pregnancy and postpartum, and to assess TAF and TFV cord blood concentrations at time of delivery.

The study was conducted in compliance with the principles of the "Declaration of Helsinki." Informed consent was obtained from each participant before inclusion. The study was approved by the medical ethical committees from each individual center involved and, when applicable, by the national authorities. The study has been registered at ClinicalTrials.gov under number NCT00825929.

Study Population

Women were eligible for inclusion when they were (I) HIV-infected, (II) pregnant, (III) > 18 years at screening, and (IV) treated with an antiretroviral regimen containing TAF for at least 2 weeks before first pharmacokinetic evaluation. Women using interacting comedication or with a current condition that might interfere with TAF drug absorption, distribution, metabolism, or excretion were excluded. Women who presented with grade III/IV anemia (i.e., Hb < 4.6 mmol/L or < 7.4 g/dL) at screening were also excluded.

Pharmacokinetic Sampling

Pharmacokinetic sampling was performed at third trimester of pregnancy (preferably week 33) and postpartum (approximately 4–6 weeks). During these 2 study visits, EDTA blood samples were collected at t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after observed TAF intake with a moderate fat breakfast (650 kcal, 30% fat). Matching cord blood and maternal blood plasma samples were taken at delivery to estimate placental transfer. The plasma was centrifuged, and the plasma samples were stored at ≤ −18°C until shipment on dry ice to the central laboratory for analysis. The bioanalytical method is described in Supplementary Text 1.

Pharmacokinetic and Statistical Analysis

TAF and TFV pharmacokinetic parameters were determined with noncompartmental analysis using WinNonlin (Phoenix 64 version 8.3, Certara) and were described as geometric mean (GM) and associated coefficient of variation (%CV). To evaluate the influence of pregnancy on the pharmacokinetics, a linear mixed-model (with pregnancy as fixed-effect and random effect for participant) was used on the log transformed pharmacokinetic parameters to calculate the geometric mean ratios (GMRs) and 90% confidence interval (CI). A stratified analysis for treatment with TAF 10 mg coadministered with cobicistat, and TAF 25 mg was also performed and is included in the Supplementary Data.

An exposure-response analysis of TAF reported a similar virologic response over the wide range of observed TAF area

under the curve (AUC_{tau}) deciles; the median TAF AUC_{tau} in the lowest decile was 53.1 ng*h/mL [20]. Accordingly, the proportion of pregnant and postpartum women with AUC_{last} below 53.1 ng*h/mL was determined in our study.

Clinical Outcomes and Safety Assessment

At every study visit maternal human immunodeficiency virus type 1 (HIV-1) RNA load and CD4 counts were collected, and the infant HIV status was determined by DNA polymerase chain reaction (PCR) according to routine medical care. Safety assessment was performed by collecting adverse events, use of concomitant medication, maternal serum biochemistry, and hematology at each visit. Also, data on gestational age at delivery, infant birth weight, and infant congenital abnormalities were collected.

RESULTS

Twenty women were recruited from 5 hospitals across Europe between June 2017 and May 2021. The characteristics and pregnancy outcomes of these patients are depicted in Table 1. Median maternal age at delivery was 33 (range, 19–44) years. The majority (80%) of the women were Black, whereas the minority were White (15%) or Asian (5%). More women were on a regimen including TAF 25 mg (65%) than TAF 10 mg with cobicistat (35%). All women used TAF in a regimen combined with emtricitabine, in combination with rilpivirine (50%), elvitegravir/cobicistat (30%), bictegravir (10%), nevirapine (5%), or darunavir/cobicistat (5%). Five women were lost to follow-up postpartum, resulting in clinical data of 20 women at third trimester and of 15 women postpartum. Median maternal weight at the third trimester was 81 (range, 55-132) kg, and the median creatinine clearance was 140 (range, 115–178) mL/minute. At postpartum visit, the median maternal weight was 74 (range, 49–132) kg, and the median creatinine clearance was 124 (range, 110–145) mL/minute.

Pharmacokinetic Analysis of TAF

TAF pharmacokinetic analysis was performed in 17 women at third trimester and 12 women postpartum. TAF concentrations were not quantifiable in all samples of 2 women at third trimester and of 3 women postpartum potentially because of protocol deviations during sample storage. One woman did not meet the inclusion criteria for third trimester pharmacokinetic analysis because TAF-treatment was only initiated 4 days before third trimester visit. One nonevaluable ascending postpartum curve was excluded. Furthermore, 1 woman was excluded for the GMR calculation because of treatment switch from 10 mg to 25 mg TAF just after delivery. Pharmacokinetic analysis of TFV, the major plasma metabolite, was performed in the remnant plasma samples of 16 women at third trimester and 11 women postpartum.

Table 1. Patient Characteristics

	Median (Range) or n (%)
Maternal age at delivery, years	33 (19–44)
Race/Ethnicity	
Black	16 (80%)
White	3 (15%)
Asian	1 (5%)
ART naive at conception	2 (10%)
Time on TAF before first PK sampling, weeks	48 (1–136)
TAF dose at third trimester:	
25 mg	13 (65%)
10 mg	7 (35%)
ART regimen at third trimester, TAF combined with:	
Emtricitabine, rilpivirine (Odefsey®)	10 (50%)
Emtricitabine, elvitegravir, cobicistat (Genvoya®)	6 (30%)
Emtricitabine, bictegravir (Biktarvy®)	2 (10%)
Emtricitabine, nevirapine 400 mg once daily	1 (5%)
Emtricitabine, darunavir, cobicistat (Symtuza®)	1 (5%)
Third trimester (n = 20)	
Gestational age, weeks	33 (31–37)
Weight, kg	81 (55–132)
HIV-1 RNA viral load > 50 copies/mL	1 (5%); 317 copies/mL
CD4 count, cells/μL	572 (297–1117)
Creatinine concentration, μmol/L	51 (34–60)
Creatinine clearance, mL/min[a]	140 (115–178)
Postpartum (n = 15)	
Time after delivery, weeks	5 (4–17)[b]
Weight, kg	74 (49–132)
HIV-1 RNA viral load > 50 copies/mL	0 (0%)
CD4 count, cells/μL	665 (298–1165)
Creatinine concentration, μmol/L	71 (55–89)
Creatinine clearance, mL/min[a]	124 (110–145)
Pregnancy outcomes	
Gestational age at delivery, weeks	39 (37–41)
Caesarian section	8 (40%)
Infant small for gestational age[c,d,e]	5 (24%)
Infant VL detectable by HIV DNA PCR test[d]	0 (0%)

Abbreviations: ART, antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; PCR, polymerase chain reaction; PK, pharmacokinetic; TAF, tenofovir alafenamide; VL, viral load.

[a]Calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [21, 22].

[b]The postpartum visit of one woman was > 8 weeks postpartum. This visit was delayed because of the COVID-19 crisis.

[c]Small for gestational age was determined as < 10th percentile of the fetal-infant growth chart by Fenton et al [23].

[d](n = 21); 1 twinbirth.

[e]Genvoya® (n = 2), Odefsey® (n = 1), Biktarvy® (n = 2).

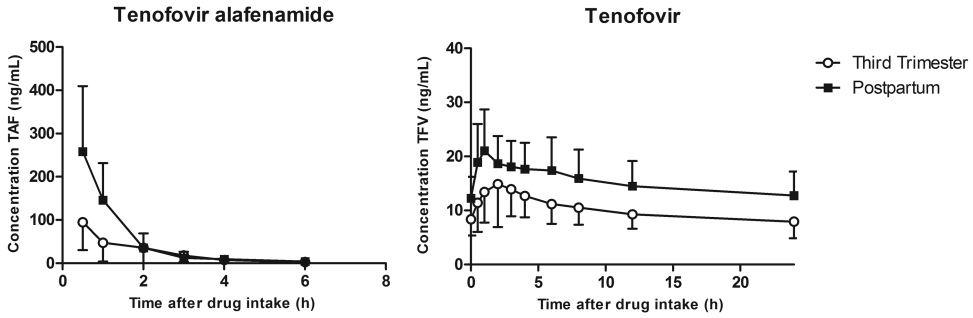

Figure 1. Plasma concentrations of tenofovir alafenamide (*left*) and tenofovir (*right*) over time after drug intake in third trimester and postpartum women treated with tenofovir alafenamide 10 mg or 25 mg once daily. Data are shown as mean (CV%). Abbreviations: CV, coefficient of variation; TAF, tenofovir alafenamide; TFV, tenofovir.

The observed mean TAF and TFV plasma concentrations over time after drug intake for women at third trimester and postpartum are shown in Figure 1. TAF plasma concentrations were quantifiable until 6 hours after drug intake. For both TAF and TFV, lower mean plasma concentrations were observed during third trimester compared to postpartum, but there was large inter-subject variability.

At the third trimester, TAF GM AUC_{last} (%CV) was 101 (44) ng*h/mL, and the GM C_{max} (%CV) was 91 (57) ng/mL (Table 2). This corresponded to a 46% and 52% decrease in AUC_{last} and C_{max}, respectively, compared with postpartum. However, the pregnancy effect on TAF was variable (Figure 2). Looking at the women with paired data, TAF exposure decreased during pregnancy in 9 women, was similar to postpartum in 2 women and increased in 1 woman. No difference in the pregnancy effect on TAF between women treated with and without cobicistat could be observed, and the stratified pharmacokinetic data are included in the Supplementary Tables 1 and 2. The number of women with an AUC_{last} below the target of 53.1 ng*h/mL was 1 out of 17 at third trimester and 0 out of 12 women postpartum.

With regards to TFV pharmacokinetic parameters, GM $AUC_{0\text{-}24h}$ (%CV) was 232 (30) ng*h/mL, the GM (CV%) C_{max} was 16 (41) ng/mL, and the GM C_{trough} (%CV) was 7 (36) ng/mL at the third trimester (Table 1). This corresponded to a 33%, 30%, and 34% decrease in $AUC_{0\text{-}24h}$, C_{max}, and C_{trough}, respectively,

Table 2. Pharmacokinetics of Tenofovir Alafenamide and Tenofovir in the Third Trimester of Pregnancy and Postpartum Determined in Women Treated With Tenofovir Alafenamide 10 mg or 25 mg Once Daily

Parameter	Third Trimester, GM (%CV)[a]	Postpartum, GM (%CV)[a]	Third Trimester vs Postpartum GMR (90% CI)	Historical Reference of Nonpregnant Individuals[b], mean (%CV)[c]
Tenofovir alafenamide				
	n = 17	n = 12	n = 16	
AUC_{last}, ng*h/mL	101 (44)	217 (57)	0.54 (.43–.68)	277 (38)
C_{max}, ng/mL	91 (56)	215 (66)	0.48 (.38–.62)	200 (44)
T_{max}, h	1.0 (0.5–3.0)	0.5 (0.5–2.0)	1.47 (1.15–1.87)	1.5 (1.0–2.0)
CL/F_{ss}, L/h	198 (63)	84 (98)	1.78 (1.41–2.25)	
Vd/F_{ss}, L	123 (87)	68 (90)	1.50 (1.07–2.10)	
$T_{1/2}$, h	0.5 (29.8)[d]	0.6 (45.3)	1.05 (.89–1.24)	0.5 (0.4–0.6)
Tenofovir				
	n = 16	n = 11	n = 16	
$AUC_{0\text{-}24h}$, ng*h/mL	232 (30)	348.51 (33.3)	0.67 (.62–.74)	268 (23)
C_{max}, ng/mL	16 (41)	21.58 (33.0)	0.70 (.62–.80)	16 (22)
C_{trough}, ng/mL	7 (36)	12 (38)	0.66 (.60–.71)	9 (25)
T_{max}, h	1.8 (0.5–4.0)	1.0 (0.5–6.0)	1.20 (.73–2.00)	4.0 (3.0–4.0)
$T_{1/2}$, h	35 (45)[e]	53 (34)[f]	0.76 (.61–.94)	32 (28–38)

Abbreviations: AUC, area under the curve; CI, confidence interval; CL/F_{ss}, apparent clearance at steady state; C_{max}, maximum concentration; C_{trough}, concentration before next dose administration; CV, coefficient of variation; GM, geometric mean; GMR, geometric mean ratio; $T_{1/2}$, apparent half-life; T_{max}, time to reach maximum concentration; Vd/F_{ss}, apparent central volume of distribution at steady state.

[a]Except for T_{max} and which is denoted as median (range).

[b]Historical reference data from a pharmacokinetic study in 42 healthy volunteers using tenofovir alafenamide/emtricitabine/rilpivirine 25/200/25 mg in fed state [24].

[c]Except for T_{max} and $T_{1/2}$ which are denoted as median (interquartile range).

[d]n = 11.

[e]n = 12.

[f]n = 10.

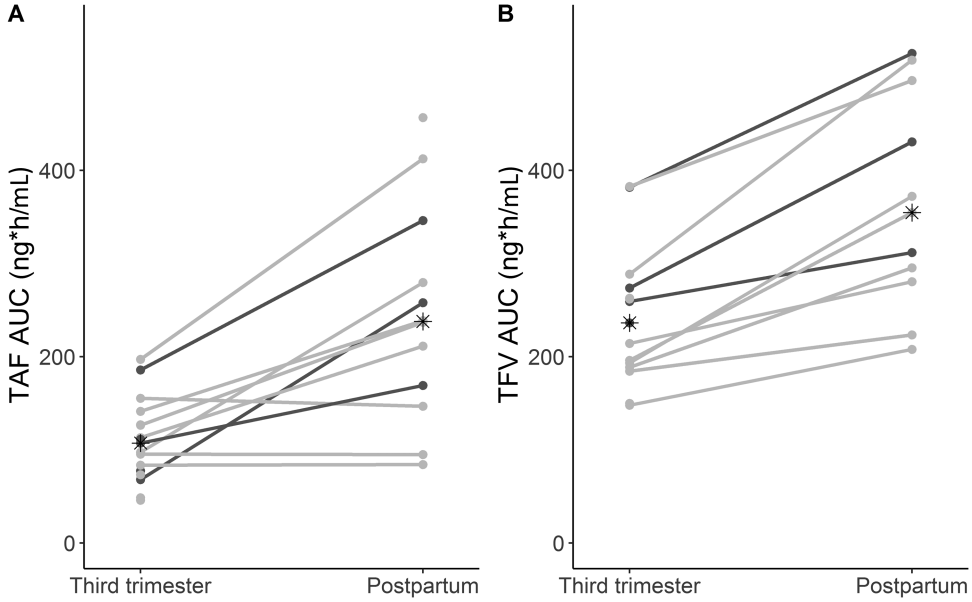

Figure 2. Individual comparison of AUC during third trimester and postpartum for (*A*) tenofovir alafenamide (TAF) and (*B*) tenofovir (TFV). The dark grey lines represent women treated with TAF 10 mg and cobicistat, and the light grey lines women treated with TAF 25 mg. Stars represent the median AUC in third trimester and postpartum. Abbreviation: AUC, area under the curve.

compared with postpartum. The TFV exposure decreased in all 11 women with paired TFV data (Figure 2).

Placental Transfer

To estimate placental transfer, cord blood and maternal plasma was drawn at delivery in 13 women. In all cord blood and maternal samples, which ranged from 4 to 20 hours after drug intake, TAF concentration was not quantifiable. TFV concentrations were quantifiable, and the median ratio of umbilical cord plasma/maternal plasma was 0.81 (range, 0.65–1.25). The ratio of umbilical cord plasma/maternal plasma may differ over time after drug intake, but no trend over time after drug intake was observable for the TFV ratio (Figure 3).

Maternal and Infant Efficacy and Safety

At the third trimester visit, 1 of 20 women had a viral load of > 50 copies/mL. This woman started antiretroviral drug treatment 6 years before inclusion and was switched to elvitegravir/cobicistat/emtricitabine/TAF during pregnancy. A viral load of 317 copies/mL was observed at 34 weeks of pregnancy, which was attributed to prior nonadherence. The woman had a TAF AUC_{last} of 111.4 ng*h/mL at third trimester and elvitegravir/cobicistat concentrations have been described previously [25]. The patient was switched to a regimen containing raltegravir, darunavir, ritonavir and emtricitabine/TAF and had a viral load < 50 copies/mL at delivery. Just after delivery, this woman was switched to bictegravir/emtricitabine/TAF. All women had a viral load < 50 copies/mL at the postpartum visit.

The women delivered at a median gestational age of 39 (range, 37–41) weeks. No mother-to-child transmission occurred; all babies had a negative HIV DNA PCR test. The median infant birth weight was 3200 (range, 2050–4500) g. The birth weight of 5 infants (24%) was considered to be small for gestational age, including one infant from a twin birth [23].

In total, 19 adverse events were reported in 9 participants. None were considered to be ≥ grade 3, and none were possibly related to the study medication. One serious adverse event, unlikely related to study medication, was reported; dextrocardia of the fetus was observed on an ultrasound in early pregnancy. No anomalies were found in genetic testing during pregnancy, and the woman delivered of a baby without further health issues.

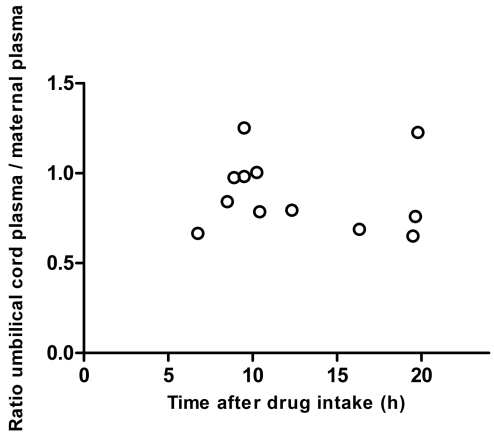

Figure 3. Tenofovir ratio umbilical cord plasma/ maternal plasma over time after maternal drug intake.

DISCUSSION

In this pharmacokinetic study in European pregnant women living with HIV, a TAF AUC_{last} decrease of approximately 50% was observed at third trimester compared with postpartum. This TAF AUC_{last} decrease observed in this study is larger than observed in an earlier study of Brooks et al. That study observed no significant difference in pregnant women using TAF 10 mg with a booster compared to postpartum. A ~40% decrease was observed in pregnant women using TAF 25 mg compared with postpartum, but no difference was observed compared to historical references [18]. In addition to the high variability in TAF exposure, this difference in study results is probably caused by the difference in sampling schedule. The current study uses a more intensive sampling scheme and therefore captures more accurately the absorption phase of the PK profile.

Which physiological alterations contribute to the TAF exposure decrease is difficult to point out. The major elimination pathway of TAF is intracellular hydrolysis by cathepsin A, but it is currently unknown if cathepsin A activity is changed during pregnancy [12, 26]. This also accounts for intestinal P-gp and BCRP, for which TAF is a substrate [4, 27, 28]. Binding of TAF to plasma proteins is approximately 80% [26]. Decreased plasma protein concentrations during pregnancy may decrease total TAF plasma concentrations, although free TAF plasma concentrations are less affected [4]. Although a low number of women were included in the cobicistat co-administration subgroup and high variability was observed, no difference in TAF exposure could be observed between the subgroups with and without cobicistat co-administration. Cobicistat levels are known to substantially decreased during pregnancy, but this lack of difference suggests cobicistat still inhibits P-gp transport during pregnancy [18, 29].

A TFV exposure decrease of approximately 30% was observed in pregnant compared to postpartum women with TAF, which is similar to a previous study examining pregnant women treated with TDF [30, 31]. However, higher tenofovir exposure was observed in postpartum women compared to historical controls due to an unclear mechanism. Increased renal clearance is most likely the primary cause of the TFV exposure decrease, which increased from median 124 mL/minute to 140 mL/minute in this study [4]. Notably, the TFV exposure decrease was smaller than the TAF exposure decrease of ~50% observed in this study. The fact that TFV plasma protein binding is very limited (<0.7%) in comparison to TAF can explain this difference, as only total plasma concentration of TAF may be decreased by the decreased plasma protein concentrations during pregnancy [26]. Also, TAF plasma instability and high variability may have contributed to this difference.

The observed median TFV umbilical cord plasma/maternal plasma ratio of 0.81 indicates placental passage, but no fetal accumulation, of TFV during the third trimester. Similar TFV ratios were previously observed in pregnant women treated with TDF [30, 31]. However, the observed absolute TFV concentrations in cord blood were lower compared to pregnant women using TDF.

Determining the clinical relevance of the TAF plasma exposure decrease during pregnancy is challenging. An exposure-response analysis in patients using various TAF-containing regimens has reported that an AUC_{last} of at least 53.1 ng*h/mL is associated with adequate virologic efficacy [20]. This is in line with a phase 1 dose-finding study of TAF monotherapy that observed similar virologic activity of TAF 8 mg once daily resulting in a mean AUC_{last} of 55 ng*h/mL compared with the already registered TDF 300 mg once daily [16]. In this study, a TAF AUC_{last} < 53.1 ng*h/mL was observed in 6% of the women in third trimester. Thus, it seems that the majority of the women treated with TAF during the third trimester had effective TAF plasma concentrations. Next, tenofovir exposure is associated with toxicity, and plasma TFV concentrations are approximately 90% lower when using TAF compared to TDF [12, 32]. As plasma TFV concentrations are even lower with TAF use during pregnancy, different renal and bone toxicity would not be expected in pregnant women.

A limitation of this study was that the active anabolite of TAF, TFV-dp, was not measured. Intracellular TFV-dp concentrations were previously measured in an interaction study with rifampicin [33]. Although rifampicin decreased mean TAF plasma concentrations by 55%, intracellular TFV-dp concentrations were still approximately 4 times higher than observed during TDF treatment. This suggests that TAF is very efficient in concentrating the active TFD-dp in HIV-target cells, resulting in a broad therapeutic window, which may also apply to the pregnancy period. This is supported by the high clinical and virologic efficacy observed in our study, although the number of subjects was too limited to draw definitive conclusions about clinical efficacy. In a previous clinical study with more participants, 88% of the 217 pregnant women treated with TAF in combination with dolutegravir and emtricitabine had a viral load of < 200 copies/mL [19]. Another limitation is that pregnant women treated with TAF that experienced virologic failure before third trimester were missed in this study. Therefore, the observed clinical efficacy only reflects the sustained virologic suppression during third trimester. Also, TAF is unstable in human blood, making quick centrifugation and correct storage of the study samples essential. Protocol deviations in these processes can quickly impact absolute TAF exposures. However, if this was the case, we assume that study sites handled study samples of third trimester and postpartum women in the same manner, resulting in an adequate comparison. In addition, postpartum TAF concentrations in this study are similar to the historical reference, indicating that we were able to adequately describe absolute TAF exposures [24].

In conclusion, this European study observed that TAF plasma concentrations are reduced by about half in pregnant women living with HIV with 94% of the pregnant women having an AUC_{last} above the predefined target of 53.1 ng*h/mL. The plasma concentrations of TFV, the major plasma

metabolite, are reduced by approximately 30% during pregnancy. Concentrations of the active anabolite TFV-dp were not measured. Despite the observed exposure decrease high virologic efficacy was observed, and no mother-to-child transmission occurred in this study.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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