Clinically Significant Lower Elvitegravir Exposure During the Third Trimester of Pregnant Patients Living With Human Immunodeficiency Virus: Data From the Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) Network

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This phase 4 study investigated the influence of pregnancy on the pharmacokinetics of elvitegravir/cobicistat in 14 women with human immunodeficiency virus type 1. The results support the recommendation against elvitegravir/cobicistat use during pregnancy, as the elvitegravir concentration at the end of the dosing interval (C_{trough}) was reduced by 77%, with 85% of pregnant women having a C_{trough} below the effective concentration (EC_{90}).

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Maternal antiretroviral therapy has the capacity to essentially eliminate the risk of mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV). However, physiological alterations during pregnancy can affect antiretroviral drug (ARV) absorption, distribution, metabolism, and elimination and, thus, ARV efficacy. To ensure adequate efficacy and safety, the pharmacokinetics of every ARV must be examined in pregnant women living with HIV. Elvitegravir is an ARV that inhibits the HIV integrase enzyme, and is formulated in fixed-dose combination tablets with the CYP3A4 inhibitor cobicistat together with 2 nucleoside reverse transcriptase inhibitors. Momper et al observed in a United States–based population that elvitegravir exposure decreased by 24%–44% in pregnant women treated with once-daily elvitegravir/cobicistat 150 mg/150 mg [1]. Based on these data, product labels of elvitegravir/cobicistat-based tablets now recommend against their use during pregnancy [2]. We aimed to describe elvitegravir/cobicistat pharmacokinetics in the European population and to extend the elvitegravir/cobicistat data in this special patient population.

METHODS

The Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) Network is an open-label, nonrandomized, multicenter, within-patient, pharmacokinetic phase 4 study in pregnant women with HIV in Europe (ClinicalTrials.gov NCT00825929). The primary objective of the current analysis was to compare elvitegravir pharmacokinetic parameters in the third trimester with the postpartum period. Secondary objectives were to report safety and efficacy outcomes for elvitegravir-based regimens, to determine cobicistat pharmacokinetic parameters, to assess cobicistat and elvitegravir cord blood concentrations at time of delivery, and to report safety and virological outcomes for elvitegravir/cobicistat-exposed infants. The protocol of this study has extensively been described in an earlier publication [3] and is summarized below. The enrollment of pregnant patients on elvitegravir/cobicistat was stopped prematurely to adhere to the product label revision.

We included pregnant women living with HIV using regimens containing elvitegravir/cobicistat 150/150 mg once daily, for at least 2 weeks prior to the first pharmacokinetic assessment. At the third trimester (approximately 33 weeks) and postpartum (preferably 4–6 weeks), intensive pharmacokinetic assessment was performed. Ethylenediaminetetraacetic acid blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after observed intake of elvitegravir/cobicistat with food (650 kcal; 30 g fat). Matching cord blood and maternal blood plasma samples were taken at delivery to estimate placental transfer. Plasma concentrations were centrally analyzed by the laboratory of the Department of Pharmacy of the Radboud University Medical Center, using a validated liquid chromatography–based assay (lower limit of quantification: 0.05 mg/L for elvitegravir, 0.03 mg/L for cobicistat). The laboratory participates in external quality assurance programs for ARV drug

quantification [4]. Elvitegravir and cobicistat pharmacokinetic parameters were determined using noncompartmental analysis (Phoenix 64 version 8.1, Certara). A linear mixed model (with pregnancy as fixed effect and random effect for participant) was used on log-transformed pharmacokinetic parameters to calculate the geometric mean ratios and 90% confidence intervals. The geometric mean ratios were compared by means of a bioequivalence approach. In addition, we compared the number of subjects with an elvitegravir sample taken at 24 hours (C_{trough}) < 0.13 mg/L during pregnancy and postpartum [5]. Safety assessment was performed by collecting adverse events, use of concomitant medication, maternal HIV type 1 RNA load, CD4 cell counts, serum biochemistry, and hematology at each visit. Also, data on gestational age (GA) at delivery, infant birth weight, congenital abnormalities, and infant HIV status were collected.

RESULTS

In total, 14 pregnant women taking elvitegravir/cobicistat were included between December 2014 and October 2018. Median maternal age at delivery was 33 (range, 22–41) years. 71% of the women were black, and 86% of the women were already using elvitegravir at time of conception. At third trimester, the pregnant women weighed a median of 75 (range, 55–94) kg and had an albumin plasma concentration of 36 (range,

29–38) g/L. Postpartum data were available in 12 women because 2 women switched to non-elvitegravir-containing regimens between the third trimester and delivery. Postpartum women weighed a median of 72 (range, 52–87) kg and had an albumin plasma concentration of 41 (range, 38–50) g/L, which was significantly higher than in third trimester ($P < .001$, Wilcoxon signed-rank test).

Pharmacokinetic Analysis

We assessed 14 third trimester and 12 postpartum curves. Both curves of 1 woman were excluded because of incorrect drug administration, and 1 nonevaluable ascending postpartum curve was excluded. Pharmacokinetic profiles were estimated for 13 third trimester women and 10 postpartum women (Table 1).

In the third trimester of pregnancy, the geometric mean elvitegravir AUC_{0-24h} was 14.1 hour × mg/L, a 34% decrease compared to postpartum. Geometric mean elvitegravir C_{trough} was 0.06 mg/L in pregnant women, which correlates with a 77% decrease. The C_{trough} was lower in third trimester vs postpartum in 8 of 10 women with paired samples; in the other women a similar C_{trough} was observed. The cobicistat AUC_{0-24h} decreased by 49% during pregnancy. No bioequivalence of elvitegravir and cobicistat in the third trimester compared to postpartum could be established. Additionally, 85% of the third trimester women had an elvitegravir C_{trough} < 0.13 mg/L, and none at the postpartum visit.

Table 1. Comparison of the Elvitegravir and Cobicistat Pharmacokinetic Parameters in the Third Trimester of Pregnancy and Postpartum

Parameter	Third Trimester, GA 33 (31–36) wk (n = 13) median (range) GM (CV%)	Postpartum, 6 (4–8) wk Postdelivery (n = 10) median (range) GM (CV%)	Nonpregnant Women With HIV [6] Mean (SD)	Third Trimester vs Postpartum GMR (90% CI)
Elvitegravir				
AUC_{0-24h}, h × mg/L	14.1 (39)	21.7 (29)	23 (7.5)	66 (53–83)
C_{trough}, mg/L	0.06 (104)	0.28 (63)	0.45 (0.3)	23 (14–39)
C_{max}, mg/L	1.4 (42)	1.8 (26)	1.7 (0.4)	79 (65–97)
T_{max}, h	4.0 (2.0–6.0)[a]	5.0 (3.0–7.8)[a]	…	…
CL/F_{ss}, L/h	10.7 (39)	6.9 (29)	…	151 (121–190)
$T_{1/2}$, h	4.3 (37)	7.7 (30)	…	56 (44–72)
Vd/F_{ss}, L	65.7 (60)	76.5 (28)	…	84 (63–113)
Cobicistat				
AUC_{0-24h}, h × mg/L	4.3 (57)	9.4 (35)	8.3 (3.8)	51 (42–62)
C_{trough}, mg/L	NQ[b]	NQ[c]	0.05 (0.1)	…
C_{max}, mg/L	0.8 (47)	1.3 (36)	1.1 (0.4)	65 (52–81)
T_{max}, h	2.0 (1.0–5.9)[a]	2.0 (1.0–4.0)[a]	…	…
CL/F_{ss}, L/h	34.9 (57)	15.9 (35)	…	196 (162–238)
$T_{1/2}$, h	3.2 (38)	3.5 (12)[d]	…	91 (72–115)
Vd/F_{ss}, L	159.0 (55)	77.9 (33)[d]	…	189 (141–252)

Abbreviations: AUC_{0-24h}, area under the curve from 0 to 24 hours; CI, confidence interval; CL/F_{ss}, apparent clearance under steady-state conditions; C_{max}, maximum concentration; C_{trough}, concentration at the end of the dosing interval; CV, coefficient of variation; GA, gestational age; GM, geometric mean; GMR, geometric mean ratio; HIV, human immunodeficiency virus; NQ, nonquantifiable; SD, standard deviation; $T_{1/2}$, apparent half-life; T_{max}, time to reach maximum concentration; Vd/F_{ss}, apparent volume of distribution under steady-state conditions.

[a]Reported as median (range).

[b]Thirteen of 13 samples were below the limit of quantification.

[c]Seven of 10 samples were below the limit of quantification.

[d]n = 9.

Placental Transfer

Seven quantifiable paired elvitegravir samples showed a median cord blood to maternal blood (CB:MB) plasma ratio of 0.75 (range, 0.35–0.99). The CB:MB ratio of the only quantifiable paired cobicistat sample was 0.16 at 8.5 hours after the last dose.

Maternal and Infant Efficacy and Safety

At the third trimester visit, 2 of 12 women had a viral load of > 50 copies/mL (2 unknown). A viral load of 6363 copies/mL, with multidrug resistance, was observed at GA 34 weeks. At screening, this patient had already used elvitegravir-based therapy for 7 months and had a viral load of 27 358 copies/mL, and adherence problems could not be ruled out. The other woman started elvitegravir-based therapy during pregnancy and had a viral load of 317 copies/mL at 34 weeks' GA, which was attributed to nonadherence. Both patients were switched to other ARV regimens, and all patients had viral loads < 50 copies/mL at delivery. At the postpartum visit, all women but 1 had undetectable viral loads (1 unknown).

The median GA at delivery was 39 (range, 36–41) weeks. All infants had a negative HIV DNA polymerase chain reaction at birth. The median infant birth weight was 2975 (range, 2050–4480) g; the birth weight of 2 infants was considered to be small for GA [7].

During the study period, a total of 22 adverse events was reported in 9 subjects. None were attributed to the study medication and none were > 2 on the severity scale. One serious adverse event was reported, which was unlikely related to study medication; dextrocardia of the fetus was discovered on an ultrasound in early pregnancy. No anomalies were found in genetic testing during pregnancy and a baby without health issues was born.

DISCUSSION

This European study confirms that elvitegravir exposure is substantially decreased in the third trimester of pregnancy. Elvitegravir $AUC_{0–24h}$, C_{trough}, and maximum concentration (C_{max}) were respectively decreased by 34%, 77%, and 21% in comparison to postpartum. A C_{trough} < 0.13 mg/L was observed in 85% of the third trimester women.

The observed elvitegravir pharmacokinetic parameters in our population are representative of the third trimester and are similar to those in earlier reports. Momper et al have studied elvitegravir pharmacokinetics in 30 pregnant women from the United States [1]. $AUC_{0–24h}$, C_{trough}, and C_{max} are similar to our results: 14.0 vs 14.1 mg × hour/L, 0.05 vs 0.06 mg/L, and 1.4 vs 1.4 mg/L, respectively. An earlier case report has also reported similar pharmacokinetic parameters [8].

In our study, elvitegravir C_{trough} postpartum seems lower than in the historical data from nonpregnant participants (mainly men) [5]. Since elvitegravir exposure has been reported to be approximately 12% higher in women, the relative decrease in elvitegravir exposure could possibly be even larger than observed in our study [5]. Also, the women's physiology might not have returned to a state similar to that of nonpregnant women at 4–6 weeks postpartum.

Various factors may contribute to the confirmed decreased elvitegravir exposure in pregnant women. Measurements of CYP3A4 biomarkers show CYP3A4 induction during pregnancy [9]. The decreased cobicistat exposure in the third trimester suggests that the decreased elvitegravir exposure may also be caused indirectly by reduced CYP3A4 inhibition. CYP3A4 inhibition by cobicistat declines quickly with decreasing cobicistat exposures [10]. This is consistent with the observed increased clearance and shorter half-life of elvitegravir in pregnancy. Also, elvitegravir is a highly protein-bound drug (~99%), and albumin plasma concentrations decrease during pregnancy as significantly observed in our study [5, 11]. Elvitegravir clearance is likely restricted by protein binding, possibly resulting in lower total drug and similar unbound ("active") concentrations during pregnancy as already reported in 1 patient [8, 12].

Two of 14 women experienced virologic failure in the third trimester, possibly due to nonadherence. The viral suppression rate is similar to the 81.3% recently observed in a large elvitegravir-treated pregnancy cohort at delivery and the 92% at third trimester observed by Momper et al [1, 13].

These results support the recommendation against elvitegravir/cobicistat use during pregnancy, as the elvitegravir C_{trough} was reduced by 77%, resulting in a C_{trough} under the effective concentration (EC_{90}) in 85% of the pregnant women. Dose increases may overcome this reduction in exposure, but the exclusive availability of fixed-dose combination tablets makes this difficult. Administration of additional tablets of cobicistat may be a practical solution, but the pharmacokinetic parameters in this situation have yet to be investigated.

References

1. Momper JD, Best BM, Wang J, et al; IMPAACT P1026s Protocol Team. Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV. AIDS **2018**; 32:2507–16.
2. US Food and Drug Administration. FDA revises certain antiretroviral drug labeling to not recommend cobicistat during pregnancy. In: FDA News, Issue 33, **2018**. Available at: https://www.ascpt.org/Resources/ASCPTNews/View/ArticleId/22744/FDA-News-Issue-33-November-2018. Accessed 8 January 2020.
3. Blonk MI, Colbers AP, Hidalgo-Tenorio C, et al; Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-Infected Pregnant Women PANNA Network; PANNA Network. Raltegravir in HIV-1-infected pregnant women: pharmacokinetics, safety, and efficacy. Clin Infect Dis **2015**; 61:809–16.
4. DiFrancesco R, Tooley K, Rosenkranz SL, et al. Clinical pharmacology quality assurance for HIV and related infectious diseases research. Clin Pharmacol Ther **2013**; 93:479–82.
5. Ramanathan S, Mathias AA, German P, Kearney BP. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. Clin Pharmacokinet **2011**; 50:229–44.
6. European Medicines Agency. Genvoya; summary of product characteristics Available at: https://www.ema.europa.eu/en/documents/product-information/genvoya-epar-product-information_en.pdf. Accessed 8 January 2020.
7. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr **2013**; 13:59.
8. Marzolini C, Decosterd L, Winterfeld U, et al. Free and total plasma concentrations of elvitegravir/cobicistat during pregnancy and postpartum: a case report. Br J Clin Pharmacol **2017**; 83:2835–8.
9. Aweeka FT, Hu C, Huang L, et al; International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) P1026s Protocol Team. Alteration in cytochrome P450 3A4 activity as measured by a urine cortisol assay in HIV-1-infected pregnant women and relationship to antiretroviral pharmacokinetics. HIV Med **2015**; 16:176–83.
10. US Food and Drug Administration. Tybost: clinical pharmacology and biopharmaceutical review(s). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/203094Orig1Orig2s000ClinPharmR.pdf. Accessed 8 January 2020.
11. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. Clin Pharmacokinet **2005**; 44:989–1008.
12. Schalkwijk S, Greupink R, Burger D. Free dug concentrations in pregnancy: bound to measure unbound? Br J Clin Pharmacol **2017**; 83:2595–8.
13. Badell ML, Sheth AN, Momplaisir F, et al. A multicenter analysis of elvitegravir use during pregnancy on HIV viral suppression and perinatal outcomes. Open Forum Infect Dis **2019**; 6: ofz129.