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Pharmacokinetics of tenofovir alafenamide with and without cobicistat in pregnant and postpartum women living with HIV: Results from IMPAACT P1026s

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Authors' contributions: AMS, EB, DES, ES, NC, EVC, MM, and BMB designed the study and monitored participant data throughout the study. KG was the clinical trials specialist who coordinated the study within the IMPAACT network. KD was the protocol data manager. KR was the laboratory data coordinator. EB, AW, JGD, ILF, AMS, and MC were key investigators at study sites with high enrollment. RE and BMB performed the analytical work. KMB, JDM, MP, AMS, DES, EVC, MM, and BMB analyzed and interpreted the data. MP and DES provided statistical expertise. All authors critically reviewed the article and approved the final version.

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Abstract

Objective: To evaluate the pharmacokinetics of tenofovir alafenamide (TAF) 10 mg with cobicistat and 25 mg without boosting in pregnant and postpartum women with HIV and to characterize TAF placental transfer and infant washout pharmacokinetics.

Design: Open-label, multicenter phase IV prospective study of TAF pharmacokinetics during pregnancy, postpartum, delivery and infant washout.

Methods: Pregnant women receiving TAF 10 mg with cobicistat or TAF 25 mg without boosting as part of clinical care had intensive pharmacokinetic assessments performed during the second and third trimesters, and 6–12 weeks postpartum. Maternal and cord blood samples were collected at delivery, and washout pharmacokinetic samples were collected in infants. TAF concentrations were quantified using LC/MS. Comparisons between pregnancy and postpartum were made using geometric mean ratios (90% confidence intervals) and Wilcoxon signed-rank tests.

Results: Thirty-one pregnant women receiving TAF 10 mg with cobicistat-boosting and 27 women receiving TAF 25 mg without boosting were enrolled. TAF exposures did not significantly differ between pregnancy and postpartum when administered as 10 mg with cobicistat. Antepartum TAF exposures with the 25 mg dose were 33–43% lower in comparison to postpartum, but comparable to those measured in non-pregnant adults. TAF was below the lower limit of quantitation in 43/44 cord blood, 41/45 maternal blood at delivery, and all infant washout samples.

Conclusions: TAF exposures were comparable or higher than those measured in non-pregnant adults during pregnancy and postpartum. These findings provide reassurance on adequate TAF exposures during pregnancy, and support efforts to expand the use of TAF in pregnant women with HIV.

Keywords

tenofovir; TAF; cobicistat; pregnancy; pharmacokinetics; HIV

INTRODUCTION

The clinical study of newer antiretroviral therapies in pregnant women lags behind non-pregnant adults due to the routine exclusion of pregnant women from drug development programs.[1,2] Antiretroviral treatment during pregnancy is critical for suppressing HIV replication and preventing perinatal HIV transmission,[3–7] but physiological changes during pregnancy and postpartum can alter the pharmacokinetics of antiretroviral medications.[8] Of particular concern are subtherapeutic drug levels, which may result in virologic breakthrough, antiretroviral treatment resistance, and an increased risk of perinatal HIV transmission. Notable recent examples of this include cobicistat-containing regimens, which are not recommended during pregnancy[9] due to markedly lower levels of cobicistat, elvitegravir,[10] darunavir,[11,12] and atazanavir[13] subsequent to increased expression of CYP3A4 during pregnancy. Thus, pharmacokinetic data from pregnant women are essential for informing the appropriate dosing and use of antiretroviral medications during pregnancy.

Tenofovir alafenamide (TAF) is a newer prodrug of the nucleotide reverse transcriptase inhibitor, tenofovir, and is a key component of multiple antiretroviral regimens for non-pregnant adults living with HIV.[14–17] Despite its initial approval in 2015, TAF is not currently recommended for use during pregnancy due to limited pharmacokinetic and safety data.[3,17] Tenofovir in the form of tenofovir disoproxil fumarate (TDF) is recommended during pregnancy in combination with other antiretroviral medications and has been used for several years in pregnant women.[3] Though TDF is considered safe during pregnancy, some studies have shown a higher risk of adverse pregnancy outcomes with TDF-based therapy, such as very preterm delivery before 34 weeks and early infant death,[7] and variable findings on infant growth and development in TDF-exposed infants.[7,18] These studies were also complicated by the concomitant use of other antiretroviral medications, and a clear mechanistic link between TDF specifically and adverse outcomes has not been established.[19]

Given the improved safety profile of TAF in non-pregnant adults and differing pharmacology from TDF, TAF may be another valuable addition to HIV treatment options available during pregnancy. However, TAF pharmacokinetics may be altered during pregnancy through changes in hydrolase or transporter expression, volume expansion, or other mechanisms,[8] and thus pharmacokinetic data are needed to support uptake in this population. The primary objectives of this study were to characterize the pharmacokinetics of TAF when administered at doses of 10 mg with cobicistat-boosting and 25 mg without boosting during pregnancy and postpartum. Primary outcomes included comparisons of TAF exposures to historical data in non-pregnant adults living with HIV, and within-subject comparisons to characterize the influence of pregnancy on TAF exposures in comparison to the postpartum period. Secondary objectives were to determine the transplacental passage of TAF from maternal to fetal circulation and to describe maternal and infant safety and clinical outcomes.

METHODS

Study Population & Design

IMPAACT P1026s was a prospective, opportunistic, open-label, multi-center phase IV study of the pharmacokinetics and safety of multiple antiretroviral medications in pregnant women living with HIV (NCT00042289). Pregnant women with confirmed HIV infection receiving either TAF 10 mg with cobicistat-boosting or TAF 25 mg without boosting as part of standard care were eligible for these study arms. Antiretroviral medications were prescribed by the participant's clinical provider. The study team was not involved in clinical decision making over the initiation or alteration of treatment regimens.

Women could enroll either during the 2nd trimester (20 0/7 to 26 6/7 weeks gestation) or the 3rd trimester (30 0/7 to 37 6/7 weeks gestation) and underwent PK assessments during the 2nd trimester (if enrolled), 3rd trimester, and 6–12 weeks postpartum. Additional study visits for pharmacokinetic and safety assessments took place at delivery and at birth through day 3, 5–9 days, and 16–24 weeks of life in infants. All women provided written informed consent. Infants were enrolled *in utero*, after maternal enrollment. All study procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki, as revised

in 2000, and underwent review by relevant ethical review boards at each institution where the study was being conducted.

Women were required to be on therapy for at least two weeks prior to the first pharmacokinetic sampling and have plans to continue on their prescribed therapy through the postpartum pharmacokinetic assessment. Key exclusion criteria included the concomitant use of medications that may alter TAF pharmacokinetics (except cobicistat), pregnant with twin or higher order gestation, or clinical/laboratory toxicities that would likely lead to ARV regimen changes during the study. For the infant washout pharmacokinetic assessments, infants were required to weigh at least 1000 grams, not be receiving any medications that could alter TAF pharmacokinetics, and not have severe congenital malformations or other medical conditions deemed incompatible with life or that would interfere with study participation.

Bioanalytical Methods

TAF concentrations were measured using a validated LC-MS/MS method. Briefly, plasma proteins were precipitated with 100% acetonitrile, centrifuged, and injected directly onto a C18 reversed phase HPLC column (MacMod Ace-5, 2.1 × 150 mm). TAF was eluted using a gradient mobile phase consisting of 98%−0.1% formic acid in water and 2–0.1% to 5–0.1% formic acid in acetonitrile at a flow rate of 0.8 mL/min, with an alternating acetonitrile washout interval at the end of each run. MS/MS detection was made in positive ionization mode, with MRM monitoring of transitions for TAF (477.3→270) and d_5-TAF (482.3→270). Mean recovery efficiency of drug from plasma was 100.2%. The method had a dynamic range of 3.9–2000 ng/mL, and a lower limit of quantitation (LLOQ) of 3.9 ng/mL. Calibration standards were used to generate a curve using a quadratic regression algorithm to plot the peak area ratio of TAF/d_5-TAF versus concentration with 1/y weighting. The lowest calibrator was the LLOQ. Participant plasma samples were kept frozen at −70°C prior to analysis.

Pharmacokinetic Sampling & Analysis

Intensive pharmacokinetic assessments were performed during the second and/or third trimesters (depending on gestational age at enrollment), and 6–12 weeks postpartum. Blood samples were collected at 0, 1, 2, 4, 6, 8, 12, and 24 hours post-dose in both TAF groups. Maternal plasma and cord blood samples were collected at delivery. Infant washout samples were collected from infants at 2–10, 18–28, and 36–72 hours and 5–9 days after birth. Plasma was isolated from women, cord blood, and infants across all time points. PK parameters were calculated using posthoc Bayesian estimation methods in NONMEM, analogous to a therapeutic drug monitoring program, as TAF concentrations were only quantifiable through 4–6 hours post-dose. Posthoc PK parameter estimates were calculated using a simple one-compartment model with first-order absorption and elimination and a proportional error model with an additional error component for samples below the LLOQ. Initial parameter estimates for apparent oral clearance (CL/F), apparent volume of distribution (V/F), and the absorption rate constant from the rilpivirine/TAF/emtricitabine (Odefsey®, Gilead Sciences, Inc.; Foster City, CA) package insert.

Statistical Analysis

The enrollment target was a total of at least 25 women with evaluable pharmacokinetic data during the third trimester, with a minimum of 12 women with second trimester data, per arm. Sample size estimates were based on a two-tiered approach as previously described.[20,21] Pharmacokinetic parameters were analyzed by first determining individual TAF area under the concentration vs. time curve over the dosing interval (AUC_{tau}) and comparing values to the 10th percentile AUC_{tau} value of 132 ng*h/mL in non-pregnant adults in real-time. Interim pharmacokinetic exposure monitoring criteria were defined for all drugs under study *a priori* such that if six or more women fell below the 10th percentile cutoff, then the study team would decide if enrollment should be stopped early to avoid enrollment of additional women with subtherapeutic drug concentrations. Comparisons were also later made to the 10th percentile AUC_{tau} value of 88 ng*h/mL reflecting pooled results from phase III clinical trials with elvitegravir/cobicistat/TAF/emtricitabine.[22] Within-subject comparisons of 2nd and 3rd trimester PK results vs. those measured during the postpartum period were calculated using geometric mean ratios with 90% confidence intervals (CIs). Descriptive statistics were used to summarize pharmacokinetic parameters during pregnancy and postpartum, infant washout pharmacokinetics, and safety results. Statistical comparisons of continuous pharmacokinetic outcomes were made using a two-tailed Wilcoxon signed rank test. Two-sided $P<0.10$ was considered statistically significant.

Safety Monitoring

Each maternal study visit included a physical examination and clinical/safety laboratory assessments. Maternal laboratory assessments consisted of HIV-1 RNA, CD4+ lymphocyte cell count, hematology, and renal/hepatic panels. Infants received physical examinations following birth, and laboratory assessments were performed if clinically indicated. Infant HIV infection status was collected through the final visit at age 16–24 weeks. All medications were prescribed by the participant's clinician. Adverse events (AEs) were reported at each study visit and management was determined by each participant's clinician. All clinical and laboratory AEs were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric AEs, Version 2.0.

RESULTS

Study Population

A total of 31 women were enrolled into the TAF 10 mg with cobicistat arm between March 2016 and July 2017, and 27 women in the TAF 25 mg without boosting arm between May 2016 and May 2018. All women were from the United States. Key demographic characteristics are summarized in Table 1. In the TAF 10 mg arm, all women were on the fixed dose combination of elvitegravir/cobicistat/TAF/emtricitabine (Genvoya®, Gilead Sciences, Inc.). Zidovudine was added in two women during the second and third trimesters, and three women during the postpartum period per the discretion of their clinical care provider. In the TAF 25 mg arm, all women were on emtricitabine in combination with rilpivirine (n=20), dolutegravir (n=5), raltegravir (n=1), and/or nevirapine (n=1). Two women received zidovudine in addition to the remainder of their antiretroviral regimen.

TAF 10 mg Pharmacokinetics with Cobicistat

TAF AUC_{tau} did not differ significantly during the second or third trimester in comparison to postpartum (Table 2, and Figures 1a and 2a). The same was true for apparent oral clearance (CL/F), apparent volume of distribution (V/F), peak concentration (C_{max}), and time to peak concentration (T_{max}). TAF elimination half-life did not differ significantly between the second trimester and postpartum but was 29% higher (p=0.079) during the third trimester versus postpartum. In comparison to the 10th percentile AUC_{tau} cutoff for real-time feedback (132 ng*h/mL), 83–85% of women exceeded targets during pregnancy, and 89–96% exceeded the 10th percentile cutoff from phase 3 studies (88 ng*h/mL) (Figure 2a). Twenty-two maternal and 21 cord blood samples were collected at delivery at a median (IQR [range]) of 15.4 (6.0–21.1 [1.0–37.4]) hours after the last TAF dose. Only two maternal samples were above the LLOQ (10.4 and 14.3 ng/mL), and only one cord blood sample was above the LLOQ at 13.9 ng/mL. The cord-to-maternal ratio for the single measurable pair was 0.97. Infant washout samples were collected at a median (range) of 16 (4–40), 35.5 (21–57), 59 (39–92), 186 (123–243) hours since the last maternal dose of TAF, but TAF concentrations in all samples were below the LLOQ.

TAF 25 mg Pharmacokinetics

TAF AUC_{tau} was 43% lower during the second trimester (p=0.091) and 33% lower during the third trimester (p=0.0035) in comparison to the postpartum period (Table 2, and Figure 1b and 2b). CL/F was 74% higher during the second trimester, although this did not reach statistical significance (p=0.17), and 50% higher during the third trimester in comparison to postpartum (p=0.0072). V/F was 71% higher (p=0.079) and 65% higher (p=0.0031) during the second and third trimesters, respectively. C_{max} was 39% lower during the second trimester, although this did not reach statistical significance (p=0.14), and was 36% lower during the third trimester (p=0.0022). T_{max} and half-life also did not differ between either trimester and postpartum. Over 85% of pregnant women exceeded the 10th percentile AUC_{tau} cutoff for real-time feedback (132 ng*h/mL), and all women were above the 10th percentile AUC_{tau} cutoff of 88 ng*h/mL (Figure 2b). A total of 23 maternal and cord blood samples were collected at a median (IQR [range]) of 11.1 (7.8–20.8 [2.4–35.3]) hours post-dose. Only two maternal samples had levels above the LLOQ (53.1 and 16.2 ng/mL). TAF levels were below the LLOQ in all cord blood samples, thus cord-to-blood ratios were not calculated. Infant washout pharmacokinetic samples were collected at a median (range) of 14.5 (7–39), 34 (24–55), 55 (46–89), and 171.5 (120–213) hours since the last maternal dose of TAF. No infant washout samples had TAF concentrations above the LLOQ.

Maternal Viral & Delivery Outcomes

Delivery outcomes were available in 30 women and infants in the TAF 10 mg arm, and 27 women and infants in the TAF 25 mg arm (Table 3). In the TAF 10 mg arm, 26 (86.7%) women had viral load below 50 copies/mL, and 29 (96.7%) were below 400 copies/mL at delivery. In the TAF 25 mg arm, 24 (88.9%) had viral load below 50 copies/mL, and 25 (92.6%) were below 400 copies/mL at delivery. Infants were born at a median of 38.5 and 38.9 weeks of gestation in the TAF 10 mg with cobicistat and TAF 25 mg arms, respectively. No perinatal transmissions of HIV occurred in either study arm.

Safety Results

Maternal AEs with any relatedness to TAF included two preterm deliveries in the TAF 10 mg arm at 35 weeks (grade 1, probably not related); and 27 weeks (grade 3, possibly related), and one case of hepatic steatosis in the TAF 25 mg arm (grade 1, possibly treatment-related). Grade 3 or higher AEs (none deemed related to TAF) occurred in seven women in the TAF 10 mg arm, and included calcific tendonitis, pyelonephritis, premature rupture of membranes with amniotic fluid loss, preeclampsia with headache, low hemoglobin, chorioamnionitis, and nausea/vomiting with chronic hypertension of pregnancy (n=1 each); and ten women in the TAF with 25 mg arm, which included low hemoglobin (n=7), hypertension (n=2), postpartum preeclampsia (n=1), low bicarbonate and calcium (n=1 each), and uterine rupture (n=1).

Infant abnormalities were observed at birth in the TAF 10 mg with cobicistat arm (regardless of attribution) in five different infants. Three abnormalities occurred in infants whose mothers started TAF before the end of the first trimester (muscular VSD, supernumerary digits (ulnar postaxial polydactyly), and left brachial plexopathy), and two (patent foramen ovale and ventricular septal defect [VSD]) occurred in infants whose mothers initiated TAF after the first trimester. Grade 3 or higher AEs occurred in eight infants, and included bronchiolitis (n=2), neutropenia (n=1), neonatal sepsis (n=1), hyperbilirubinemia (n=1), viral gastroenteritis (n=1), low glucose (n=1), pneumothorax of the left lung (n=1), and seizure like activity with hypertonia later reported (n=1 each).

Infant birth abnormalities in the TAF 25 mg arm (regardless of attribution) consisted of one infant with a renal cyst on the right kidney (TAF started before the end of the first trimester); a second infant with neonatal compartment syndrome, duplicated collecting system of the right kidney (TAF started after the first trimester), and congenital pseudoarthrosis of the right clavicle; and a third infant with skin tags on the right ear (TAF started after the first trimester). Grade 3 or higher AEs occurred in five infants and included low glucose (n=3), hyperbilirubinemia (n=1), high potassium (n=1), probable sepsis (n=1), neonatal abstinence syndrome (n=1), and acute viral bronchiolitis (n=1), none of which were deemed related to TAF.

DISCUSSION

TAF exposures did not differ significantly between pregnancy and postpartum in women taking TAF 10 mg with cobicistat. In women taking TAF 25 mg without boosting, TAF plasma exposures during pregnancy were similar to historical data in non-pregnant adults but were 33–43% lower in comparison to postpartum. Only one maternal-cord blood pair had plasma TAF concentrations above the LLOQ, and none of the infant washout pharmacokinetic samples had plasma TAF concentration above the LLOQ. No perinatal transmissions of HIV occurred, and TAF in combination with other antiretroviral medications was well-tolerated by women in both study arms.

TAF and TDF are key components of multiple recommended antiretroviral regimens in children, adolescents, and adults.[3,14,16] Though both are prodrug forms of tenofovir, the pharmacology of these two moieties differ significantly. In comparison to TDF, TAF is more

stable in plasma and preferentially loads peripheral blood mononuclear cells (PBMCs), resulting in ~2–10-fold higher concentrations of its active anabolite, tenofovir-diphosphate, and ~75–91% lower plasma tenofovir levels.[23–25] TAF has a short half-life in plasma of ~30 minutes, is hydrolyzed by carboxylesterase type (CES1) in the liver, and is less than 1% renally excreted.[26–28] In contrast, parent tenofovir is renally excreted and has a half-life of ~15 hours with TDF and 40 hours with TAF.[23] TAF is a substrate for multiple efflux and uptake transporters, including P-glycoprotein, breast cancer resistance protein (BCRP), and organic anion transporter protein family 1B1 and 1B3 (OATP1B1/3), and thus is susceptible to alterations in drug disposition due to drug-drug interactions or changes in transporter expression.

Sex has been identified as a significant covariate in a few population pharmacokinetic analyses with TAF. The combination of female sex and HIV was associated with ~46% higher TAF exposures in comparison to males without HIV in a population PK analysis of bictegravir/TAF 25 mg/emtricitabine, equating to a mean AUC_{tau} estimate of 197 ng*h/mL.[29] A separate population PK model using data from healthy volunteers, PWH, and chronic hepatitis B identified relative bioavailability was 39% higher in females, translating to AUC estimates of 268 ng*h/mL in females versus 184 ng*h/mL in males with hepatitis B.[30] The magnitudes of difference by sex were deemed not clinically relevant in these analyses,[29,29] other clinical pharmacology reviews did not identify sex as a covariate,[30,32] and concomitant antiretroviral medications can also alter TAF pharmacokinetics,[33] making direct comparisons to historical data in females challenging. Though the influence of pregnancy on TAF pharmacokinetics differed between study arms in this study, TAF exposures were within range of those measured in non-pregnant adults, and more specifically females with HIV.[29,30] Furthermore, all TAF AUCs in this study were above 55 ng*h/mL, which demonstrated similar antiviral activity to TDF 300 mg.[23]

The exact mechanisms behind the differences in study arms are unclear. Plasma tenofovir exposures with TDF are approximately 20% lower during pregnancy versus postpartum[34–37] due in part to increases in glomerular filtration rate (GFR) by up to 50%.[38] TAF is less than 1% renally excreted,[26] thus pregnancy-related GFR increases is an unlikely factor. CYP3A activity increases during pregnancy,[10,12,13,20,39] but this is a minor metabolic pathway for TAF. CES1 activity also does not appear to be altered in pregnancy.[40,41] Both CL/F and V/F were increased by a similar magnitude during the second and third trimesters in the TAF 25 mg arm, and peak concentrations were lower, suggesting that lower exposures between pregnancy and postpartum may be due in part to changes in bioavailability. The magnitude of change in the activity/expression of P-glycoprotein[42,42] and BCRP[43] during pregnancy varies across studies and species, but some suggest increased expression, which would reduce TAF absorption. No differences were identified between pregnancy and postpartum in the TAF 10 mg with cobicistat arm, suggesting that cobicistat can still adequately inhibit intestinal and hepatic transporters involved in TAF bioavailability,[45] and furthermore may counteract some of the expressional changes that occur during pregnancy and revert during the postpartum period. Despite this finding, cobicistat-containing regimens should still not be used during pregnancy as plasma cobicistat concentrations are too low[3,9] to adequately inhibit hepatic first-pass metabolism of atazanavir,[13] darunavir,[11,12] and elvitegravir.[10] These recommendations from the U.S. Food and Drug Administration were based on

pharmacokinetic data originating from P1026s, and many of the women receiving TAF with cobicistat in this study arm contributed results to the elvitegravir with cobicistat findings.[10]

The lack of quantifiable TAF in cord and maternal blood and infant washout samples may be due to the timing of drug administration compared to when samples were drawn. Collection of samples in closer proximity to drug intake may have provided a clearer picture of TAF placental transfer. Parent tenofovir has cord-to-maternal blood ratios between ~0.6 to 1.0 with TDF administration,[35,35,46] thus parent tenofovir may also cross over with TAF. Placental P-glycoprotein expression increases during pregnancy, and TDF placental transfer is limited by drug efflux transporters,[47] thus TAF placental transfer may also be limited. However, medications that are P-glycoprotein substrates have been linked with a higher risk of certain congenital anomalies, which may be increased with the use of P-glycoprotein inhibitors.[48]

Eight out of 57 infants in this study had clinical abnormalities observed at birth. Two infants had abnormalities involving different components of the renal system, one of which was a benign renal cyst, and the other a duplicated collecting system in an infant with multiple other abnormalities. Three infants had abnormalities involving the cardiovascular system. The Antiretroviral Pregnancy Registry reported congenital anomalies in 5.15% of infants exposed to TAF during the first trimester and 1.2% exposed during the second/third trimesters through July 2019.[49] IMPAACT 2010 reported one major congenital anomaly in the dolutegravir/TAF/emtricitabine arm out of 217 women,[50] and lower rates of adverse pregnancy outcomes and similar rates of neonatal death were shown in comparison to dolutegravir/TDF/emtricitabine.[50] However, women in IMPAACT 2010 were randomized at a gestational age of 14 to 28 weeks. The influence of placental TAF, parent tenofovir, and intracellular tenofovir-diphosphate transfer on fetal development, long-term growth and developmental outcomes should continue to be investigated in future studies.

There are limitations to this study. The pharmacokinetic sampling strategy was designed to assess multiple antiretroviral medications and adding several sampling points earlier in the dosing interval was not logistically feasible. Maximum TAF plasma concentrations usually occur between 0.5–2 hours post-dose,[27,27] thus caution is advised in comparing peaks measured in this study against historical data in non-pregnant adults. To address this sampling gap, post hoc Bayesian estimation was used to more accurately estimate TAF exposures, but this required the same absorption rate constant as non-pregnant adults to be assumed. Additionally, food intake after drug administration was not recorded, but high-fat meals increase TAF AUC by 75%.[51] Parent tenofovir was not quantified in this study, but TAF is more stable in the blood than TDF, and loads target cells more efficiently than parent tenofovir.[52,53] Plasma tenofovir and intracellular concentrations of tenofovir-diphosphate were not measured, but will be evaluated in future studies to gain better insight into the drug disposition of TAF in pregnant and postpartum women.[54] Breast milk transfer studies were not performed, but should also be investigated. Although safety outcomes are reported, the study was not powered to detect safety signals in pregnant women or congenital anomalies in infants receiving TAF. Our study population is also biased towards women who tolerated TAF-containing therapy during pregnancy and postpartum.

In conclusion, this study provided the first pharmacokinetic data with TAF during pregnancy, and demonstrated that TAF plasma exposures in pregnant women receiving TAF 10 mg with cobicistat and TAF 25 mg without boosting were comparable to those measured in non-pregnant adults. Over 90% of women had HIV viral loads suppressed below 400 copies/mL at delivery, no perinatal HIV transmissions occurred, and TAF was well-tolerated by mothers in these small sample sizes. These findings support the continued study and uptake of TAF-based regimens in pregnant women.

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REFERENCES

1. Colbers A, Mirochnick M, Schalkwijk S, Penazzato M, Townsend C, Burger D. Importance of Prospective Studies in Pregnant and Breastfeeding Women Living With Human Immunodeficiency Virus. Clin Infect Dis. 2019;69(7):1254–1258. [PubMed: 30783649]
2. Powis KM, Huo Y, Williams PL, et al. Antiretroviral Prescribing Practices Among Pregnant Women Living With HIV in the United States, 2008–2017. JAMA Netw Open. 2019;2(12):e1917669. [PubMed: 31851347]
3. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed 2020 Feb 18.
4. Teasdale CA, Marais BJ, Abrams EJ. HIV: prevention of mother-to-child transmission. BMJ Clin Evid. 2011;2011.
5. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331(18):1173–1180. [PubMed: 7935654]

6. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. N Engl J Med. 2010;362(24):2271–2281. [PubMed: 20554982]
7. Fowler MG, Qin M, Fiscus SA, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med. 2016;375(18):1726–1737. [PubMed: 27806243]
8. Buckoreelall K, Cressey TR, King JR. Pharmacokinetic optimization of antiretroviral therapy in pregnancy. Clin Pharmacokinet. 2012;51(10):639–659. [PubMed: 23018528]
9. 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. [PubMed: 30946163]
10. Momper JD, Best BM, Wang J, et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. AIDS. 2018;32(17):2507–2516. [PubMed: 30134297]
11. Crauwels HM, Osiyemi O, Zorrilla C, Bicer C, Brown K. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019;20(5):337–343. [PubMed: 30873741]
12. Momper JD, Best BM, Wang J, et al. Pharmacokinetics of Darunavir Boosted with Cobicistat during Pregnancy and Postpartum. AIDS 2018; 23–27 7, 2018; Amsterdam, Netherlands.
13. Momper JD, Stek A, Wang J, et al. Pharmacokinetics of atazanavir boosted with cobicistat during pregnancy and postpartum. 20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs [abstract #10]; 14–16 5, 2019; Noordwijk, the Netherlands.
14. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed 18 Feb 2020.
15. WHO. Update of recommendations on first- and second-line antiretroviral regimens. Policy brief. 7 2019. https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf (PDF).
16. European AIDS Clinical Society (EACS) Guidelines version 10.0, 11 2019. https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf (PDF). Accessed 03 Jun 2020.
17. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2018 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2018;320(4):379–396. [PubMed: 30043070]
18. Nachega JB, Uthman OA, Mofenson LM, et al. Safety of Tenofovir Disoproxil Fumarate-Based Antiretroviral Therapy Regimens in Pregnancy for HIV-Infected Women and Their Infants: A Systematic Review and Meta-Analysis. J Acquir Immune Defic Syndr. 2017;76(1):1–12. [PubMed: 28291053]
19. Aizire J, Brooks KM, Mirochnick M, et al. Antenatal Intracellular Concentrations of Tenofovir Diphosphate and Emtricitabine Triphosphate and Associations Between Tenofovir Diphosphate and Severe Adverse Pregnancy Outcomes: IMPAACT-PROMISE (1077BF) Trial. J Acquir Immune Defic Syndr. 2020;83(2):173–180. [PubMed: 31929405]
20. Stek AM, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. AIDS. 2006;20(15):1931–1939. [PubMed: 16988514]
21. Best BM, Stek AM, Mirochnick M, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. J Acquir Immune Defic Syndr. 2010;54(4):381–388. [PubMed: 20632458]
22. Center for Drug Evaluation and Research. Application Package: Emtricitabine/Tenofovir Alafenamide. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208351Orig1s000ClinPharmR.pdf.
23. Ruane PJ, DeJesus E, Berger D, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. J Acquir Immune Defic Syndr. 2013;63(4):449–455. [PubMed: 23807155]
24. Brooks KM, Castillo-Mancilla JR, Morrow M, et al. Pharmacokinetics and renal safety of tenofovir alafenamide with boosted protease inhibitors and ledipasvir/sofosbuvir J Antimicrob Chemother. 2020:dkaa299.
25. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1

infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606–2615. [PubMed: 25890673]

26. Jin F, Fordyce M, Garner W, et al. Pharmacokinetics, metabolism, and excretion of tenofovir alafenamide (TAF) [abstr O-08]. 14th Int Workshop Clin Pharmacol HIV Ther; 2013.
27. Ray AS, Fordyce MW, Hitchcock MJ. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. Antiviral Res. 2016;125:63–70. [PubMed: 26640223]
28. Markowitz M, Zolopa A, Squires K, et al. Phase I/II study of the pharmacokinetics, safety and antiretroviral activity of tenofovir alafenamide, a new prodrug of the HIV reverse transcriptase inhibitor tenofovir, in HIV-infected adults. J Antimicrob Chemother. 2014;69(5):1362–1369. [PubMed: 24508897]
29. Lutz JD, Kirby BJ, Shao Y, Gao Y, Quirk E, Mathias A. No clinically relevant effect of patient demographic or disease covariates on the exposures of Bbictegravir and tenofovir alafanemide following administration of a B/F/TAF single-tablet regimen for HIV-1-infected patients [abstract P262]. HIV Drug Therapy; 28–31 10, 2018; Glasgow, UK.
30. EMA. Vemlidy Assessment Report (Procedure No. EMEA/H/C/004169/0000). 10 11 2016. https://www.ema.europa.eu/en/documents/assessment-report/vemlidy-epar-public-assessment-report_en.pdf (PDF).
31. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s): Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (E/C/F/TAF). 2014. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207561Orig1s000ClinPharmR.pdf.
32. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s): Emtricitabine/Rilpivirine/Tenofovir Alafenamide (F/RPV/TAF). 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208351Orig1s000ClinPharmR.pdf.
33. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s): Emtricitabine/Tenofovir Alafenamide. Available at: https://www.fda.gov/media/98516/download.
34. 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. [PubMed: 22123690]
35. Best BM, Burchett S, Li H, et al. Pharmacokinetics of tenofovir during pregnancy and postpartum. HIV Med. 2015;16(8):502–511. [PubMed: 25959631]
36. 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. [PubMed: 23169329]
37. Bukkems VE, Smolders EJ, Jourdain G, et al. 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. J Clin Pharmacol. 2020.
38. Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis. 2013;20(3):209–214. [PubMed: 23928384]
39. Stek A, Best BM, Wang J, et al. Pharmacokinetics of Once Versus Twice Daily Darunavir in Pregnant HIV-Infected Women. J Acquir Immune Defic Syndr. 2015;70(1):33–41. [PubMed: 25950206]
40. Beigi RH, Han K, Venkataramanan R, et al. Pharmacokinetics of oseltamivir among pregnant and nonpregnant women. Am J Obstet Gynecol. 2011;204(6 Suppl 1):S84–88. [PubMed: 21492826]
41. Fortin MC, Aleksunes LM, Richardson JR. Alteration of the expression of pesticide-metabolizing enzymes in pregnant mice: potential role in the increased vulnerability of the developing brain. Drug Metab Dispos. 2013;41(2):326–331. [PubMed: 23223497]
42. Hebert MF, Easterling TR, Kirby B, et al. Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: a University of Washington specialized center of research study. Clin Pharmacol Ther. 2008;84(2):248–253. [PubMed: 18288078]

43. Zhang H, Wu X, Wang H, Mikheev AM, Mao Q, Unadkat JD. Effect of pregnancy on cytochrome P450 3a and P-glycoprotein expression and activity in the mouse: mechanisms, tissue specificity, and time course. Mol Pharmacol. 2008;74(3):714–723. [PubMed: 18509067]
44. Wang H, Wu X, Hudkins K, et al. Expression of the breast cancer resistance protein (Bcrp1/Abcg2) in tissues from pregnant mice: effects of pregnancy and correlations with nuclear receptors. Am J Physiol Endocrinol Metab. 2006;291(6):E1295–1304. [PubMed: 17082346]
45. Lepist EI, Phan TK, Roy A, et al. Cobicistat boosts the intestinal absorption of transport substrates, including HIV protease inhibitors and GS-7340, in vitro. Antimicrob Agents Chemother. 2012;56(10):5409–5413. [PubMed: 22850510]
46. Flynn PM, Mirochnick M, Shapiro DE, et al. Pharmacokinetics and safety of single-dose tenofovir disoproxil fumarate and emtricitabine in HIV-1-infected pregnant women and their infants. Antimicrob Agents Chemother. 2011;55(12):5914–5922. [PubMed: 21896911]
47. Neumanova Z, Cerveny L, Ceckova M, Staud F. Interactions of tenofovir and tenofovir disoproxil fumarate with drug efflux transporters ABCB1, ABCG2, and ABCC2; role in transport across the placenta. AIDS. 2014;28(1):9–17. [PubMed: 24413260]
48. Daud AN, Bergman JE, Bakker MK, et al. P-Glycoprotein-Mediated Drug Interactions in Pregnancy and Changes in the Risk of Congenital Anomalies: A Case-Reference Study. Drug Saf. 2015;38(7):651–659. [PubMed: 26017034]
49. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2019. Wilmington, NC: Registry Coordinating Center; 2019. Available from URL: www.APRegistry.com.
50. Chinula L, Brummel SS, Ziemba L, et al. Safety and efficacy of DTG vs EFV and TDF vs TAF in pregnancy: IMPAACT 2010 trial. Conference on Retroviruses and Opportunistic Infections; 11 3, 2020.
51. Descovy [package insert]. Foster City, CA: Gilead Sciences, Inc.; 2020.
52. Lee WA, He GX, Eisenberg E, et al. Selective intracellular activation of a novel prodrug of the human immunodeficiency virus reverse transcriptase inhibitor tenofovir leads to preferential distribution and accumulation in lymphatic tissue. Antimicrob Agents Chemother. 2005;49(5):1898–1906. [PubMed: 15855512]
53. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. Mol Pharm. 2013;10(2):459–466. [PubMed: 22738467]
54. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT04518228, Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum. 2020 Aug 19 [cited 12 Oct 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT04518228.

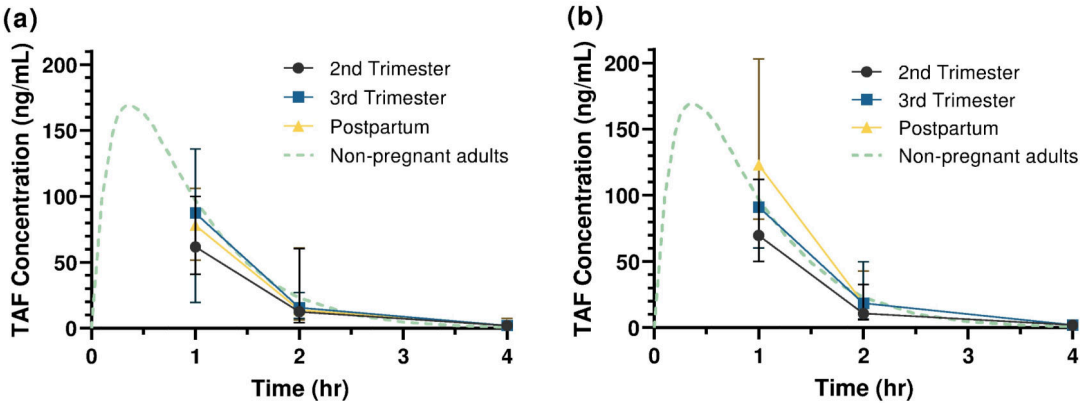
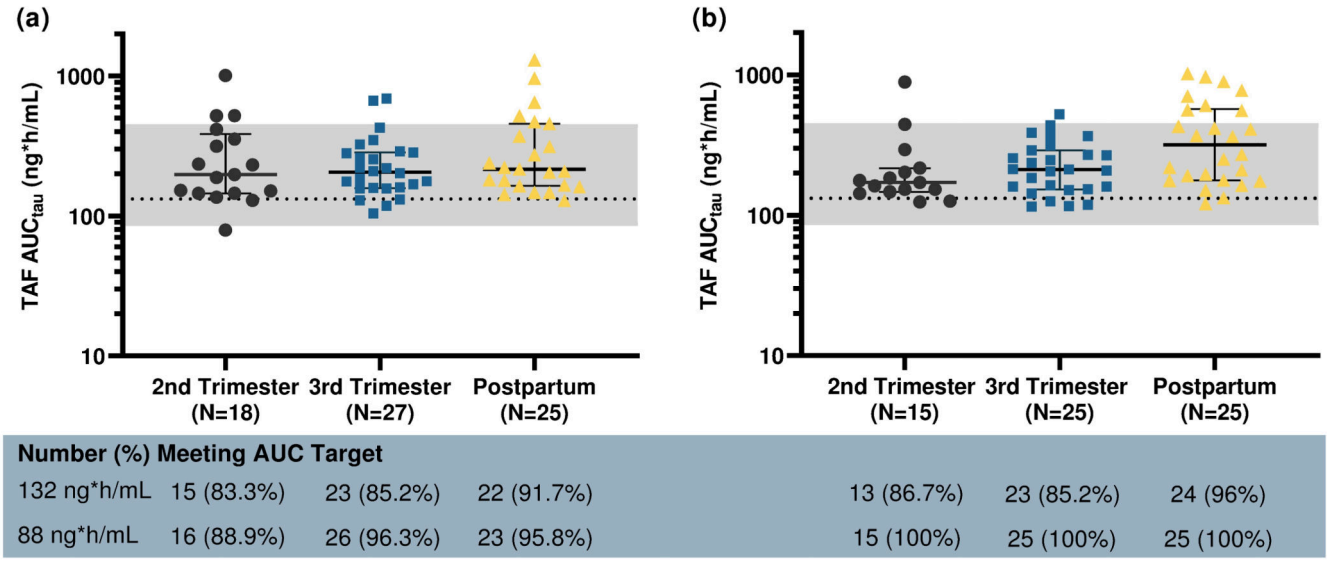


Figure 1.

Median (IQR) concentration-time curves during the 2nd trimester, 3rd trimester, and postpartum for (a) TAF 10 mg with cobicistat and (b) TAF 25 mg (without boosting). Dotted lines indicate 50th percentile concentrations measured in non-pregnant adults.



Number (%) Meeting AUC Target						
132 ng*h/mL	15 (83.3%)	23 (85.2%)	22 (91.7%)	13 (86.7%)	23 (85.2%)	24 (96%)
88 ng*h/mL	16 (88.9%)	26 (96.3%)	23 (95.8%)	15 (100%)	25 (100%)	25 (100%)

Figure 2.

Median (IQR) TAF exposures during the 2nd trimester, 3rd trimester, and postpartum for (a) TAF 10 mg with cobicistat and (b) TAF 25 mg (unboosted). Gray shading indicates 10th and 90th percentile exposures from phase II/III studies in non-pregnant adults, and the dashed line indicates the threshold for real-time comparisons. In the TAF 10 mg with cobicistat arm, there was one woman during the second trimester and a second woman during the third trimester and postpartum with drug concentrations below the LLOQ at all time points (not included). The summary tables below each figure reflect number (N) (percentage [%]) of women exceeding the AUC target for real-time comparisons (132 ng*h/mL) and phase 3 data (88 ng*h/mL).

Table 1.

Participant Demographics

Characteristic	TAF 10 mg with Cobicistat (n=31)	TAF 25 mg (n=27)
Race, n (%)		
Asian/Pacific Islander	0 (0%)	1 (4%)
Black	18 (58%)	10 (37%)
White	11 (35%)	12 (44%)
American Indian	1 (3%)	1 (4%)
Unknown	1 (3%)	3 (11%)
Ethnicity, n(%)		
Hispanic or Latino	10 (32%)	14 (52%)
Not Hispanic or Latino	21 (68%)	13 (48%)
Age (yr), median (IQR)		
Second Trimester	34.8 (25.9–36.3)	30.2 (24.0–36.3)
Third Trimester	33.9 (27.4–35.3)	29.5 (24.1–35.1)
Weight (kg), median (IQR)		
Second Trimester	78.1 (67.0–88.2)	69.0 (57.6–90.6)
Third Trimester	85.2 (75.2–101.8)	79.3 (66.6–93.9)
Delivery	87.5 (75.7–96.8)	85.0 (71.8–94.3)
Postpartum	81.0 (73.7–90.6)	71.3 (65.3–88.9)
Gestational Age or Time after Delivery (weeks), median (range)		
Second Trimester	24.6 (20.4–27.1)	23.4 (21.2–27.4)
Third Trimester	33.0 (30.0–36.4)	33.3 (30.0–37.6)
Postpartum	8.6 (4.4–20.6)	10.0 (6.0–14.4)
Duration of TAF Therapy (weeks), median (IQR)		
Second Trimester	10.9 (7.0–20.3)	14.1 (10.9–20.6)
Third Trimester	22.0 (13.0–29.3)	20.1 (12.1–24.9)
TAF initiated before end of first trimester, n (%)	15 (48%)	9 (33%)
HIV Viral Load ≤50 copies/mL, n (%)		
Second Trimester	13/17 (76.5%)	13/15 (86.7%)
Third Trimester	24/27 (88.9%)	24/27 (88.9%)
Postpartum	23/25 (92.0%)	22/26 (84.6%)
HIV Viral Load ≤400 copies/mL, n (%)		
Second Trimester	15/17 (88.2%)	14/15 (93.3%)
Third Trimester	27/27 (100.0%)	26/27 (96.3%)
Postpartum	23/25 (92.0%)	23/26 (88.5%)

Table 2.

Pharmacokinetic Parameters of TAF 10 mg with Cobicistat and TAF 25 mg during Pregnancy and Postpartum

PK Parameter	2nd trimester	3rd trimester	Postpartum	2nd Trimester vs. Postpartum		3rd Trimester vs. Postpartum	
				GMR (90% CI)	P-value	GMR (90% CI)	P-value
TAF 10 mg with Cobicistat							
N per group	18	27	25	13		21	
AUC_{tau} (ng*h/mL)	197 (145 – 354)	206 (158 – 284)	216 (164 – 457)	0.79 (0.50, 1.27)	0.27	0.86 (0.66, 1.12)	0.70
CL/F (L/hr)	127 (71 – 172)	122 (88 – 158)	116 (55 – 152)	1.26 (0.79, 2.02)	0.24	1.17 (0.89, 1.52)	0.80
T_{max} (hr)	1 (1 – 4)	1 (1 – 4)	1 (1 – 2)	0 (0 – 2)	0.50	0 (0 – 2)	0.36
$t_{1/2}$ (hr)	0.36 (0.25 – 0.52)	0.36 (0.27 – 0.48)	0.30 (0.26 – 0.50)	0.90 (0.69, 1.19)	0.68	1.29 (0.94, 1.76)	0.08
C_{max} (ng/mL)	80.4 (57.5 – 121.0)	91.2 (51.4 – 136.0)	98.2 (71.2 −141.0)	0.77 (0.49, 1.23)	0.24	0.84 (0.60, 1.17)	0.53
V/F (L)	59.8 (54.9 – 62.7)	59.1 (48.8 – 81.1)	57.9 (46.4 – 67.5)	1.14 (0.78, 1.67)	0.41	1.5 (1.06, 2.12)	0.23
TAF 25 mg							
N per group	15	27	25	14		25	
AUC_{tau} (ng*h/mL)	171 (147 – 217)	212 (153 – 290)	271 (178 – 561)	0.57 (0.34, 0.98)	0.09	0.67 (0.54, 0.82)	0.004
CL/F (L/hr)	146 (115 – 170)	118 (86 – 164)	92 (45 – 140)	1.74 (1.02, 2.98)	0.17	1.50 (1.22, 1.85)	0.007
T_{max} (hr)	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	0 (0 – 0)	>0.99	0 (0 – 0)	0.50
$t_{1/2}$ (hr)	0.26 (0.23 – 0.35)	0.29 (0.24 – 0.49)	0.29 (0.27 – 0.43)	0.98 (0.85, 1.14)	>0.99	1.10 (0.88, 1.37)	0.99
C_{max} (ng/mL)	69.7 (50.0 – 112.0)	96.0 (63.1 – 112.0)	133 (88 – 230)	0.61 (0.34, 1.09)	0.14	0.64 (0.50, 0.81)	0.002
V/F (L)	56.2 (53.8 – 64.1)	57.6 (54.1 – 64.9)	45.4 (28.2 – 55.7)	1.71 (1.03, 2.84)	0.08	1.65 (1.26, 2.16)	0.003

AUC_{tau}: area under the concentration vs. time curve over the dosing interval; Cmax: maximum plasma concentration; CL/F: apparent oral clearance; t1/2: half-life; Tmax: time to maximum plasma concentration; V/F: apparent volume of distribution. Summary statistics for $2^{nd}/3^{rd}$ trimester and postpartum presented as median (IQR), except T_{max} which is presented as median (range); comparisons between pregnancy and postpartum reflect geometric mean ratios (GMR) (90% CI), except T_{max} which is presented as the median (range) difference.

Table 3.

Maternal Viral Suppression and Delivery Outcomes

Characteristic	TAF 10 mg with Cobicistat (n=30)	TAF 25 mg (n=27)
Maternal Viral Load ≤50 copies/mL at Delivery, n (%)	26 (86.7%)	24 (88.9%)
Maternal Viral Load ≤400 copies/mL, n (%)	29 (96.7%)	25 (92.6%)
Birth Weight (gm), median (range)	3035 (1835 – 4170)	3084 (2100 – 4102)
Birth Length (cm), median (range)	48.7 (43.2 – 54.0)	49.5 (41.5 – 53.0)
Gestational Age at Delivery (weeks), median (range)	38.5 (27.1 – 41.3)	38.9 (36.0 – 40.9)
HIV Status, n (%)		
Uninfected	30 (100%)	26 (96%)
Unknown[a]	0 (0%)	1 (4%)

Note: numbers and percentages vary depending on the total number of women and infants with results available at each time point; one woman in the TAF with cobicistat arm withdrew prior to delivery.

[a]No HIV testing results available.