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Pharmacokinetics of tenofovir alafenamide with boosted protease inhibitors in pregnant and postpartum women living with HIV: Results from IMPAACT P1026s

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Abstract

Background: Tenofovir alafenamide (TAF) is a key component of HIV treatment, but pharmacokinetic data supporting the use of TAF during pregnancy are limited. Here, we report pharmacokinetic, safety, and birth outcomes with TAF 25 mg with a boosted protease inhibitor (PI) in pregnant women living with HIV (PWLH).

Methods: IMPAACT P1026s was a multicenter, nonrandomized, open-label, phase IV prospective study. PWLH receiving TAF 25 mg with a boosted PI were eligible. Intensive pharmacokinetic assessments were performed during the second and third trimesters and 6–12 weeks postpartum. Maternal and cord blood samples were collected at delivery. Infant washout samples were collected through 5–9 days post-birth. Comparisons of paired pharmacokinetic data between pregnancy and postpartum were made using geometric mean ratios (GMR) (90% confidence intervals [CIs]) and Wilcoxon signed-rank tests with $p<0.10$ considered significant.

Results: Twenty-nine women were enrolled from the United States (median age 31 years and weight 84.5 kg during the third trimester; 48% black, 45% Hispanic/Latina). TAF AUC_{tau} did not significantly differ in the second (GMR 0.62 [90% CI 0.29, 1.34]; p=0.46) or third trimester (GMR 0.94 [90% CI 0.63, 1.39]; p=0.50) versus postpartum and were comparable to historical data in non-pregnant adults. TAF was only quantifiable in 2/25 maternal delivery samples and below the limit of quantification in all cord blood and infant washout samples, likely due to the short half-life of TAF.

Conclusion: TAF AUC_{tau} did not significantly differ between pregnancy and postpartum. These findings provide reassurance as TAF use during pregnancy continues to expand.

Keywords

TAF; cobicistat; ritonavir; pregnancy; pharmacology; HIV

INTRODUCTION

Tenofovir is a key component of several recommended HIV regimens.[1–5] Tenofovir is available as two different prodrugs: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). Both prodrugs yield the same active moiety, tenofovir-diphosphate, within cells but the pharmacology and safety profiles of the two drugs differ markedly.[6–10] TDF is administered at a 300 mg dose in adults and adolescents with HIV.[11] TAF dosing varies depending on the concomitant antiretroviral medications and region of use: in the United States, it is administered as either a 10 mg dose in cobicistat-containing fixed dose combinations[12,13] or a 25 mg dose with all other antiretroviral combinations in adults,[14] and in Europe, TAF is administered as a 10 mg dose with all cobicistat- or ritonavir-containing regimens and 25 mg without a pharmacoenhancer.[15] TAF yields ~75–90% lower plasma tenofovir area under the concentration-time curve over the dosing interval (AUC_{tau}) and ~2–10-fold higher tenofovir-diphosphate concentrations in peripheral blood mononuclear cells (PBMCs).[7,8,10] In recent years, patterns of clinical use have shifted towards TAF-containing regimens in the United States,[16] and this will likely increase globally as access expands.[3,17] However, data supporting TAF use during pregnancy have lagged behind non-pregnant adults, with guidelines only recently conditionally recommending its use.[1,5]

One of the primary concerns with using antiretroviral drugs in pregnant women living with HIV (PWLH) is that drug exposures may differ and be too low to adequately suppress viral replication, leading to virologic failure and/or resistance in the PWLH and an increased risk of perinatal HIV transmission. The safety of newer medications in PWLH and infants are also critical to assess. We previously showed that TAF AUC_{tau} did not significantly differ between pregnancy and postpartum when administered as a 10mg dose with cobicistat, but were higher postpartum in comparison to pregnancy when administered at a 25 mg dose without boosters.[18] The PANNA network reported a similar magnitude of difference between pregnancy and postpartum with pooled pharmacokinetic results from these same dose combinations.[19] TAF AUC_{tau} during pregnancy and postpartum in both arms of the IMPAACT 1026s study were comparable or higher than historical AUC_{tau} in non-pregnant adults.[18] Separately, the International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPAACT) 2010/VESTED study showed the combination of dolutegravir with TAF/emtricitabine was associated with lower rates of adverse pregnancy outcomes vs. TDF-containing comparator regimens, and was also associated with higher rates of virologic suppression in comparison to efavirenz/TDF/emtricitabine.[20] Collectively, these findings provide reassurance that plasma TAF AUC_{tau} during pregnancy are likely adequate and that TAF-containing regimens will become additional safe and effective treatment options in PWLH.

Though available data for TAF 10 mg with cobicistat and TAF 25 mg without boosting suggests that TAF AUC_{tau} is likely adequate in pregnancy,[18,19] TAF is also licensed for administration at a 25 mg dose in combination with emtricitabine when given as a separate product along with a protease inhibitor (PI) boosted with either ritonavir or cobicistat in the United States. There are currently no pharmacokinetic data with this combination during pregnancy and postpartum. In non-pregnant adults, coadministration of 25 mg TAF and a boosted PI may increase plasma TAF exposure by up to 135% depending on the specific

concomitant booster and PI.[14] Ritonavir-boosted atazanavir and darunavir are preferred PI regimens during pregnancy,[5] thus it is critical to understand the pharmacokinetics of TAF 25 mg when co-administered with boosted PIs. The primary objective of this study was to characterize the pharmacokinetics (PK) of TAF when administered at a 25 mg dose in combination with boosted PIs during pregnancy and postpartum. Primary outcomes included comparisons of TAF pharmacokinetics between pregnancy and postpartum and to historical data in non-pregnant adults living with HIV. Secondary objectives were to examine transplacental TAF transfer and describe maternal and infant safety and clinical outcomes.

METHODS

Study Design

IMPAACT P1026s was a prospective, opportunistic, open-label, multi-center, multi-arm phase IV study of the pharmacokinetics and safety of antiretroviral medications prescribed as part of clinical care in PWLH (NCT00042289). The current study arm enrolled PWLH who were receiving TAF 25 mg with a boosted PI. The study team was not involved in initiating or altering the person's prescribed regimens during the study. All participants provided written informed consent, and infants were enrolled *in utero* immediately 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 ethical review boards at each institution where the study was being conducted and by the National Institute of Allergy and Infectious Disease Division of AIDS (DAIDS).

Eligible participants could enroll during the second trimester (20 0/7 to 26 6/7 weeks gestation) or the third trimester (30 0/7 to 37 6/7 weeks gestation). Participants underwent up to three PK assessments during the second trimester (if enrolled), third trimester, and 6–12 weeks postpartum. Participants were required to be on TAF 25 mg and a PI combined with either ritonavir or cobicistat for at least two weeks prior to the first pharmacokinetic assessment and were expected to continue on the same combination through the postpartum pharmacokinetic assessment. Exclusion criteria for mothers included receipt of medications that interact with TAF, pregnancy with twin or higher order gestation, or clinical/laboratory abnormalities that would likely result in discontinuing the drug combination under study. Infants were eligible for washout pharmacokinetic assessments if they weighed at least 1000 grams, were not on any medications that could interact with TAF and did not have medical conditions or severe congenital malformations incompatible with life or that could interfere with study participation.

Pharmacokinetic Sampling & Analysis

TAF plasma concentrations were quantified using LC/MS methods.[18] The lower limit of quantification (LLOQ) was 3.9 ng/mL. Intensive pharmacokinetic assessments were performed during the second and/or third trimesters (depending on gestational age at enrollment), and 6–12 weeks postpartum. Plasma samples for all once-daily antiretroviral medications, including TAF, were collected at the following standardized times: 0, 1, 2, 4, 6, 8, 12 and 24 hours post-dose. Maternal peripheral blood and cord blood samples were collected at delivery. Infant washout samples were collected at 2–10, 18–28, and 36–72

hours and 5–9 days after birth. PK parameters were calculated using posthoc Bayesian estimation methods in NONMEM as previously described.[18]

Statistical Analysis

Sample size estimates were based on a two-tiered approach of drug exposure comparisons against historical data in non-pregnant adults and within-subject comparisons between pregnancy and postpartum, as previously described.[21,22] The target sample size was 25 participants with evaluable PK data during the third trimester, with at least 12 participants with second trimester data. Real-time comparisons of TAF area under the concentration-time curve over the dosing interval (AUC_{tau}) were made against a cutoff of 132 ng*h/mL based on historical data available at the time of study initiation on the 10^{th} percentile in non-pregnant adults. Comparisons were also made to an AUC_{tau} cutoff of 88 ng*h/mL, based on a recent 10^{th} percentile estimate from phase III clinical trials.[23] Within-subject comparisons of TAF PK parameters during the second or third trimester vs. postpartum were calculated using geometric mean ratios with 90% confidence intervals (CIs), and statistical comparisons were made using a two-tailed Wilcoxon signed-rank test with a two-sided p-value <0.10 considered statistically significant. Exploratory analyses to compare TAF AUC_{tau} between individual boosted PI combinations (atazanavir/cobicistat or atazanavir/ritonavir, darunavir/cobicistat, and darunavir/ritonavir) were also performed.

Safety Assessments

Maternal safety monitoring included clinical and safety laboratory assessments (HIV-1 RNA, CD4+ lymphocyte cell count, hematology, and comprehensive metabolic panel) at each study visit. Physical examinations were performed for infants following birth, with laboratory assessments only performed if clinically indicated. Infant HIV infection status was assessed at multiple time points through the final visit at age 16–24 weeks. Clinical and laboratory adverse events (AEs) were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric AEs, Version 2.0 (November 2014) and were managed by the participant's clinician. AE relatedness was assessed by both the study site investigator and study team.

RESULTS

Participant Demographics

A total of 29 participants were enrolled in the United States beginning in November 2016, with the last study visit occurring in February 2020. Demographics are summarized in Table 1. Participants were on TAF for a median (range) 17.4 (2.0–129.6) weeks prior to the second trimester PK assessment and 27.7 (5.0–141.6) weeks prior to the third trimester PK assessment. All participants received TAF in combination with emtricitabine. Concomitant boosted protease inhibitors included the following: atazanavir/cobicistat (2 in the second trimester, 4 in the third trimester, and 3 postpartum); atazanavir/ritonavir (1 in the second trimester, 3 in the third trimester, and 4 postpartum); darunavir/cobicistat (5 in the second trimester, 12 in the third trimester, and 8 postpartum); and darunavir/ritonavir (4 in the second trimester, 8 in the third trimester, and 7 postpartum). Other concomitant antiretroviral medications included abacavir (1 on atazanavir/ritonavir during

the third trimester and postpartum); dolutegravir (1 on darunavir/ritonavir during the third trimester and postpartum; 1 on darunavir/cobicistat postpartum); raltegravir (1 on darunavir/ritonavir during the second and third trimesters and postpartum; 1 on darunavir/cobicistat during the third trimester); and zidovudine (1 on atazanavir/cobicistat in the second and third trimesters; 1 on darunavir/cobicistat in the third trimester).

Pharmacokinetic Results

TAF PK results were available in 12, 27, and 21 women during the second trimester, third trimester, and postpartum, respectively. Paired data for GMR comparisons were available in eight women between the second trimester and postpartum, and 20 women between the third trimester and postpartum. A total of seven women had results available from all three intensive PK assessments. TAF was eliminated rapidly after oral administration (Figure 1a). No statistically significant differences in AUC_{tau}, maximum plasma concentrations (C_{max}), time to C_{max}, apparent oral clearance, apparent volume of distribution, or half-life were identified between the second trimester and postpartum, or the third trimester and postpartum (Table 2). In comparison to the original AUC target of 132 ng*h/mL, 83.3%, 88.9%, and 81.8% of participants exceeded this threshold during the second trimester, third trimester, and postpartum, respectively. In comparison to the AUC target of 88 ng*h/mL (10^{th} percentile estimate from phase III studies in non-pregnant adults), 92%, 100%, and 95% of participants exceeded this threshold (Figure 1b).

For the exploratory analyses comparing individual combinations of boosted protease inhibitors, the median TAF AUC_{tau} was highest for participants who were co-administered atazanavir with cobicistat or ritonavir and were numerically similar across pregnancy and postpartum (Table 3). Median TAF AUC_{tau} for darunavir/cobicistat were lower than darunavir/ritonavir during the second trimester, and higher than darunavir/ritonavir during the third trimester and postpartum. However, no pairwise comparisons were statistically significant, likely due to the small sample sizes and variability in TAF AUC_{tau} across groups.

A total of 23 cord blood samples and 25 maternal delivery samples were collected. Paired samples were collected at a median (IQR) 10.4 (6.2–19.1) hours after the last maternal TAF dose. All cord blood samples were below the lower limit of quantification (BLQ) of 3.9 ng/mL,[18] and 23/25 maternal delivery samples were BLQ. The two quantifiable maternal samples were collected at 8.7 and 26.1 hours post-dose and had TAF concentrations of 5.31 and 6.31 ng/mL, respectively. A total of 81 infant washout samples were collected following birth (19 between 2–10 hours, 22 between 18–28 hours, 21 between 36–72 hours, and 19 between 5–9 days post-birth). All infant washout samples were BLQ.

Delivery Outcomes

Data related to delivery outcomes were available in 28 participants and 27 infants (Table 4). Of the original 29, there was one stillbirth at 29.6 weeks gestation and one woman withdrew consent for her infant *in utero*; these infants were not included in any summaries. Most participants were virologically suppressed at delivery, with 85.7% below 50 copies/mL and 92.9% below 400 copies/mL. No confirmed perinatal HIV transmissions occurred.

Safety Results

Ten participants experienced grade 3 or higher AEs. Grade 3 or higher AEs deemed not related to study treatment by the study site included: low hemoglobin (n=4), hyperkalemia (n=1), hypertension (n=1), elevated aspartate aminotransferase (AST) (n=1), placental dysfunction followed by stillbirth (n=1), elevated total bilirubin in a participant on atazanavir (n=1), and endometritis (n=1). Grade 3 or higher AEs with any relatedness to study treatment according to study site assessment included elevated total bilirubin in two different participants on atazanavir (both deemed definitely related to treatment), one preterm labor (deemed possibly related), and abdominal pain and preterm labor (both deemed probably not related). The P1026s team differed from site assessments for grade 3 or higher AE relatedness as follows: one elevated bilirubin event was classified as non-treatment-related and abdominal pain was deemed possibly treatment-related. Additional AEs that differed between study sites and the study team included one case of gestational diabetes (grade 2) that was assessed as not related to study treatment by the study site and possibly treatment-related by the study team; and one preterm labor (grade 1) deemed probably not related by the site and possibly treatment related by the team.

Five infants experienced grade 3 or higher AEs, none of which were deemed related to treatment. These grade 3 or higher AEs included hypoglycemia (n=2), respiratory distress (n=2), infant reflux (n=1), and hemolytic disease of the newborn with elevated total bilirubin (n=1). Both infants with grade 3 respiratory distress were born premature (grades 1 and 2). A third infant was born premature (grade 1) and both the site and P1026s team classified this as possibly treatment-related. There were two AEs with discrepancies between site and team classification: a grade 2 decreased hemoglobin classified as probably not related by the site and not related by the study team, and a grade 2 elevated AST classified by the site as possibly related and by the study team as not related. Four infants were born with abnormalities, which included a sacral dimple, microcephaly, and two infants with congenital dermal melanocytosis. All were deemed unrelated to treatment.

DISCUSSION

The pharmacokinetics of TAF 25 mg when co-administered with boosted PIs did not significantly differ between pregnancy and postpartum. All participants except one during the second trimester and one during the postpartum period exceeded the 10th percentile TAF AUC_{tau} of 88 ng*h/mL from recent phase III studies. Exploratory analyses by concomitant PI did not reveal any statistically significant differences, though the atazanavir combinations yielded higher median TAF AUC_{tau} measures than those measured with darunavir/cobicistat or darunavir/ritonavir. Nearly all maternal delivery samples, and all cord blood and washout samples were BLQ, precluding further assessment of TAF placental transfer and washout pharmacokinetics. These drug combinations were well-tolerated during pregnancy and postpartum. Most participants were suppressed throughout pregnancy, delivery, and postpartum, and no confirmed perinatal HIV transmissions occurred.

The TAF AUC_{tau} in this study arm (TAF 25mg co-administered with boosted PIs) were comparable or higher than those we measured in the other P1026s TAF study arm,[18] though numerical differences were apparent depending on the timing of pharmacokinetic

assessments. During the second trimester, the median TAF AUC_{tau} for TAF 25 mg with boosting was 181 ng*h/mL, which was comparable to what we measured previously in the TAF 10 mg with cobicistat study arm (median AUC_{tau} 197 ng*h/mL) and the TAF 25 mg without boosting arm (median AUC_{tau} 171 ng*h/mL).[18] During the third trimester, the median TAF AUC_{tau} for TAF 25 mg with boosting was 257 ng*h/mL, which is higher than what we measured previously for both TAF 10 mg with cobicistat (median AUC_{tau} 206 ng*h/mL) and TAF 25 mg without boosting (median AUC_{tau} 212 ng*h/mL).[18] During the postpartum period, the median TAF AUC_{tau} for TAF 25 mg with boosting was 283 ng*h/mL, which was numerically higher than TAF 10 mg with boosting (median AUC_{tau} 216 ng*h/mL) and comparable to TAF 25 mg without boosting (median AUC_{tau} 271 ng*h/mL).[18] Though some numerical differences are apparent between the P1026s study arms, it is unclear whether these differences are clinically meaningful. Furthermore, TAF AUC_{tau} measures in this study were comparable or higher than those measured in non-pregnant adults,[23] indicating plasma TAF exposures in pregnant women receiving a 25 mg dose with boosted PIs are likely adequate.

The differences in exposures between trimesters and the wider ranges of TAF exposures in comparison to the previous P1026s study arms[18] is likely due in part to the use of a higher TAF dose in combination with boosted PIs. Boosted PIs have differential effects on TAF pharmacokinetics and a number of other medications, including but not limited to contraceptives, direct-acting antivirals, and anticoagulants,[2] depending on the PI combination that is being administered. Atazanavir with cobicistat increases TAF AUC_{tau} by 135% in non-pregnant adults[14] due to inhibition of efflux transporters and potentially carboxylesterase 1, a key enzyme involved in TAF hydrolysis.[24] Cobicistat alone can increase TAF AUC_{tau} by 165% through inhibition of efflux transporters.[14] Darunavir/cobicistat and darunavir/ritonavir do not significantly change TAF AUC_{tau}, but the latter combination can increase peak concentrations by 42%.[14] Darunavir/ritonavir is administered twice daily during the third trimester of pregnancy,[5] thus was analyzed separately from darunavir/cobicistat due to the potential for differential boosting effects of mixed P-glycoprotein induction/inhibition by darunavir[25,26] and ritonavir[27,28] in comparison to cobicistat.[29] TAF AUC_{tau} with boosted atazanavir were numerically higher than those measured with darunavir, which aligned with known effects these different PIs can have on TAF disposition. Interestingly, TAF AUC_{tau} in those receiving darunavir/ritonavir across pregnancy and postpartum were closest to those receiving TAF 10 mg with cobicistat in the prior study, and the combination of darunavir/cobicistat yielded the lowest median AUC_{tau} during the second trimester, though the sample size was very small and median estimates were comparable to those measured with darunavir/cobicistat/TAF 10 mg/emtricitabine in non-pregnant adults with HIV.[26] The potential for differing TAF exposures by concomitant antiretroviral medications in pregnancy and subsequent relationships with efficacy, safety and birth outcomes should continue to be evaluated in longer-term, large scale clinical studies.

Atazanavir,[30] darunavir[31], elvitegravir,[32] and cobicistat[30–32] exposures are all significantly decreased during pregnancy due to increased CYP3A4 expression in the gut and liver.[21,30,32–34] These collective findings along with lack of safety data led to the recommendation to avoid the use of cobicistat-containing regimens during pregnancy[5,35]

due to concerns over subtherapeutic exposures and higher risk of virologic breakthroughs. Despite these findings, TAF AUC_{tau} in this study arm were similar to historical data and unchanged between pregnancy and postpartum. TAF only has a minor component of CYP3A metabolism (<10%) and is a substrate for multiple efflux and uptake transporters in the gut and liver.[36] Our findings suggest that inhibition of drug transporters in the gut by PK enhancers and PIs is still adequate,[29,37] as was also previously suggested for the TAF 10 mg with cobicistat study arm.[18] Though TAF AUC_{tau} are adequate with boosted PIs, this does not negate the current recommendations to avoid use of cobicistat-containing regimens as cobicistat exposures are reduced, resulting in lesser circulating drug to inhibit CYP3A4 in the gut and liver, and ultimately lower anchor drug exposures.[30–32] Additional studies are needed to better understand changes in transporter expression during pregnancy and their associated influence on drug disposition.

TAF combined with boosted PIs appeared safe and well-tolerated during pregnancy, and 83–92% of women had HIV viral loads <50 copies/mL throughout the study. A separate larger clinical study, IMPAACT 2010/VESTED, showed that the combination of dolutegravir with TAF/emtricitabine was associated with superior rates of virologic suppression, and similar rates of grade 3 or higher AEs as those on the TDF-containing comparator regimens.[20] No perinatal HIV transmissions occurred in our study. Four of 27 infants were born with abnormalities, the majority of which were minor and posed no health threats, and one stillbirth occurred. The dolutegravir/TAF/emtricitabine arm in IMPAACT 2010/VESTED had the lowest composite adverse pregnancy outcomes in comparison to the dolutegravir or efavirenz arms with TDF/emtricitabine, though a higher proportion of stillbirths did occur in the dolutegravir treatment arms.[20] Whether the efficacy and safety data from IMPAACT 2010/VESTED extends to pregnant women receiving boosted PIs with TAF and their infants warrants further investigation in a larger clinical study. The most recent analysis of the Antiretroviral Pregnancy Registry (APR) identified birth defects in 4.2% of infants exposed to TAF during the first trimester, which did not significantly differ from the background rates of 2.7% from the Center for Disease Control birth defects surveillance system or 4.2% from the Texas Birth Defects Registry.[38] No patterns in birth defects were identified in the APR, but updated results will continue to be monitored.

There are limitations to this study. The sampling design likely did not capture the peak concentrations of TAF, which usually occurs between 0.5–2 hours post-dose.[36,39] The original sampling design was targeted at characterizing all once-daily antiretroviral medications across several study arms, and additional sampling time points earlier in concentration-time profile were not logistically feasible. Posthoc Bayesian estimation methods were performed to estimate TAF AUC_{tau} and other pharmacokinetic parameters, but caution is advised in directly comparing peak estimates in this study with those measured in other studies. No placental TAF transfer was detected, similarly to the previous P1026s TAF arms,[18] but this may be due to the timing of the last maternal dose in relation to when the delivery samples were detected. Placental tenofovir transfer with TAF has separately been reported with a cord blood-to-maternal ratio of 0.81. Plasma tenofovir also was not measured in this study. However, TAF is the predominant moiety that loads target cells,[40] not tenofovir,[40–42] thus our findings are still important for better understanding TAF pharmacokinetics and efficacy in pregnancy. From a safety perspective, plasma tenofovir

AUC_{tau} is ~75–90% lower with TAF vs. TDF in non-pregnant adults,[7,8,10] and a similar magnitude of difference was separately observed in pregnant and postpartum women with HIV.[19] Further assessments of the parent tenofovir form in plasma and intracellular tenofovir-diphosphate in PBMCs and dried blood spots will be critical to informing TAF use during pregnancy,[43] and these will be examined in the next iteration of this study.[44] No significant differences among TAF AUC_{tau} by boosted PI type were identified in our exploratory investigations, but samples sizes were limited. Finally, though safety and birth outcomes are reported, the sample size in this study is limited and should be viewed in the context of available and future data that arise with TAF-containing combinations during pregnancy. This study also selected for women who were already tolerating TAF with boosted PIs, thus our safety findings may not be generalizable to all pregnant women receiving this combination.

The pharmacokinetics of TAF 25 mg with boosted PIs did not significantly differ between pregnancy and postpartum and were comparable to or higher than historical data in non-pregnant adults. These combinations appeared safe and well-tolerated during pregnancy and postpartum. Most women remained suppressed throughout the study, and no perinatal HIV transmissions occurred. These findings provide reassurance as TAF use during pregnancy continues to expand.

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REFERENCES

1. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society-USA Panel. JAMA Oct 27 2020;324(16):1651–1669. doi:10.1001/jama.2020.17025 [PubMed: 33052386]
2. 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 09 Jun 2021.

3. WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach 2021:594. Accessed 02 Aug 2021. https://www.who.int/publications/i/item/9789240031593
4. European AIDS Clinical Society (EACS) Guidelines version 10.0, November 2019. https://www.eacsociety.org/files/2019_guidelines-10.0_final.pdf (PDF).
5. 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 2021 Jun 09.
6. Podany AT, Bares SH, Havens J, et al. Plasma and intracellular pharmacokinetics of tenofovir in patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. AIDS Mar 27 2018;32(6):761–765. doi:10.1097/QAD.0000000000001744 [PubMed: 29334548]
7. 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. doi:10.1093/jac/dkaa299
8. 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 Aug 1 2013;63(4):449–55. doi:10.1097/QAI.0b013e3182965d45 [PubMed: 23807155]
9. Custodio J, Garner W, Callebaut C. The pharmacokinetics of tenofovir and tenofovir diphosphate following administration of tenofovir alafenamide versus tenofovir disoproxil fumarate presented at: 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy; 26–28 May 2015; Washington, DC.
10. 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 Jun 27 2015;385(9987):2606–15. doi:10.1016/S0140-6736(15)60616-X [PubMed: 25890673]
11. Truvada [package insert] Foster City, CA: Gilead Sciences, Inc.; 2020.
12. Genvoya [package insert] Foster City, CA: Gilead Sciences, Inc.; 2021.
13. Symtuza [package insert] Foster City, CA: Gilead Sciences, Inc.; 2021.
14. Descovy [package insert] Foster City, CA: Gilead Sciences, Inc.; 2020.
15. European Medicines Agency. European Public Assessment Report (EPAR) of Product Information for Descovy (emtricitabine/tenofovir alafenamide) https://www.ema.europa.eu/en/documents/product-information/descovy-epar-product-information_en.pdf.
16. Hung A, Sinclair M, Hemmersbach-Miller M, Edmonston D, Wyatt C. Prescribing rates and characteristics of recipients of tenofovir-containing regimens before and after market entry of tenofovir alafenamide. J Manag Care Spec Pharm Dec 2020;26(12):1582–1588. doi:10.18553/jmcp.2020.26.12.1582 [PubMed: 33251997]
17. Initiative CHA. HIV Market Report 2020 Sep 2020. Accessed 02 Aug 2021. https://3cdmh310dov3470e6×160esb-wpengine.netdna-ssl.com/wp-content/uploads/2020/09/2020-CHAI-HIV-Market-Report.pdf
18. Brooks KM, Momper JD, Pinilla M, et al. Pharmacokinetics of tenofovir alafenamide with and without cobicistat in pregnant and postpartum women living with HIV. AIDS Mar 1 2021;35(3):407–417. doi:10.1097/QAD.0000000000002767 [PubMed: 33252495]
19. Bukkems VE, Necsoi C, Tenorio CH, et al. Tenofovir alafenamide plasma concentrations are reduced in pregnant women living with HIV: data from the PANNA Network. Clin Infect Dis Dec 5 2021;doi:10.1093/cid/ciab1010
20. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3

trial. Lancet Apr 3 2021;397(10281):1276–1292. doi:10.1016/S0140-6736(21)00314-7 [PubMed: 33812487]

21. Stek AM, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. AIDS Oct 3 2006;20(15):1931–9. doi:10.1097/01.aids.0000247114.43714.90 [PubMed: 16988514]
22. Best BM, Stek AM, Mirochnick M, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. J Acquir Immune Defic Syndr Aug 2010;54(4):381–8. doi:10.1097/qai.0b013e3181d6c9ed [PubMed: 20632458]
23. 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.
24. Rhoades JA, Peterson YK, Zhu HJ, Appel DI, Peloquin CA, Markowitz JS. Prediction and in vitro evaluation of selected protease inhibitor antiviral drugs as inhibitors of carboxylesterase 1: a potential source of drug-drug interactions. Pharm Res Apr 2012;29(4):972–82. doi:10.1007/s11095-011-0637-9 [PubMed: 22161308]
25. Konig SK, Herzog M, Theile D, Zembruski N, Haefeli WE, Weiss J. Impact of drug transporters on cellular resistance towards saquinavir and darunavir. J Antimicrob Chemother Nov 2010;65(11):2319–28. doi:10.1093/jac/dkq324 [PubMed: 20817741]
26. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s): Emtricitabine/Tenofovir Alafenamide Available at: https://www.fda.gov/media/98516/download.
27. Kumar P, Gordon LA, Brooks KM, et al. Differential Influence of the Antiretroviral Pharmacokinetic Enhancers Ritonavir and Cobicistat on Intestinal P-Glycoprotein Transport and the Pharmacokinetic/Pharmacodynamic Disposition of Dabigatran. Antimicrob Agents Chemother Nov 2017;61(11)doi:10.1128/AAC.01201-17
28. Perloff MD, von Moltke LL, Fahey JM, Greenblatt DJ. Induction of P-glycoprotein expression and activity by ritonavir in bovine brain microvessel endothelial cells. J Pharm Pharmacol Jul 2007;59(7):947–53. doi:10.1211/jpp.59.7.0006 [PubMed: 17637189]
29. 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 Oct 2012;56(10):5409–13. doi:10.1128/AAC.01089-12 [PubMed: 22850510]
30. Momper JD, Stek A, Wang J, et al. Pharmacokinetics of atazanavir boosted with cobicistat during pregnancy and postpartum presented at: 20th International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs [abstract #10]; 14–16 May 2019; Noordwijk, the Netherlands.
31. Momper JD, Wang J, Stek A, et al. Pharmacokinetics of darunavir and cobicistat in pregnant and postpartum women with HIV. AIDS Jul 1 2021;35(8):1191–1199. doi:10.1097/QAD.0000000000002857 [PubMed: 34076612]
32. Momper JD, Best BM, Wang J, et al. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. AIDS Nov 13 2018;32(17):2507–2516. doi:10.1097/QAD.0000000000001992 [PubMed: 30134297]
33. Momper JD, Best BM, Wang J, et al. Pharmacokinetics of Darunavir Boosted with Cobicistat during Pregnancy and Postpartum presented at: AIDS 2018; 23–27 Jul 2018; Amsterdam, Netherlands.
34. 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 Sep 1 2015;70(1):33–41. doi:10.1097/QAI.0000000000000668 [PubMed: 25950206]
35. Boyd SD, Sampson MR, Viswanathan P, Struble KA, Arya V, Sherwat AI. Cobicistat-containing antiretroviral regimens are not recommended during pregnancy: viewpoint. AIDS May 1 2019;33(6):1089–1093. doi:10.1097/QAD.0000000000002163 [PubMed: 30946163]
36. Ray AS, Fordyce MW, Hitchcock MJ. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. Antiviral Res Jan 2016;125:63–70. doi:10.1016/j.antiviral.2015.11.009 [PubMed: 26640223]
37. Drewe J, Gutmann H, Fricker G, Torok M, Beglinger C, Huwyler J. HIV protease inhibitor ritonavir: a more potent inhibitor of P-glycoprotein than the cyclosporine analog SDZ PSC

833. Biochem Pharmacol May 15 1999;57(10):1147–52. doi:10.1016/s0006-2952(99)00026-x [PubMed: 11230802]

38. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 January 2020 Wilmington, NC: Registry Coordinating Center; 2020. Available from URL: www.APRegistry.com.
39. 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 May 2014;69(5):1362–9. doi:10.1093/jac/dkt532 [PubMed: 24508897]
40. 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 May 2005;49(5):1898–906. doi:10.1128/AAC.49.5.1898-1906.2005 [PubMed: 15855512]
41. Brooks KM, Ibrahim ME, Castillo-Mancilla JR, et al. Pharmacokinetics of tenofovir monoester and association with intracellular tenofovir diphosphate following single-dose tenofovir disoproxil fumarate. J Antimicrob Chemother Aug 1 2019;74(8):2352–2359. doi:10.1093/jac/dkz187 [PubMed: 31093649]
42. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) Tenofovir Disoproxil Fumarate http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-356_Viread_biopharmr.pdf.
43. Eke AC, Brooks KM, Gebreyohannes RD, Sheffield JS, Dooley KE, Mirochnick M. Tenofovir alafenamide use in pregnant and lactating women living with HIV. Expert Opin Drug Metab Toxicol Apr 2020;16(4):333–342. doi:10.1080/17425255.2020.1738384 [PubMed: 32125906]
44. 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 Jul 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT04518228.

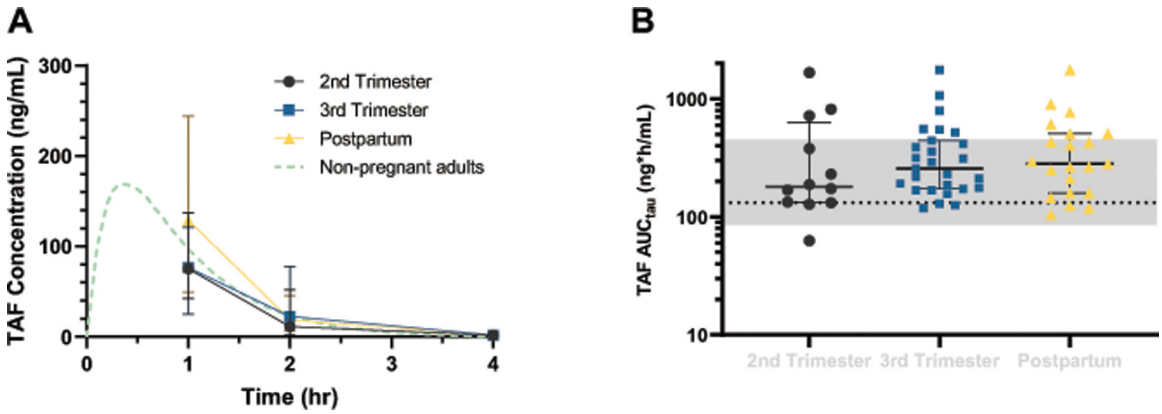

Figure 1. TAF concentration vs. time profiles (A) and TAF AUC_{tau} (B) during pregnancy and postpartum.

Data in both figures presented as median (interquartile range). All concentration results in one participant during the postpartum period were below the LLOQ, and thus results from this individual are not displayed in the figures.

Table 1.

Participant Demographics

Characteristic	N=29
Race/Ethnicity, n (%)	
Black/Not Hispanic or Latina	14 (48.3%)
Black/Hispanic or Latina	2 (6.9%)
White/Not Hispanic or Latina	1 (3.4%)
White/Hispanic or Latina	4 (13.8%)
Unknown/Hispanic or Latina	4 (13.8%)
American Indian/Hispanic or Latina	2 (6.9%)
Pacific Islander/Hispanic or Latina	1 (3.4%)
More than one race/Not Hispanic or Latina	1 (3.4%)
Age (yr), median (IQR)	
Second Trimester	30.7 (26.2–34.9)
Third Trimester	31.0 (24.0–36.1)
Weight (kg), median (IQR)	
Second Trimester	89.1 (75.0–115.5)
Third Trimester	84.5 (78.5–107.3)
Delivery	86.3 (78.0–107.5)
Postpartum	78.4 (72.4–98.0)
Gestational Age or Time after Delivery (weeks), median (range)	
Second Trimester	23.1 (20.1–26.9)
Third Trimester	32.7 (30.3–37.7)
Postpartum	9.0 (6.0–13.0)
CD4 Count (cells/mm^3), median (IQR)	
Second Trimester	709 (622–896)
Third Trimester	494 (324–733)
Postpartum	684 (557–776)
Duration of TAF Therapy (weeks), median (IQR)	
Second Trimester	17.4 (10.0–60.0)
Third Trimester	27.7 (16.3–73.0)
HIV Viral Load ≤50 copies/mL, n (%)	
Second Trimester	10/12 (83.3%)
Third Trimester	23/25 (92.0%)
Postpartum	18/20 (90.0%)
HIV Viral Load ≤400 copies/mL, n (%)	
Second Trimester	11/12 (91.7%)
Third Trimester	25/25 (100.0%)
Postpartum	19/20 (95.0%)

Table 2.

Pharmacokinetic Parameters of TAF 25 mg with Boosted PIs 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
N per group	12	27[a]	21[b]	8		20[c]	
AUC_{tau} (ng*h/mL)	181.1 (133.0–549.5)	257.2 (173.1–445.0)	283.3 (161.0–506.6)	0.62 (0.29, 1.34)	0.46	0.94 (0.63, 1.39)	0.50
C_{max} (ng/mL)	87.8 (44.0–186.5)	107.0 (72.9–157.0)	141.0 (51.6–244.0)	0.58 (0.30, 1.11)	0.20	0.95 (0.58, 1.55)	0.12
T_{max} (hr)	1 (1–2)	1 (1–4)	1 (1–2)	NR	>0.99	NR	0.27
CL/F (L/hr)	138.2 (50.4–188.0)	97.2 (56.2–144.4)	92.9 (49.4–155.3)	1.59 (0.74, 3.43)	0.20	1.06 (0.72, 1.58)	0.57
V/F (L)	54.7 (32.8–61.7)	54.3 (44.2–66.0)	46.1 (24.9–59.2)	1.43 (0.83, 2.49)	0.15	1.01 (0.68, 1.50)	0.86
$t_{1/2}$ (hr)	0.29 (0.20–0.39)	0.35 (0.24–0.63)	0.30 (0.25–0.43)	0.90 (0.67, 1.20)	0.46	1.03 (0.75, 1.41)	0.77

[a] A total of 26 observed values available for $t_{1/2}$ and V/F

[b] A total of 22 values available for C_{max}

[c] Paired comparisons of $t_{1/2}$ and V/F based on 19 observed values; C_{max} based on 21 observed values

AUC_{tau}: area under the concentration vs. time curve over the dosing interval; C_{max}: maximum plasma concentration; CI: confidence interval; CL/F: apparent oral clearance; NR: not reported; $t_{1/2}$: half-life; T_{max}: time to maximum plasma concentration; V/F: apparent volume of distribution. Summary statistics for 2nd/3rd trimester and postpartum presented as median (interquartile range), except T_{max} which is presented as median (range); comparisons between pregnancy and postpartum presented as geometric mean ratios (GMR) (90% CI).

Table 3.

Maternal TAF AUC_{tau} Comparison by Concomitant PI during Pregnancy and Postpartum

Time Point	Summary Statistic	Boosted PI			GMR (90% CI)		
		ATV/c or ATV/r	DRV/c	DRV/r	ATV/c or ATV/r vs. DRV/c	ATV/c or ATV/r vs. DRV/r	DRV/c vs. DRV/r
2nd trimester	n	3	5	4			
	Median (IQR)	378.8 (134.3–818.7)	131.7 (128.3–174.5)	209.1 (178.2–951.4)	2.06 (0.52, 8.20)	1.04 (0.23, 4.81)	0.51 (0.14, 1.88)
3rd trimester	n	7	12	8			
	Median (IQR)	390.1 (192.5–522.0)	301.8 (188.3–484.0)	181.8 (170.7–221.5)	1.29 (0.77, 2.16)	1.60 (0.82, 3.12)	1.24 (0.68, 2.28)
Postpartum	n	7	8	6			
	Median (IQR)	405.9 (211.3–508.1)	346.7 (213.2–523.2)	204.6 (125.4–296.1)	1.15 (0.56, 2.33)	1.64 (0.72, 3.70)	1.43 (0.72, 2.83)

ATV: atazanavir; /c: cobicistat; CI: confidence interval; DRV: darunavir; GMR: geometric mean ratio; IQR: interquartile range; PI: protease inhibitor; /r: ritonavir.

Table 4.

Maternal Viral Suppression and Delivery Outcomes

Characteristic	N	Summary Statistics
Maternal Viral Load ≤50 copies/mL at Delivery, n (%)	28	24 (85.7%)
Maternal Viral Load ≤400 copies/mL at Delivery, n (%)	28	26 (92.9%)
CD4 Count (cells/mm^3) at Delivery, median (IQR)	27	665 (448–957)
Gestational Age at Delivery (weeks), median (range)	27	38.6 (33.7–40.7)
Birth Weight (g), median (range)	26	3010 (2335–4445)
Birth Length (cm), median (range)	25	50 (43–56)
HIV Status, n (%)		27
Uninfected		21 (78%)
Negative based on best available data[a]		2 (7%)
Indeterminate[b]		4 (15%)

Note: numbers and percentages vary depending on the total number of women and infants with results available at each time point; one woman withdrew consent for her infant *in utero*, and thus this infant is not included in any summaries. IQR: interquartile range.

[a] Sites unable to provide additional information.

[b] All tests were negative, but unable to confirm “uninfected” status from follow-up testing due to study exit.