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Pharmacokinetics of atazanavir boosted with cobicistat in pregnant and postpartum women with HIV

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Abstract

Background: This study evaluated atazanavir and cobicistat pharmacokinetics during pregnancy compared to postpartum and in infant washout samples.

Setting: A nonrandomized, open-label, parallel-group, multi-center prospective study of atazanavir and cobicistat pharmacokinetics in pregnant women with HIV and their children.

Methods: Intensive steady-state 24 hour pharmacokinetic profiles were performed after administration of 300 mg of atazanavir and 150 mg of cobicistat orally in fixed dose combination once-daily during the second trimester, third trimester, and postpartum. Infant washout samples

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were collected after birth. Atazanavir and cobicistat were measured in plasma by validated HPLC-UV and LC-MS/MS assays, respectively. A two-tailed Wilcoxon signed-rank test (α=0.10) was employed for paired within-participant comparisons.

Results: A total of 11 pregnant women enrolled in the study. Compared to paired postpartum data, atazanavir AUC_{0-24} was 26% lower in the second trimester (n=5, P=0.1875, Geometric mean of ratio (GMR)=0.739, 90% CI 0.527 – 1.035) and 54% lower in the third trimester (n=6, GMR=0.459, P=0.1563, 90% CI 0.190 – 1.109), while cobicistat AUC_{0-24} was 35% lower in the second trimester (n=5, P=0.0625, GMR=0.650, 90% CI 0.493 – 0.858) and 52% lower in the third trimester (n=7, p=0.0156, GMR=0.480, 90% CI 0.299 – 0.772). The median (interquartile range) 24-hour atazanavir trough concentration was 0.21 μg/mL (0.16 – 0.28) in the second trimester, 0.21 μg/mL (0.11 – 0.56) in the third trimester, and 0.61 μg/mL (0.42 – 1.03) postpartum. Placental transfer of atazanavir and cobicistat was limited.

Conclusions: Standard atazanavir/cobicistat dosing during pregnancy results in lower exposure which may increase the risk of virologic failure and perinatal transmission.

Keywords

Atazanavir; cobicistat; HIV; pharmacokinetics; perinatal transmission; pregnancy

Introduction

Antiretroviral treatment is recommended for all pregnant individuals with HIV to optimize their health and to prevent perinatal HIV transmission. The use of potent antiretroviral regimens and other strategies by pregnant individuals living with HIV has reduced the rate of perinatal HIV transmission to 1% or less in the United States and Europe.[1] Although the availability of safe and effective antiretroviral treatment options for use during pregnancy has increased, pharmacokinetic and safety data on newer agents during pregnancy remain limited.

A variety of physiological changes during pregnancy alter the absorption, distribution, metabolism, and excretion of drugs.[2,3] For example, the activity of hepatic cytochrome P450 3A (CYP3A) is increased by approximately 35% during all stages of pregnancy.[4–9] For individuals living with HIV, altered pharmacokinetics during pregnancy often leads to subtherapeutic antiretroviral exposure, which may result in increased risk of treatment failure, perinatal transmission, and drug resistance.[10,11]

Atazanavir is a protease inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.[12] The US Department of Health and Human Services Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends atazanavir as a preferred agent for pregnant women who require a protease inhibitor-based regimen during pregnancy.[13] Atazanavir has a higher barrier to resistance than non-nucleoside reverse transcriptase inhibitors (NNRTIs).[13] Atazanavir is metabolized and eliminated primarily by CYP3A-mediated hepatic metabolism and is typically boosted by coadministration with either ritonavir or cobicistat.[12] Atazanavir boosted with ritonavir has been studied in pregnancy[14]; however,

the pharmacokinetics of atazanavir boosted with cobicistat have not yet been reported. Prior pharmacokinetic studies of darunavir and elvitegravir boosted with cobicistat have shown that cobicistat is an inadequate pharmacokinetic booster during pregnancy for antiretroviral drugs that are primarily eliminated by CYP3A-mediated hepatic metabolism.[15–17] The primary objective of this study was to evaluate the pharmacokinetics and safety of atazanavir and cobicistat in pregnant women with HIV-1.

Methods

Study population and design

IMPAACT P1026s "Pharmacokinetic Properties of Antiretroviral and Related Drugs during Pregnancy and Postpartum" (ClinicalTrials.gov NCT00042289), was a non-randomized, open-label, parallel-group, multi-center, phase IV prospective study. The study included an arm for pregnant individuals living with HIV receiving fixed-dose combination atazanavir 300 mg/cobicistat 150 mg once daily (EVOTAZ®, Bristol-Myers Squibb Company, Princeton, NJ) which enrolled between 4/11/2016 and 7/23/2019. Atazanavir/cobicistat was prescribed for clinical care as part of participant's antiretroviral regimen. Participants had to be between 20 and 38 weeks gestation, be stable on their antiretroviral regimen for at least two weeks, and intend to continue the same regimen through 6 – 12 weeks postpartum. Maternal exclusion criteria were multiple gestation, a clinical or laboratory toxicity necessitating a medication change during the study, and the use of specific medications known to interact with atazanavir or cobicistat.

Each study site received local institutional review board approval. All participants gave informed consent prior to study participation. Medications were prescribed by each participant's clinical care provider. Pharmacokinetic sampling was performed during the third trimester (30–38 weeks gestation), and postpartum, as well as the second trimester (20–26 weeks gestation) for participants enrolling before 26 weeks gestation. Samples collected during pregnancy were assayed in real time with results reported to each study participant and her clinician.

Infant enrollment occurred immediately after maternal enrollment with maternal consent, with eligibility confirmed at birth. Infant inclusion criteria were birth weight >1,000 grams, singleton delivery, and maternal enrollment in P1026s. Infant exclusion criteria included presence of a severe congenital malformation or medical condition that would interfere with study participation as deemed by site clinicians or use of specific medications known to interfere with atazanavir or cobicistat disposition.

Clinical and laboratory monitoring

Each study visit included monitoring of HIV-1 RNA, CD4+ lymphocyte cell count, hematology, and serum biochemistry tests. All infants received physical examinations after birth and laboratory evaluations were performed only if clinically indicated. All infant HIV test results performed as part of clinical care were recorded through chart abstraction. Infants with positive HIV test results were classified as infected. Infants with two negative HIV test results, one after age 1 month and one after age 4 months were classified as uninfected.

Infants with negative test results that did not meet these criteria were classified as either uninfected based on best available data or indeterminate, depending on the available HIV test data. Adverse events were reported at each study visit and management was determined by each participant's clinician. The National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, dated November 2014, was used to grade adverse event severity.

Sample collection

Intensive 24-hour pharmacokinetic evaluations were performed during the second trimester (20–26 weeks gestation), third trimester (30–38 weeks gestation) and postpartum (6–12 weeks following delivery). Requirements prior to pharmacokinetic sampling were self-reported atazanavir and cobicistat adherence for two weeks and consistent dosing times for the last three doses. On sampling days the pre-dose sample was drawn and study medications were administered under observation. Post-dose samples were drawn at 1, 2, 4, 6, 8, 12 and 24 hours. At delivery, cord blood and maternal plasma samples were collected when possible. Four plasma samples were collected from study infants at 2–10 hours, 18–28 hours, 36–72 hours, and 5–9 days after birth.

Atazanavir and cobicistat plasma concentration measurements

Quantitative determination of atazanavir and cobicistat in human plasma was accomplished by the use of protein precipitation and high pressure liquid chromatography with UV detection and high-performance liquid chromatography with tandem mass spectrometry detection (LC-MS/MS), respectively. Atazanavir was precipitated from 200 μL of plasma with 240 μL of 100% acetonitrile (MeCN). A total of 50 μL of supernatant was injected directly onto a C-18 reversed phase HPLC column (Ace 5, 4.6 x 150 mm). Atazanavir was separated isocratically using a mobile phase consisting of 43% buffer (10mM potassium phosphate buffer, pH 3.0 – 3.1) and 57% ACN at a flow rate of 0.75mL/min. UV detection was at 245nm. Mean recovery of drug from plasma was 105.77%. The method was linear over the range of 0.039–10.0 μg/mL. Quantitation was by external calibration standards used to generate a curve using a least-squares linear regression algorithm to plot the peak area versus concentration with 1/response weighting. The lower limit of quantification of the assay was 0.039 μg/mL.

Cobicistat was precipitated from 10 μL of plasma with 300 μL of 100% acetonitrile (MeCN) plus the internal standard [$^{2}H_{8}$]-Cobicistat (D8-Cobicistat) (300ng/mL). A total of 5 μL of supernatant was injected directly onto a C-18 reversed phase HPLC column (MacMod Ace-5, 2.1 x 150 mm). Cobicistat was eluted using an gradient mobile phase consisting of 90% 0.1% formic acid in water and 10% 0.1% formic acid in MeCN to 5% 0.1% formic acid in water and 95% 0.1% formic acid in MeCN at a flow rate of 0.6mL/min to 0.8mL/min. MS/MS detection was made in positive electrospray ionization mode, with MRM monitoring of transitions (776.5→606.2) and (784.5→614.5) for cobcistat and D8-cobcistat, respectively. Mean recovery efficiency of drug from plasma was 100.8%. The method had a dynamic range of 4.9–2,500 ng/mL. Calibration standards are used to generate a curve using a linear regression algorithm to plot the peak area ratio of cobcistat/D8-cobicistat versus

concentration with 1/x weighting, over the full dynamic range of analyte concentrations. Concentrations of incurred and quality control samples are calculated with the same regression analysis.

Pharmacokinetic analysis

Atazanavir and cobicistat maximum, minimum, and last plasma concentrations (C_{max}, C_{min}, C_{24}) along with corresponding time points (T_{max}, T_{min}) were observed directly. Steady-state area under the plasma concentration versus time curve over the 24-hour dosing interval ($AUC_{0–24}$) was estimated with the trapezoidal rule. The terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$, where λ_z is the elimination rate constant derived from the terminal slope of the log concentration versus time curve. For participants with pre-dose concentrations below the assay quantitation limit, single-dose AUC from time 0 to infinity was estimated as $AUC_{0–24}$ plus the C_{24} divided by λ_z. Apparent oral clearance (CL/F) was calculated as dose divided by $AUC_{0–24}$. Concentrations that were below the limit of quantitation of the assay were set at half the lower limit of quantitation to calculate summary statistics. Absorption lags were defined as 1-hour post-dose concentrations that were lower than observed pre-dose concentrations. The minimum exposure target for atazanavir was the 10th percentile $AUC_{0–24}$ in non-pregnant adults with HIV (28.4 μg*hr/mL), which was estimated from published pharmacokinetic parameters.[12]

Statistical analysis

Each woman's atazanavir exposure during pregnancy was determined in real time, compared with $AUC_{0–24}$ values for non-pregnant adult historical controls, and reported to each participant's care provider. Descriptive statistics were calculated for pharmacokinetic parameters during each study period. Pharmacokinetic parameters during the second trimester versus postpartum and during the third trimester versus postpartum were compared at the within-participant level using the Wilcoxon signed-rank test, with a two-sided P-value ≤0.10 considered statistically significant. Within-participant geometric mean ratios (GMR) and 90% confidence intervals (CI) for pharmacokinetic parameters in the pregnant versus non-pregnant conditions were calculated for atazanavir and cobicistat to estimate the range of percentage changes between the two conditions consistent with the observed data and to assess clinical importance in order to inform dosing recommendations. Participants with no data or non-evaluable data in any study period were excluded from the matched comparisons.

Results

Participant Characteristics

Eleven pregnant women receiving atazanavir and cobicistat once-daily enrolled in the study. Evaluable atazanavir pharmacokinetic data were available for 6, 8, and 9 participants in the second trimester, third trimester, and postpartum, respectively. Evaluable cobicistat pharmacokinetic data were available for 6, 9, and 9 participants in the second trimester, third trimester, and postpartum, respectively. All atazanavir concentrations in one participant in the third trimester period were below the limit of quantitation of the assay, consistent with lack of absorption. Third trimester atazanavir pharmacokinetic data from this participant

were deemed non-evaluable and excluded from both third trimester summary statistics and from matched comparisons. Overall, evaluable paired pregnancy and postpartum atazanavir pharmacokinetic data were available for 5 of 6 participants who had second trimester visits and for 6 of 9 participants who had third trimester visits. Evaluable paired pregnancy and postpartum cobicistat pharmacokinetic data were available for 5 of 6 participants who had second trimester visits and for 7 of 9 participants who had third trimester visits. The median (range) duration of atazanavir/cobicistat prior to PK sampling was 16.6 weeks (4.1, 303.4, n=6) in the second trimester and 23.4 weeks (7.0, 312.3, n=9) in the third trimester. Clinical characteristics are summarized in Table 1.

Atazanavir Pharmacokinetics

The median (IQR) atazanavir $AUC_{0–24}$ in the second trimester, third trimester, and postpartum periods was 25.33 μg*hr/mL (20.95 – 27.32), 18.85 (11.90 – 31.48), and 36.20 (24.09 – 46.14), respectively (Figure 1, Table 2). Compared to paired postpartum data, atazanavir $AUC_{0–24}$ was 26% lower in the second trimester (n=5, P=0.1875, GMR=0.739, 90% CI 0.527 – 1.035) and 54% lower in the third trimester (*n*=6, GMR=0.459, P=0.1563, 90% CI 0.190 – 1.109). The median (IQR) 24-hour trough concentration was 0.21 μg/mL (0.16 – 0.28) in the second trimester, 0.21 μg/mL (0.11 – 0.56) in the third trimester, and 0.61 μg/mL (0.42 – 1.03) postpartum. The frequency of participants meeting the atazanavir $AUC_{0–24}$ target (28.4 μg*hr/mL) was 1/6 (17%) in the second trimester, 2/9 (22%) in the third trimester, and 5/9 (56%) postpartum. Atazanavir C_{min} was 66% lower in the second trimester and 72% lower in the third trimester compared to paired postpartum data (p=0.0625 and p=0.0313, respectively).

Eight maternal plasma samples at delivery and 8 cord blood samples were available. Of these, 2 maternal plasma samples and 5 cord blood samples were below the lower limit of quantitation of the assay for atazanavir (0.039 μg /mL). The median (IQR) concentration of atazanavir in maternal plasma at delivery was 0.61 μg/mL (0.05 – 0.89, *n*=8). The highest atazanavir concentration observed in cord blood was 0.13 μg/mL. Six sets of paired samples had quantifiable atazanavir concentrations in maternal plasma at delivery along with a cord blood sample (including cord blood samples below the limit of quantitation). Of these paired samples, the median (IQR) ratio of cord blood to maternal plasma was 0.07 (0.02 – 0.19).

A total of 38 washout samples were collected from 10 infants after birth. In 6 infants, all samples were below the quantitation limit for atazanavir (0.039 μg /mL). The remaining 4 infants provided 7 samples which had a quantifiable atazanavir concentration. Of these samples, the median (IQR) plasma atazanavir concentration was 0.10 μg/mL (0.07 – 0.26).

Cobicistat Pharmacokinetics

The median (IQR) cobicistat $AUC_{0–24}$ in the second trimester, third trimester, and postpartum periods was 7.39 μg*hr/mL (5.39 – 8.31), 4.89 μg*hr/mL (2.98 – 6.89), and 9.38 μg*hr/mL (8.57 – 10.28), respectively. Compared to paired postpartum data, cobicistat $AUC_{0–24}$ was 35% lower in the second trimester (*n*=5, P=0.0625, GMR=0.65, 90% CI 0.49 – 0.86) and 52% lower in the third trimester (*n*=7, p=0.0156, GMR=0.48, 90% CI 0.30 – 0.77) (Figure 2, Table 3). Cobicistat concentrations at 24 hours post-dose (C_{24}) were

below the quantitation limit in 3/6 (50%), 4/9 (44%), and 0/9 (0%) participant in the second trimester, third trimester, and postpartum, respectively.

A total of 8 maternal plasma samples at delivery and 8 cord blood samples were available. Of these, 2 maternal plasma samples and 4 cord blood samples were below the lower limit of quantitation of the assay for cobicistat (4.9 ng/mL). The median (IQR) concentration of cobicistat in maternal plasma at delivery was 47.95 ng/mL (12.16 – 219.25, n=8). The highest cobicistat concentration observed in cord blood was 576.0 ng/mL. A total of 6 sets of paired samples had quantifiable cobicistat concentrations in maternal plasma at delivery along with a cord blood sample (including cord blood samples below the limit of quantitation). Of these paired samples, the median (IQR) ratio of cord blood to maternal plasma was 0.10 (0.10 – 0.16). Cobicistat was not quantifiable in any neonatal washout plasma samples after birth.

Clinical Outcomes

Five mothers had DAIDS grade 3 or higher adverse events. All maternal adverse events were considered unrelated to study drugs by site investigators and the study team except for elevated total bilirubin in three participants and gestational diabetes in one participant. The percentage of women with suppression of HIV replication (defined as HIV-1 RNA < 50 copies/mL) at the second trimester (n=6), third trimester (n=9), delivery (n=11), and postpartum (n=9) visits was 100%, 100%, 100%, and 77.8%, respectively.

Three infants had adverse events grade 3 or higher. All infant adverse events were considered unrelated to study drugs by site investigators and the study team except for the grade 2 hyperbilirubinemia in one infant. The only clinical abnormality observed at birth was a unilateral undescended testicle in one infant. Eight infants had sufficient virologic testing to be classified as uninfected and three infants with incomplete virologic testing were classified as uninfected based on best available data.

Discussion

In pregnant individuals living with HIV receiving atazanavir in combination with cobicistat, atazanavir exposure was lower during pregnancy compared to postpartum. Compared to paired postpartum data, atazanavir $AUC_{0–24}$ was 26% lower in the second trimester and 54% lower in the third trimester. Atazanavir 24-hour trough concentrations were 74% lower in the second and third trimesters of pregnancy as compared to previously reported values in non-pregnant adult patients with HIV receiving once-daily dosing of 300/150 mg atazanavir/cobicistat.[12] Subtherapeutic antiretroviral exposure during pregnancy may increase the risk of virologic failure in the mother and of perinatal HIV transmission. In this study, the minimum AUC target for atazanavir (28.4 μg*hr/mL) was the 10th percentile $AUC_{0–24}$ in non-pregnant adults with HIV which was taken from published pharmacokinetic parameters.[18] Fewer participants met this minimum threshold during pregnancy (17% in second trimester; 22% in third trimester) compared to postpartum (56%).

In November 2019 the U.S. Food and Drug Administration (FDA) revised drug labeling for cobicistat products with a recommendation that cobicistat should not be used

during pregnancy to boost atazanavir, darunavir, and elvitegravir due to substantially lower exposures of darunavir and elvitegravir with cobicistat boosting in pregnant individuals.[15,16,19] The results of the present study support the recommendation that cobicistat at the standard adult dose of 150 mg daily is an inadequate pharmacokinetic booster during pregnancy for antiretroviral drugs that are primarily eliminated by CYP3A-mediated hepatic metabolism, including atazanavir.

Atazanavir boosted with ritonavir has been studied in pregnancy. Among 18 pregnant women receiving atazanavir/ritonavir 300mg/100mg once daily, the atazanavir AUC was reduced by approximately 30% compared to postpartum data.[14] Despite the lower atazanavir exposure, atazanavir/ritonavir 300mg/100mg once daily is recommended in pregnant women with HIV.[13] The differences between ritonavir and cobicistat boosting in pregnancy may be due to low systemic cobicistat concentrations in pregnant women.

The atazanavir population estimated protein binding adjusted effective concentration at 90% (EC90) is 0.014 μg/mL.[20] In this study, 2 participants in the third trimester had pre-dose trough concentrations below the lower limit of quantitation of the assay for atazanavir (0.039 μg/mL) suggesting that exposures in these participants may have fell below the EC_{90}. However, no clear exposure-response relationship was observed. For example, although the percentage of participants with suppression of HIV replication (defined as HIV-1 RNA < 50 copies/mL) was lowest postpartum, atazanavir exposures were highest during this period. Prior studies in adults with HIV have shown only a weak correlation between atazanavir exposure and virologic response.[20,21]

Physiologic changes during pregnancy likely contribute to the observed altered pharmacokinetics of atazanavir and cobicistat. Pregnancy-related hormones may modify the expression and activity of gastrointestinal and hepatic drug metabolizing enzymes – including CYP3A – through activation of nuclear receptors, including the pregnane X receptor (PXR) and the constitutive androstane receptor (CAR).[22] Separately, increases in blood volume and total body water can have a dilutional effect on drug concentrations and plasma proteins.[23] The elimination of both atazanavir and cobicistat is primarily by CYP3A-mediated metabolism. Cobicistat is used as a pharmacokinetic booster to inhibit CYP3A-mediated metabolism of atazanavir, increasing atazanavir systemic exposure. In this study, cobicistat $AUC_{0–24}$ was 35% lower during the second trimester and 52% lower during the third trimester relative to paired postpartum data. Reduced cobicistat exposure during pregnancy likely also plays a role in the decreased atazanavir exposure.

Atazanavir is 86% to 89% bound to human serum proteins (albumin and alpha-1-acid glycoprotein). The concentrations of both albumin and alpha-1-acid glycoprotein are reduced during pregnancy.[23–25] In addition, atazanavir binding to serum proteins may potentially be displaced by increased hormone binding during pregnancy. Although the unbound atazanavir concentration is responsible for anti-HIV activity, unbound drug concentrations were not measured in this study. While lower atazanavir exposure was observed during pregnancy, the therapeutic unbound free fraction during pregnancy is unknown.

This study assessed in utero transfer of atazanavir and cobicistat and the washout kinetics of these drugs transferred in utero across the placenta in infants born to mothers receiving atazanavir and cobicistat during pregnancy. For atazanavir, the median ratio of cord blood to maternal plasma was 0.07 (from 6 available paired sets of cord blood and maternal plasma at delivery). For cobicistat, the median ratio of cord blood to maternal plasma was 0.10 (from 6 available paired sets of cord blood and maternal plasma at delivery). A total of 38 washout plasma samples were collected from 10 infants during the first 9 days of life. Of these, only 7 samples (18%) were quantifiable for atazanavir (≥ 0.039 μg/mL) while cobicistat was not quantifiable in any neonatal washout samples. These data suggest that the placental transfer of both drugs is limited and infant washout elimination could not be assessed.

A limitation of this study is the opportunistic approach of only enrolling pregnant women receiving atazanavir and cobicistat as part of clinical care. This study design results in enrollment of pregnant women who respond virologically to the atazanavir/cobicistat combination without developing treatment-limiting toxicity, as women who virologically fail or have severe toxicity will be switched to other antiretroviral regimens. This selection bias may overestimate positive outcomes and underestimate adverse outcomes, including inadequate virologic response and drug toxicity. In addition, our sample size of 11 is smaller than other IMPAACT 1026s study arms. This small sample size was due to fewer pregnant women receiving this combination compared to other cobicistat combinations for routine clinical care during pregnancy at study sites prior to the FDA labelling revisions. No additional participants were recruited once the FDA issued the revised labeling recommending against the use of cobicistat as pharmacologic booster during pregnancy[19]. Therefore, although the sample size is small, it is likely these data will represent the only clinical pharmacokinetic data on atazanavir boosted with cobicistat during pregnancy. Another limitation is that the infant washout analysis included wide sampling windows with sparse time points.

In conclusion, standard atazanavir/cobicistat dosing during pregnancy results in lower atazanavir exposure which may increase the risk of virologic failure and perinatal transmission, and this drug combination should be avoided during pregnancy. These results support the FDA recommendations in revised drug labeling.

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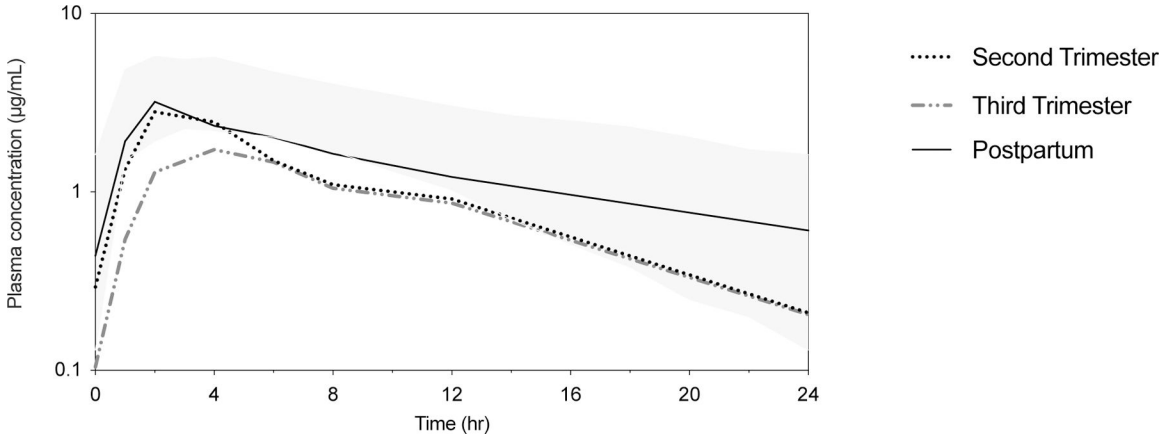

Figure 1.

Atazanavir antepartum and postpartum median plasma concentration versus time profiles following once-daily dosing of 300/150 mg atazanavir/cobicistat. The shaded area displays the 10th to 90th percentile concentrations in non-pregnant HIV patients receiving once daily atazanavir and ritonavir.

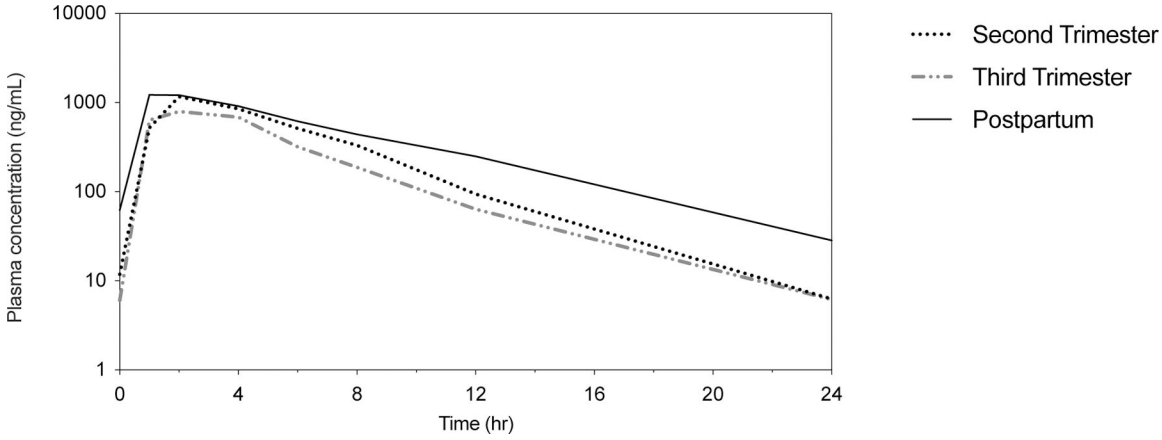

Figure 2.

Cobicistat antepartum and postpartum median plasma concentration versus time profiles following once-daily dosing of 300/150 mg atazanavir/cobicistat.

Table 1.

Clinical Characteristics.

	N (%) or Median (Range)
Maternal Demographics (n = 11 enrolled)	
Age at Delivery (years)	34.2 (21.0 – 43.0)
Weight at Delivery (kg)	97.2 (60.9 – 134.6)
Race/Ethnicity – Black Non-Hispanic; Hispanic (Regardless of Race); Asian, Pacific Islander; White Non-Hispanic	6 (55%); 2 (18%); 2 (18%); 1 (9%)
Concomitant ARVs 2T PK visit: FTC; TAF; TDF; DTG; EVG; RTV; ZDV	6 (100%); 3 (50%); 3 (50%); 2 (33%); 1 (17%); 1 (17%); 1 (17%)
Concomitant ARVs 3T PK visit: FTC; TAF; TDF; EVG; RTV; ZDV	9 (100%); 5 (56%); 4 (44%); 2 (22%); 1 (11%); 1 (11%)
Country: United States; Thailand	10 (91%); 1 (9%)
2T: HIV-1 RNA ≤ 50 copies/mL	6/6 (100%)
3T: HIV-1 RNA ≤ 50 copies/mL	9/9 (100%)
Delivery: HIV-1 RNA ≤ 50 copies/mL	11/11 (100%)
PP: HIV-1 RNA ≤ 50 copies/mL	7/9 (77.8%)
2T: CD4 (cells/mm3)	698 (170 – 1495)
3T: CD4 (cells/mm3)	536 (172 – 1495)
Delivery: CD4 (cells/mm3)	567 (172 – 1108)
PP: CD4 (cells/mm3)	649 (120 – 1388)
Infant Demographics (n=11 enrolled)	
Gestational Age (weeks)	37.3 (28.4 – 40.0)
Birth Weight (grams)	2990 (960 – 4445)
HIV Status: Uninfected; Negative based upon best available data	8 (73%); 3 (27%)

2T, second trimester; 3T, third trimester; PP, postpartum; PK, pharmacokinetic; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; DTG, dolutegravir; EVG, elvitegravir; RTV, ritonavir; ZDV, zidovudine

Table 2.

Atazanavir Pharmacokinetic Parameters, Median (IQR)

Parameter	Second Trimester n = 6	Third Trimester n = 8	Postpartum n = 9	Non-pregnant Adults with HIV[1]	GMR[2] (90% CI) 2T/PP, n=5	GMR[2] (90% CI) 3T/PP, n=6
AUC_{0-24} (μg*hr/mL)	25.33 (20.95, 27.32)	18.85 (11.90, 31.48)	36.20 (24.09, 46.14)	46.13 ± 26.18	0.74 [0.53, 1.04]	0.46 [0.19, 1.11]
C_0 (μg/mL)	0.29 (0.22, 0.42)	0.11 (0.04, 0.27)	0.44 (0.39, 0.96)		0.57 [0.49, 0.66] *	0.22 [0.074, 0.63] *
C_{max} (μg/mL)	2.82 (2.65, 3.65)	2.20 (0.94, 3.35)	3.90 (1.93, 4.60)	3.91 ± 1.94	0.80 [0.50, 1.27]	0.53 [0.19, 1.51]
T_{max} (hr)	2 (2, 2)	4 (2, 9)	2 (1, 2)	-	-	-
C_{24} (μg/mL)	0.21 (0.16, 0.28)	0.21 (0.11, 0.56)	0.61 (0.42, 1.03)	0.80 ± 0.72	0.32 [0.20, 0.51] *	0.32 [0.11, 0.94]
C_{min} (μg/mL)	0.21 (0.16, 0.28)	0.16 (0.10, 0.56)	0.61 (0.42, 1.03)	-	0.34 [0.22, 0.51] *	0.28 [0.11, 0.73] *
CL/F (L/hr)	11.89 (10.98, 14.32)	16.08 (9.68, 26.89)	8.29 (6.50, 12.45)	-	1.35 [0.97, 1.90]	2.18 [0.90, 5.27]
$T_{1/2}$ (hr)	6.39 (5.76, 6.99)	6.85 (5.26, 8.33)	14.78 (10.98, 22.28)	-	0.50 [0.37, 0.68] *	0.47 [0.32, 0.68] *

*p<0.10 compared to postpartum

1Historical data from EVOTAZ® (atazanavir and cobicistat) package insert, represented as mean (±S.D.)

2Paired comparisons

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2023 March 01.

Table 3.

Cobicistat Pharmacokinetic Parameters, Median (IQR)

Parameter	Second Trimester n = 6	Third Trimester n = 9	Postpartum n = 9	Non-pregnant Adults with HIV[1]	GMR[2] (90% CI) 2T/PP, n=5	GMR[2] (90% CI) 3T/PP, n=7
AUC_{0-24} (μg*hr/mL)	7.39 (5.39, 8.31)	4.89 (2.98, 6.89)	9.38 (8.57, 10.28)	7.6 (± 3.7)	0.65 [0.49, 0.86]*	0.48 [0.30, 0.77]*
C_0 (ng/mL)	11.9 (2.5, 19.2)	6.0 (2.5, 15.7)	62.6 (25.0, 87.8)	-	0.17 [0.068, 0.44]*	0.11 [0.041, 0.323]*
C_{max} (ng/mL)	1238.5 (830, 1530)	857 (634, 981)	1450 (1130, 1700)	990 (± 300)	0.77 [0.57, 1.04]	0.61 [0.43, 0.87]*
T_{max} (hr)	2 (2, 2)	2 (2, 4)	2 (1, 2)	-	-	-
C_{24} (ng/mL)	6.3 (2.5, 10.9)	6.2 (2.5, 29.8)	28.6 (23.7, 37.0)	30 (±100)	0.17 [0.086, 0.35]*	0.46 [0.075, 2.79]
C_{min} (ng/mL)	6.3 (2.5, 10.9)	2.5 (2.5, 29.8)	28.6 (23.7, 37.0)	-	0.17 [0.086, 0.35]*	0.27 [0.081, 0.90]
CL/F (L/hr)	20.4 (18.1, 27.8)	30.7 (21.8, 50.2)	15.9 (14.6, 17.5)	-	1.54 [1.17, 2.03]*	2.08 [1.30, 3.35]*
$T_{1/2}$ (hr)	2.77 (2.43, 3.01)	2.84 (2.55, 3.15)	4.01 (3.42, 4.42)	-	0.71 [0.61, 0.83]*	0.70 [0.64, 0.77]*

*p<0.10 compared to postpartum

[1]Historical data from TYBOST® (cobicistat) package insert, represented as mean (±S.D.)

[2]Paired comparisons