

**Tenofovir alafenamide plasma concentrations are reduced in pregnant women living with HIV:
data from the PANNA Network**

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Key points: This European pharmacokinetic study included 20 pregnant women living with HIV, and showed that tenofovir alafenamide plasma concentrations are reduced by approximately 50% in the third trimester compared with postpartum. No mother-to-child transmission occurred in this study.

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Abstract

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 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 AUC_{tau} 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_{0-24h}, 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.

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

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Introduction

Pregnant women living with 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 25mg once-daily, but fixed-dose combination tablets consisting of both TAF and the boosting agent cobicistat contain 10mg of TAF because TAF exposure increases around twofold 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 25mg and TAF 10mg co-administered with cobicistat [10].

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 result, 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 U.S. guideline recommends TAF as an alternative drug because of the limited data, while the European guideline includes TAF-containing regimens among the preferred treatment regimens for pregnant women [6, 17]. The limited pharmacokinetic data consist of one study including 58 pregnant women [18]. This study observed no significant difference between pregnancy and postpartum in women taking TAF 10mg with cobicistat, while a decrease in exposure of approximately 40% was seen during pregnancy in women taking TAF 25mg [18]. Clinical outcomes were investigated in one 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 is lacking. Therefore, our study aims to examine the pharmacokinetics of TAF and TFV in pregnant women from Europe.

Method

A non-randomized, open-label, multi-center, 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](https://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 two weeks before first pharmacokinetic evaluation. Women using interacting co-medication 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 anaemia (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 two study visits, EDTA blood samples were collected at t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h 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 $\leq -18^{\circ}\text{C}$ until shipment on dry ice to the central laboratory for analysis. The bioanalytical method is described in Supplementary Text S1.

Pharmacokinetic and statistical analysis

TAF and TFV pharmacokinetic parameters were determined with non-compartmental 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 (90%CI). A stratified analysis for treatment with TAF 10mg co-administered with cobicistat and TAF 25mg 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 AUC_{tau} deciles; the median TAF AUC in the lowest decile was 53.1 ng*h/mL [20]. Accordingly, the proportion of pregnant and postpartum women with AUC below 53.1 ng*h/mL was determined in our study.

Clinical outcomes and safety assessment

At every study visit maternal HIV-1 RNA load and CD4 counts were collected, and the infant HIV status was determined by DNA 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 five 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, while the minority were Caucasian (15%) or Asian (5%). More women were on a regimen including TAF 25mg (65%) than TAF 10mg 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 twenty 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/min. At postpartum visit, the median maternal weight was 74 (range, 49-132) kg, and the median creatinine clearance was 124 (range, 110-145) mL/min.

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 two women at third trimester and of three 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 four days before third trimester visit. One non-evaluable ascending postpartum curve was excluded. Furthermore, one woman was excluded for the GMR calculation because of treatment switch from 10mg to 25mg 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.

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 (Fig.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 is included in the Supplementary Table 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_{0-24h} (%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_{0-24h} , C_{max} , and C_{trough} , respectively, compared with postpartum. The TFV exposure decreased in all 11 women with paired TFV data (Fig. 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 4-20h 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 (Fig. 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 six 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 [21]. 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 bicittegravir/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 [22].

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.

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 10mg with a booster compared to postpartum. A ~40% decrease was observed in pregnant women using TAF 25mg 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, 23]. This also accounts for intestinal P-gp and BCRP, for which TAF is a substrate [4, 24, 25]. Binding of TAF to plasma proteins is approximately 80% [23]. Decreased plasma protein concentrations during pregnancy may decrease total TAF plasma concentrations, while 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 decrease during pregnancy, but this lack of difference suggests cobicistat still inhibits P-gp transport during pregnancy [18, 26].

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 [27, 28]. However, higher tenofovir exposure was observed in postpartum women compared to

historical controls due to a unclear mechanism. Increased renal clearance is most likely the primary cause of the TFV exposure decrease, which increased from median 124 mL/min to 140 mL/min 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 [23]. 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 [27, 28]. 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 300mg 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, 29]. 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 [30]. 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. The observed clinical efficacy does, therefore, only reflect 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 [31].

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.

NOTES

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Potential conflicts of interest

O.R. has received support from Gilead Sciences to attend the EACS conference. D.B. has received honoraria and/or study grants from Janssen Pharmaceutica, Merck Sharp & Dohme Corp, Gilead Sciences and ViiV Healthcare. D.K. has received payment/honoraria from Janssen Pharmaceutica for a presentation on a HIV symposium; participates on an advisory board on HPV vaccines of Merck Sharp & Dohme Corp; received support from Gilead Sciences, Viiv Healthcare and Pfizer to attend the ID-week and the ECCMID. A.C. has received honoraria from Merck Sharp & Dohme Corp 2021, fee is paid to the institution; is an unpaid co-chair of the pediatric antiretroviral working group (PAWG). All other authors have no potential conflicts to declare. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Harris NS, Fowler MG, Sansom SL, Ruffo N, Lampe MA. Use of enhanced perinatal human immunodeficiency virus surveillance methods to assess antiretroviral use and perinatal human immunodeficiency virus transmission in the United States, 1999-2001. *AmJObstetGynecol* **2007**; 197(3 Suppl): S33-S41.
2. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. *ClinPharmacokinet* **2005**; 44(10): 989-1008.
3. Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. *ClinPharmacokinet* **1997**; 33(5): 328-43.
4. Koren G, Pariente G. Pregnancy- Associated Changes in Pharmacokinetics and their Clinical Implications. *Pharm Res* **2018**; 35(3): 61.
5. 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): 1254-8.
6. EACS. the European Guidelines for the treatment of HIV-positive adults in Europe: version 10.1. Available at: https://www.eacsociety.org/files/guidelines-10.1_30032021_1.pdf. Accessed 17 September 2021.
7. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Available at: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0>. Accessed 17 September 2020.
8. Sax PE, Zolopa A, Brar I, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr* **2014**; 67(1): 52-8.
9. 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): 5409-13.
10. FDA. Odefsey: Clinical Pharmacology and Biopharmaceutics Review(s) Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208351Orig1s000TOC.cfm. Accessed 27 September 2021
11. 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): 1898-906.
12. 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.
13. 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. *The Journal of antimicrobial chemotherapy* **2014**; 69(5): 1362-9.
14. 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): 2606-15.
15. Mills A, Crofoot G, Jr., McDonald C, et al. Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate in the First Protease Inhibitor-Based Single-Tablet Regimen for Initial HIV-1 Therapy: A Randomized Phase 2 Study. *J Acquir Immune Defic Syndr* **2015**; 69(4): 439-45.
16. 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): 449-55.

17. DHHS. 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: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Perinatal_GL_2020.pdf. Accessed 14 April 2021.
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* **2021**; 35(3): 407-17.
19. 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* **2021**; 397(10281): 1276-92.
20. Custodio JM, Ting LS, Zack JZ, et al. Tenofovir Alafenamide Has Wide Efficacious Range for Treatment of HIV-1 Infection: Pharmacokinetic-Pharmacodynamic Relationship From a Phase 3 Study. Abstract Sunday-407. . ASM Microbe, June 16–20, 2016. Boston,MA, **2016**.
21. Bukkems V, Necsoi C, Tenorio CH, et al. Clinically significant lower elvitegravir exposure during third trimester of pregnant patients living with HIV: data from the PANNA study. *Clin Infect Dis* **2020**.
22. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC pediatrics* **2013**; 13: 59.
23. EMA. Product Information: Biktarvy Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/biktarvy>. Accessed 17 September 2021
24. Hodel EM, Marzolini C, Waitt C, Rakhmanina N. Pharmacokinetics, Placental and Breast Milk Transfer of Antiretroviral Drugs in Pregnant and Lactating Women Living with HIV. *Curr Pharm Des* **2019**; 25(5): 556-76.
25. Pinheiro EA, Stika CS. Drugs in pregnancy: Pharmacologic and physiologic changes that affect clinical care. *Seminars in perinatology* **2020**; 44(3): 151221.
26. Bukkems VE, Colbers A, Marzolini C, Molto J, Burger DM. Drug-Drug Interactions with Antiretroviral Drugs in Pregnant Women Living with HIV: Are They Different from Non-Pregnant Individuals? *Clin Pharmacokinet* **2020**; 59(10): 1217-36.
27. 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): 739-48.
28. Best BM, Burchett S, Li H, et al. Pharmacokinetics of tenofovir during pregnancy and postpartum. *HIV medicine* **2015**; 16(8): 502-11.
29. 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* **2018**; 32(6): 761-5.
30. Cerrone M, Alfarisi O, Neary M, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. *The Journal of antimicrobial chemotherapy* **2019**; 74(6): 1670-8.
31. Custodio JM, Chuck SK, Chu H, et al. Lack of clinically important PK interaction between coformulated ledipasvir/sofosbuvir and rilpivirine/emtricitabine/tenofovir alafenamide. *Pharmacol Res Perspect* **2017**; 5(5).
32. Alper AB, Yi Y, Rahman M, et al. Performance of estimated glomerular filtration rate prediction equations in preeclamptic patients. *Am J Perinatol* **2011**; 28(6): 425-30.
33. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* **2009**; 150(9): 604-12.

Tables

Table : Patient characteristics

	Median (range) or n (%)
Maternal age at delivery, years	33 (19-44)
Race/Ethnicity	
- Black or African American	16 (80%)
- Caucasian	3 (15%)
- Asian	1 (5%)
ART naïve at conception	2 (10%)
Time on TAF before first PK sampling, weeks	48 (1-136)
TAF dose at third trimester:	
- 25mg	13 (65%)
- 10mg	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 400mg 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: TAF, tenofovir alafenamide; PK, pharmacokinetic; ART, antiretroviral therapy; VL, viral load; PCR, polymerase chain reaction.

^a calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula

^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.
d (n=21); 1 twinbirth
e Genvoya® (n=2), Odefsey® (n=1), Biktarvy® (n=2)

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Table : Pharmacokinetics of tenofovir alafenamide and tenofovir in the third trimester of pregnancy and postpartum determined in women treated with tenofovir alafenamide 10mg or 25mg once-daily

Parameter	Third Trimester, GM (%CV) ^a	Postpartum, GM (%CV) ^a	Third trimester vs Postpartum GMR (90%CI)	Historical reference of non-pregnant individuals ^b , mean (%CV) ^c
Tenofovir alafenamide				
	n=17	n=12	n=16	
AUC _{last} , ng*h/mL	101 (44)	217 (57)	0.54 (0.43-0.68)	277 (38)
C _{max} , ng/mL	91 (56)	215 (66)	0.48 (0.38-0.62)	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 (0.89-1.24)	0.5 (0.4-0.6)
Tenofovir				
	n=16	n=11	n=16	
AUC _{0-24h} , ng*h/mL	232 (30)	348.51 (33.3)	0.67 (0.62-0.74)	268 (23)
C _{max} , ng/ml	16 (41)	21.58 (33.0)	0.70 (0.62-0.80)	16 (22)
C _{trough} , ng/ml	7 (36)	12 (38)	0.66 (0.60-0.71)	9 (25)
T _{max} , h	1.8 (0.5-4.0)	1.0 (0.5-6.0)	1.20 (0.73-2.00)	4.0 (3.0-4.0)
T _{1/2} , h	35 (45) ^e	53 (34) ^f	0.76 (0.61-0.94)	32 (28-38)

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

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 25/200/25mg in fed state

c expect for T_{max} and T_{1/2} which are denoted as median (interquartile range)

d n=11

e n=12

f n =10

Figure legends

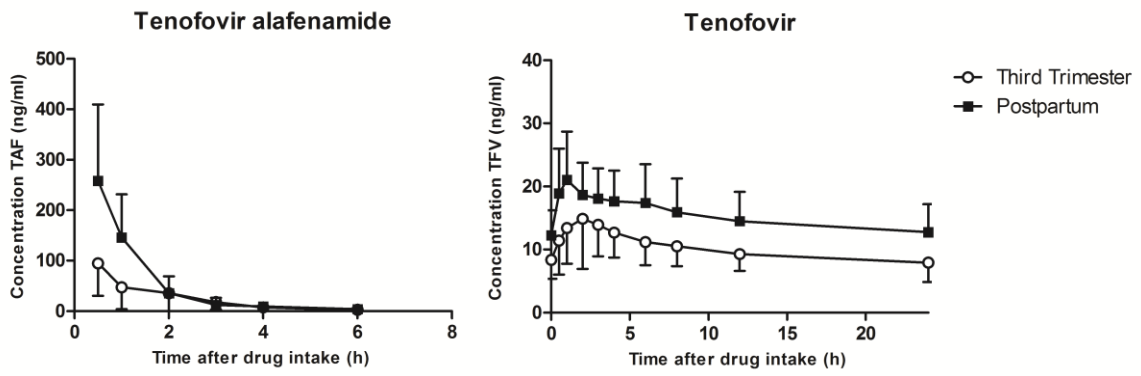
Figure : Plasma concentrations of tenofovir alafenamide (left) and tenofovir (right) over time after drug intake in third trimester and postpartum women treated with tenofovir alafenamide 10mg or 25mg once-daily. Data are shown as mean (CV%).

Figure : 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 25mg. The stars represent the median AUC in third trimester and postpartum.

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

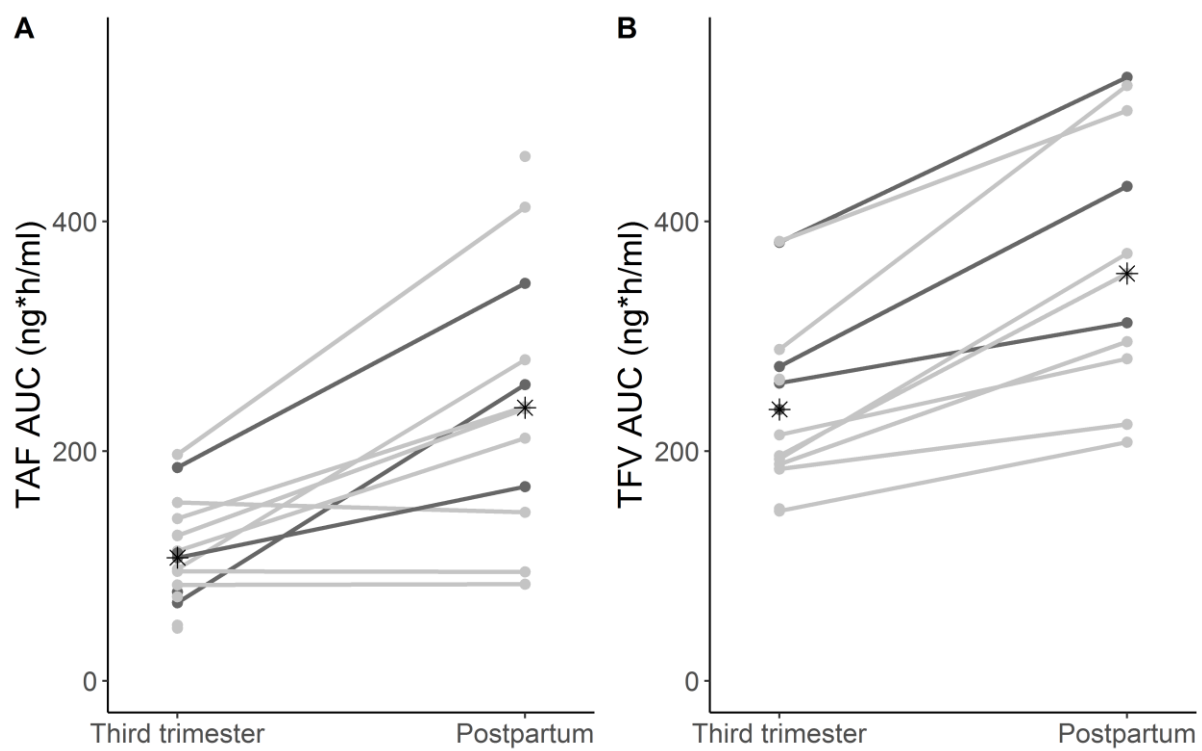
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Figure 1



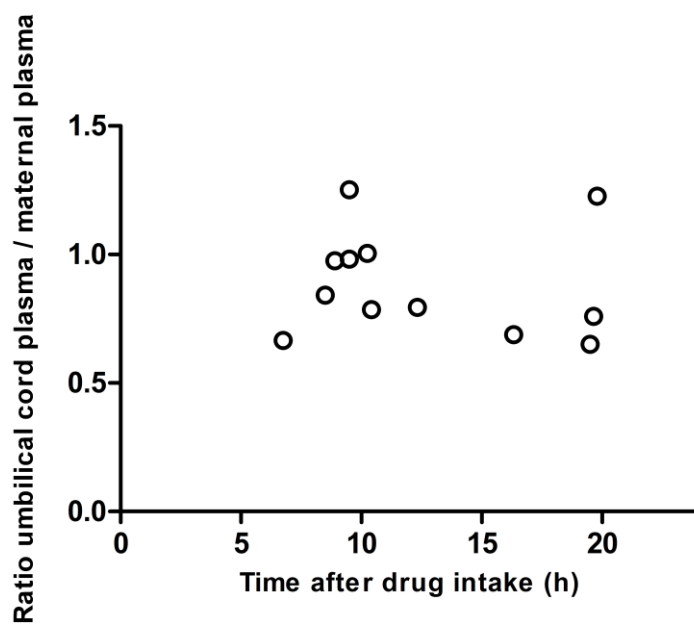
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Figure 2



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Figure 3



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