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Pharmacokinetics and safety of bictegravir in pregnant and postpartum persons with HIV and their infants

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Supp Tables--http://links.lww.com/QAI/C394

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Abstract

Background: Limited data exist on bictegravir pharmacokinetics in pregnancy among persons with HIV (PWH) and infant washout.

Setting: Nonrandomized, open-label, multi-center phase-IV prospective study of bictegravir pharmacokinetics and safety in pregnant PWH and their infants.

Methods: Steady-state 24-hour pharmacokinetic sampling of oral bictegravir 50 mg once daily (a component of fixed-dose combination bictegravir/emtricitabine/tenofovir alafenamide) during the 2nd and 3rd trimesters and postpartum was performed. Cord blood and infant washout samples were collected. Total and free bictegravir concentrations were measured by validated LC-MS/MS methods. Within-participant geometric mean ratios (GMR) with 90% confidence intervals (CI) were calculated to compare pharmacokinetics between 2nd and 3rd trimester versus postpartum. Infant HIV testing results were obtained.

Results: Twenty-seven maternal-infant pairs enrolled. Bictegravir $AUC_{0–24}$ was 46% lower in the 2nd trimester (n = 12; $P = 0.002$; GMR 0.54; 90% CI: 0.43–0.69) and 52% lower in the 3rd trimester (n=24; $P < 0.0001$; GMR 0.48; 90% CI: 0.43–0.55), compared to postpartum. C_{24} concentrations were above the estimated bictegravir protein-adjusted EC_{95} of 0.162 μg/mL. The median ratio of cord-to-maternal blood concentration was 1.38 (n=17; quartiles: 1.17, 1.63). Median $T_{1/2}$ for infant bictegravir washout was 33.2 hours (quartiles: 25.7, 45.9) with a Cmax of 2.06 μg/mL (quartiles: 1.37, 2.72). 88–92% of participants maintained suppression <40 copies/mL throughout pregnancy and postpartum. All available infant HIV testing results were negative. The safety profile for pregnant PWH and infants was acceptable.

Conclusions: Bictegravir exposure was lower during pregnancy compared to postpartum, yet C_{24} concentrations were greater than the bictegravir protein-adjusted EC_{95}.

Keywords

bictegravir; integrase strand transfer inhibitor; HIV; pharmacokinetics; pregnancy; perinatal transmission

Introduction

Antiretroviral treatment is essential for achieving and maintaining HIV viral suppression in pregnancy, protecting against HIV disease progression, maintaining the health of pregnant persons living with HIV, and preventing infant HIV acquisition[1]. In particular, integrase strand transfer inhibitors (INSTI), one of the newer antiretroviral drug classes, have been shown to achieve rapid viral suppression and are generally well tolderated[2–5].

Bictegravir is an INSTI co-formulated as a once daily fixed-dose combination with emtricitabine (FTC) and tenofovir alafenamide (TAF), with initial FDA approval for use in adults received in 2018[6,7]. Bictegravir has a higher genetic barrier to resistance than the first-generation INSTIs elvitegravir and raltegravir[8,9]. It is highly protein bound (>99%, primarily to albumin), metabolized via hepatic cytochrome P450 3A (CYP3A) and uridine diphosphate glucuronyltransferase type 1A1 (UGT1A1), and does not require boosting[10,11]. United States Department of Health and Human Services (DHHS) guidelines categorize bictegravir/FTC/TAF administration once daily as an appropriate initial regimen for most treatment naïve persons living with HIV[12]. However, bictegravir/FTC/TAF is not designated as a preferred regimen, but rather an alternative, for use in treatment naïve pregnant persons, given limited pharmacokinetic and safety data[13] and reports of lower bictegravir exposure during pregnancy[14,15], potentially risking emergence of antiretroviral drug and class resistance, viral breakthrough, and infant HIV-1 acquisition. Further evaluation of bictegravir pharmacokinetics and safety during pregnancy is needed.

The primary objective of this study was to evaluate the pharmacokinetics and safety of bictegravir in pregnant and postpartum persons with HIV. Secondary objectives included evaluation of the transplacental passage of bictegravir from maternal to fetal circulation, elimination of bictegravir in infants following birth, and to describe maternal and infant clinical outcomes.

METHODS

Study population and design

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 2026 study is a nonrandomized, open-label, multi-center phase-IV prospective study of the pharmacokinetics and safety of selected antiretroviral and anti-tuberculosis medications used during pregnancy and postpartum (ClinicalTrials.gov NCT04518228). Pregnant persons with confirmed HIV-1 infection receiving bictegravir 50 mg once daily, a component of the fixed-dose combination of bictegravir/FTC/TAF (Biktarvy®, Gilead Sciences, Foster City, CA, USA), as part of clinical care, were eligible for enrollment. Antiretroviral medications were prescribed by the participant's clinical providers. The IMPAACT 2026 study team was not involved in clinical decision-making over the initiation or modification of treatment regimens.

Participants were eligible to enroll either during the 2nd trimester (20 0/7 to 26 6/7 weeks gestation) or 3rd trimester (30 0/7 to 37 6/7 weeks gestation), so long as they had been receiving bictegravir for at least two weeks prior to enrollment and intended to

continue on the same regimen through at least 12 weeks postpartum. Exclusion criteria included use within two weeks before enrollment of specific medications known to interact with bictegravir and clinical or laboratory conditions likely to require a change from the bictegravir-containing regimen to an alternative regimen. Infant eligibility criteria for washout pharmacokinetic assessments included birth weight of at least 1000 grams, not receiving any medications with the potential to alter bictegravir pharmacokinetics, and absence of severe congenital malformations or medical conditions deemed incompatible with life or that would interfere with study participation. The enrollment target was 28 women with at least 25 participants having evaluable pharmacokinetic data during the 3rd trimester, and a minimum of at least 12 participants having 2nd trimester evaluable pharmacokinetic data.

All maternal participants provided written informed consent on their own behalf and for their infant prior to study entry. Protocol approval was obtained from all required institutional review boards, ethics committees, and applicable regulatory entities at all participating sites.

Clinical and laboratory monitoring

Maternal study visits occurred in the 2nd and 3rd trimester, at delivery, and 6–12 weeks postpartum, with monitoring of HIV-1 RNA, CD4+ lymphocyte cell count, hematology, and serum biochemistry assessments. During 2nd and 3rd trimester visits, maternal albumin and alpha-1-acid glycoprotein (AAG) were also evaluated. Infant visits occurred within 3 days of birth, 5–9 days of life, 2–8 weeks of life and 16–24 weeks of life. At each visit, infants were examined to assess for congenital anomalies and chart abstraction was performed to collect infant HIV testing results up to 24 weeks after birth. Infants with 2 negative HIV test results, one after age 1 month and one after age 4 months, were classified as not having HIV. Infants with negative test results who did not meet these criteria were classified as either not having HIV based on best available data or could not be assigned a final HIV status, 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 2.1, dated July, 2017 was used to grade adverse event severity[16].

Pharmacokinetic sampling

Intensive 24-hour pharmacokinetic assessments were performed at steady state during the 2nd trimester (if enrolled), 3rd trimester, and 6–12 weeks postpartum. Requirements prior to pharmacokinetic sampling were self-reported bictegravir adherence for two weeks and consistent dosing times for the last three doses. On sample days, the pre-dose sample was drawn and the study medication was administered under observation. Post-dose samples were drawn at 1-, 2-, 4-, 6-, 8-, 12- and 24-hours after bictegravir administration. At delivery, cord blood and maternal plasma samples were collected whenever possible.

For infants born to participants receiving bictegravir at the time of delivery and who had not missed more than one dose during the immediate period prior to delivery, infant washout

samples were collected at 2–10 hours, 18–28 hours, and 36–72 hours after birth, and again between 5–9 days after birth.

Bictegravir plasma concentration measurements

Quantitative determination of bictegravir in human plasma was accomplished by high-performance liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). For total concentration measurements, bictegravir was precipitated from 25 μL of plasma with 500 μL of 100% acetonitrile (MeCN) plus the internal standard BIC-15N,d_2. A total of 5 μL of supernatant was injected directly onto a C-18 reversed phase HPLC column (MacMod Ace-5, 2.1 × 150 mm). Bictegravir was eluted using a gradient mobile phase consisting of 30% 0.1% formic acid in water and 70% 0.1% formic acid in acetonitrile (MeCN) to 5% 0.1% formic acid in water and 95% 0.1% formic acid in MeCN at a flow rate of 0.5mL/min to 0.8mL/min. MS/MS detection was made in positive electrospray ionization mode, with MRM monitoring of transitions (450.207→288.700) and (453.167→288.6) for bictegravir and BIC-15N,d_2, respectively. Mean recovery efficiency of drug from plasma was 100.6%. The method had a dynamic range of 7.8–20,000 ng/mL. Calibration standards were used to generate a curve using a quadratic regression algorithm to plot the peak area ratio of BIC/BIC-IS versus concentration with 1/y weighting, over the full dynamic range of analyte concentrations. Concentrations of incurred and quality control samples were calculated with the same regression analysis. Total bictegravir concentrations were determined for all pharmacokinetic samples.

For unbound bictegravir concentration measurements, 100 μL of plasma was dialyzed in a commercially available rapid equilibration dialysis (RED) chamber versus rapid dialysis buffer (RDB) for 6 hours at 37°C at 80 R.P.M. Samples were protected from light with amber vials and aluminum foiling. Following the addition of the internal standard, 10μL of dialysate was directly injected onto a MacMod Ace-5.5μm RP 2.1 × 150mm LC column. Gradient elution was performed with a binary system beginning with 95% of 0.1% formic acid in water and 5% of 0.1% formic acid in MeCN at an initial flow rate of 0.4mL/min, with an MeCN washout at the end of each run. Detection was achieved by electrospray (ESI) positive ionization mass spectrometry. Precursor/product transitions (m/z) in the positive ion MRM mode were (450.21→288.7) and (453.17→288.6), respectively, for BIC and BIC-15N,d_2. Mean recovery efficiency of drug from plasma was 107.3%. The method had a dynamic range of 0.3–20 ng/mL. Calibration standards were used to generate a curve using a linear regression algorithm to plot the peak area ratio of BIC/BIC-15N,d_2 versus concentration with 1/y weighting, over the full dynamic range of analyte concentrations. Unbound bictegravir concentrations were determined only for the sample with the lowest total concentration between pre-dose and 24 hours post-dose for each participant per visit.

Pharmacokinetics analyses

Bictegravir maximum, minimum, and 24-hour trough concentration (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 ($AUC_{0–24}$ or AUC_{tau}) was estimated with linear trapezoidal interpolation. The terminal elimination half-life ($t_{1/2}$) was calculated as 0.693/λz, where λz 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 λz. 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 BIC was the 10^{th} percentile AUC_{tau} in non-pregnant adults with HIV (58.7 μg*hr/mL), which was estimated from historical pharmacokinetic data[11,17].

Interim pharmacokinetic exposure monitoring was performed in near real-time and individual AUC_{tau} values in comparison to the 10^{th} percentile AUC_{tau} in non-pregnant adults (58.7 μg*hr/mL) were reported site investigators. The IMPAACT 2026 protocol and study monitoring plan required IMPAACT Study Monitoring Committee review to continue enrollment if six or more participants experienced AUC_{tau} below the 10^{th} percentile of non-pregnant adults.

Statistical analysis

Pharmacokinetic parameters from the 2^{nd} and 3^{rd} trimesters were compared to postpartum at the within-participant level using the Wilcoxon signed rank test with a two-sided significance level of 0.10. Within-participant geometric mean ratios (GMR) and 90% confidence intervals (CIs) for continuous pharmacokinetic parameters in the pregnant versus postpartum states were calculated for bictegravir. Participants with no postpartum data or with non-evaluable data were excluded from comparisons. Unbound bictegravir concentrations were determined for samples corresponding to the highest and lowest total bictegravir concentration for each participant per visit. Unbound bictegravir concentrations, percent unbound bictegravir, albumin, and AAG concentrations at the 2^{nd} and 3^{rd} trimester were also compared to postpartum with GMRs, 90% CIs, and the Wilcoxon signed rank test. All analyses were performed in SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Participant characteristics

Twenty-seven pregnant persons receiving bictegravir once daily enrolled in the study between September 2021 and October 2022 (Table 1), over half of whom were taking a bictegravir-containing treatment regimen before pregnancy. Evaluable pharmacokinetic data were available for 12, 27, and 25 participants in the 2^{nd} trimester, 3^{rd} trimester, and postpartum, respectively. Three pre-dose concentrations - all in the 3^{rd} trimester – were below the limit of quantitation (7.8 ng/mL). Evaluable paired antepartum and postpartum bictegravir pharmacokinetic data were available from all 12 participants with 2^{nd} trimester visits, and 25 of 27 participants with 3^{rd} trimester visits. Twenty-four (89%) of the infants were followed through the final study visit at 16–24 weeks after birth. Among the remaining 3 (11%) infants, one had a parent who refused to continue prior to delivery, another had a caregiver who withdrew consent after delivery, and the third was lost to follow-up after delivery. Infant clinical characteristics are summarized in Table 1.

Bictegravir pharmacokinetics

The median (Q1, Q3) bictegravir $AUC_{0–24}$ in the 2nd trimester, 3rd trimester, and 6–12 weeks postpartum were 53.4 μg·h/mL (48.3, 71.9), 51.8 μg ·h/mL (38.8, 64.6), and 118.0 μg·h/mL (70.2, 132.0), respectively (Figure 1, Table 2). Compared with paired postpartum data, bictegravir $AUC_{0–24}$ was 46% lower in the 2nd trimester (n = 12; $P = 0.002$; GMR = 0.54; 90% CI: 0.43, 0.69) and 52% lower in the 3rd trimester (n=24; $P < 0.0001$; GMR = 0.48; 90% CI: 0.43, 0.55). Seven (58%) of 12 participants in the 2nd trimester, 16 (59%) of 27 participants in the 3rd trimester, and 3 (13%) of 24 participants postpartum had an AUC below the 10th percentile for non-pregnant persons (58.7 μg·hr/mL) (Supplemental Table 1), triggering IMPAACT safety committee review after the sixth occurrence. Three participants had pre-dose bictegravir concentrations during the 3rd trimester below the protein-adjusted 95% effective concentration ($paEC_{95}$) for bictegravir of 0.162 μg/mL[17].

The median (Q1, Q3) unbound bictegravir concentration was 3.83 (2.53, 5.12) ng/mL in the 2nd trimester, 3.01 (1.78, 3.77) ng/mL in the 3rd trimester, and 5.83 (3.55, 8.12) ng/mL postpartum. The median (Q1, Q3) percent unbound BIC was 0.403% (0.314%, 0.502%) in the 2nd trimester, 0.326% (0.255%, 0.459%) in the 3rd trimester, and 0.247% (0.212%, 0.280%) postpartum. Compared with postpartum, the percent unbound was 45% and 42% higher in the 2nd and 3rd trimesters, respectively. Albumin and AAG concentrations were significantly lower antepartum compared with postpartum (Supplemental Table 2).

The median (Q1, Q3) concentration of bictegravir in maternal plasma at delivery and cord blood (n=17 each) was 1.77 (0.99, 2.10) μg/mL and 2.31 (1.44, 3.01) μg/mL, respectively. Using paired samples, the median (Q1, Q3) ratio of cord blood to maternal plasma was 1.38 (1.17, 1.63) μg/mL. A total of 93 washout samples were obtained from 26 infants after birth. Infant bictegravir plasma concentrations are displayed in Figure 2. The median (Q1, Q3) of maximum observed plasma concentrations was 2.06 (1.33, 2.72) μg/mL. Bictegravir half-life could be estimated for 25 infants. The median (Q1, Q3) elimination half-life in these infants was 33.2 (25.7, 45.9) hours.

Clinical outcomes

HIV-1 RNA was detected above the highest limit of quantitation, 40 copies/mL, in 1 (8%) participant during the 2nd trimester, 3 (11%) during the third trimester, 2 (8%) at delivery, and 3 (12%) postpartum. Of participants with bictegravir AUC below the 10th percentile for non-pregnant persons, none had HIV-1 RNA ≥ 40 copies/mL in the 2nd or 3rd trimester. However, one participant had a detectable HIV-1 RNA level in the postpartum period, at 59 copies/mL. Two other participants who had bictegravir AUC at or above the 10th percentile during pregnancy had detectable HIV-1 RNA levels postpartum. One participant had 59 copies/mL postpartum, with an enrollment HIV-1 RNA in the 3rd that was undetectable. The other had postpartum HIV-1 RNA of 10,300 copies/ml with 2nd and 3rd trimester values of 553 copies/mL and 429 copies/mL respectively.

Five women experienced at least one grade 3 adverse event without any grade 4 events. All maternal adverse events were considered unrelated to bictegravir (**See** Supplemental Table 3a). Six infants experienced a grade 3 or higher event, with four infants experiencing a

grade 4 adverse event as their highest graded event, including two with hypoglycemia, one with jaundice, and one with neonatal respiratory distress (**See** Supplemental Table 3b). Two infants experienced grade 3 events as their highest graded event, with one experiencing two grade 3 events, including hyperbilirubinemia and infantile eczema, and the second having hypoglycemia. None of these adverse events were considered related to bictegravir. Two congenital abnormalities were reported, including a grade 1 preauricular cyst and a DAIDS grade 1 ventricular septal defect. Only the ventricular septal defect was deemed related to bictegravir.

Among the 26 infants who were followed at delivery or thereafter, 15 (58%) infants had sufficient virologic testing to be classified as being HIV-free, 9 (35%) were classified as probably being HIV-free based upon best available information and 2 (17%) could not be assigned a definitive HIV status due to lack of available testing results.

DISCUSSION

Among pregnant persons with HIV, bictegravir exposure was lower during the 2nd and 3rd trimesters of pregnancy compared to postpartum. Although over half of participants had bictegravir AUC below the 10th percentile for non-pregnant persons in the second and third trimester, none had detectable HIV-1 RNA copies above the highest limit of quantitation of 40 copies/ mL in pregnancy and only one had a detectable HIV-1 RNA viral load of 59 copies/mL subsequently at the postpartum visit. Three participants had pre-dose bictegravir concentrations during the 3rd trimester below the paEC$_{95}$ (0.162 μg/mL). None of the 25 infants with follow-up had positive HIV testing.

Physiological changes during pregnancy likely contributed to the observed altered bictegravir pharmacokinetics during pregnancy in this study. Bictegravir is eliminated primarily by CYP3A- and UGT1A1-mediated hepatic metabolism. Pregnancy-related hormonal changes increase the expression and activity of both CYP3A and UGT1A1. Additionally, increases in blood volume and total body water during pregnancy may have a dilutional effect on both drug concentrations and plasma proteins. Reduced albumin and AAG concentrations during pregnancy were seen in this study. The median bictegravir unbound fraction during the 2nd trimester, 3rd trimester, and postpartum was 0.403%, 0.326%, and 0.247%, respectively. As bictegravir has a low hepatic extraction ratio (~13%), reduced protein binding may have also contributed to increased clearance during pregnancy. Overall, these findings are consistent with a prior case report and another clinical study[14,15]

Importantly, all participants who had a bictegravir AUC below the 10th percentile for non-pregnant persons remained virologically suppressed during the 2nd and 3rd trimesters and had bictegravir concentrations in pregnancy and postpartum above the paEC$_{95}$ of 0.162 μg/mL. While the number of participants with AUC below the 10th percentile for non-pregnant persons triggered review by the IMPAACT Study Monitoring Committee, the decision was made to continue enrollment based on cumulative bictegravir efficacy and PK data.

The single participant who had detectable HIV-1 RNA in pregnancy and postpartum consistently had bictegravir AUC above the 10th percentile for non-pregnant adults. HIV-1 RNA viral loads of 553 and 429 copies/mL were noted in the 2nd and 3rd trimester respectively, with pre-dose bictegravir concentrations greater than the 75% for the study population preceding each study visit. While there have been few reports of resistance to bictegravir[18,19], the postpartum HIV-1 RNA of 10,300 copies/mL may reflect emergence of resistance. However, due to the unique opportunistic design of this study, where participants were already taking a co-formulated single-dose tablet of bictegravir/FTC/TAF prescribed by their health care provider as a condition of study enrollment, the clinical care of participants, including resistance testing, remained with the participant's care provider. Resistance testing results, if performed, were not reported to the study. In another study of bictegravir use in pregnancy and postpartum involving 29 participants, no virological failure occured[15]. It will be important to ensure that low level HIV-1 viremia in pregnancy with subsequent postpartum spikes in HIV-1 RNA copies/mL are not associated with resistance to bictegravir or the INSTI class of antiretroviral drugs, as challenges exist with waning treatment adherence postpartum[20]. Given that HIV viremia in pregnancy was uncommon in this cohort and infants were formula fed, risk of infant HIV acquisition was low. However, the opportunistic design of the study, which meant that the study team was not directly managing infant HIV testing, only resulted in 58% of infants having a high certainty of their HIV uninfected status according to published DECIPHER classification guidelines[21]. As bictegravir is increasingly used in pregnancy, it will be important to monitor HIV status in larger populations of infants using the DECIPHER criteria of high, moderate, and low certainty[21].

From our cohort and others[14,15], bictegravir appears to be safe in pregnancy. Only one infant event was deemed to be related to bictegravir, a ventricular septal defect identified in an infant where the parent initiated bictegravir three years before conception. However, cardiovascular defects are the most commonly reported infant congenital anomalies in the general population and in studies investigating teratogenicity following fetal exposure to antiretroviral drugs[22,23]. It will be important for clinicians to monitor for congenital anomalies in the growing population of bictegravir exposed neonates and to use the United States-based Antiretroviral Pregnancy Registry to report all pregnancy outcomes prospectively[24].

Bictegravir concentrations were higher in cord blood plasma than in maternal plasma (median ratio of cord-to-maternal blood 1.38). This finding is within the range reported for the integrase inhibitor dolutegravir of 0.6 to 1.38[25–27]. In a separate *ex vivo* study, bictegravir placental transfer was low (median cotyledon accumulation index of 4%)[28]. High protein binding may limit bictegravir movement across the placenta, though placental uptake and efflux transporters could also play a role. The prolonged elimination half-life of bictegravir in infants is likely related to underdevelopment of clearance pathways (i.e. CYP3A and UGT1A1-mediated metabolism). The reported infant washout bictegravir concentrations and kinetics may inform clinical trial design and dosing strategies for future bictegravir neonatal studies, including the timing of bictegravir initiation in neonates who acquire HIV or are at high risk for acquisition.

While this study has many strengths, including a study design that allows rapid assessment of the newest antiretroviral drugs being used in pregnancy, it does have some limitations. For example, the opportunistic study design whereby pregnant persons with HIV are already receiving a bictegravir containing treatment regimen introduces potential selection bias, as eligible participants would likely have experienced virological suppression and would not have experienced any treatment limiting toxicities with use of bictegravir. As such, the findings may over estimate positive outcomes and underestimate adverse outcomes. The opportunistic design and reliance on clinical care assessments of infant outcomes also precluded the ability to categorize some infants as being HIV-free prior to placing the infant off study. Lastly, infant washout analysis included wide sampling windows for sparse timepoints.

In conclusion, total and unbound bictegravir exposure were lower during pregnancy compared to postpartum. Despite lower exposure, all participants had C_{24} bictegravir concentrations above the $paEC_{95}$ levels and 90% of participants had HIV-1 RNA viral suppression at delivery. Bictegravir concentrations were higher in cord blood than maternal plasma, with a prolonged neonatal elimination half-life. No infant tested positive for HIV. Currently, the fixed-dose combination drug of bictegravir/FTC/TAF is recommended as an alternative treatment when initiating or continuing ART in pregnancy according to United States Department of Health and Human Services guidelines[13]. This fixed-dose combination appears to be well tolerated and the bictegravir component provides rapid viral suppression and a high barrier to resistance[6]. It will be important to continue to collect pregnancy and postpartum outcome data to inform the appropriate use of bictegravir/FTC/TAF among pregnant individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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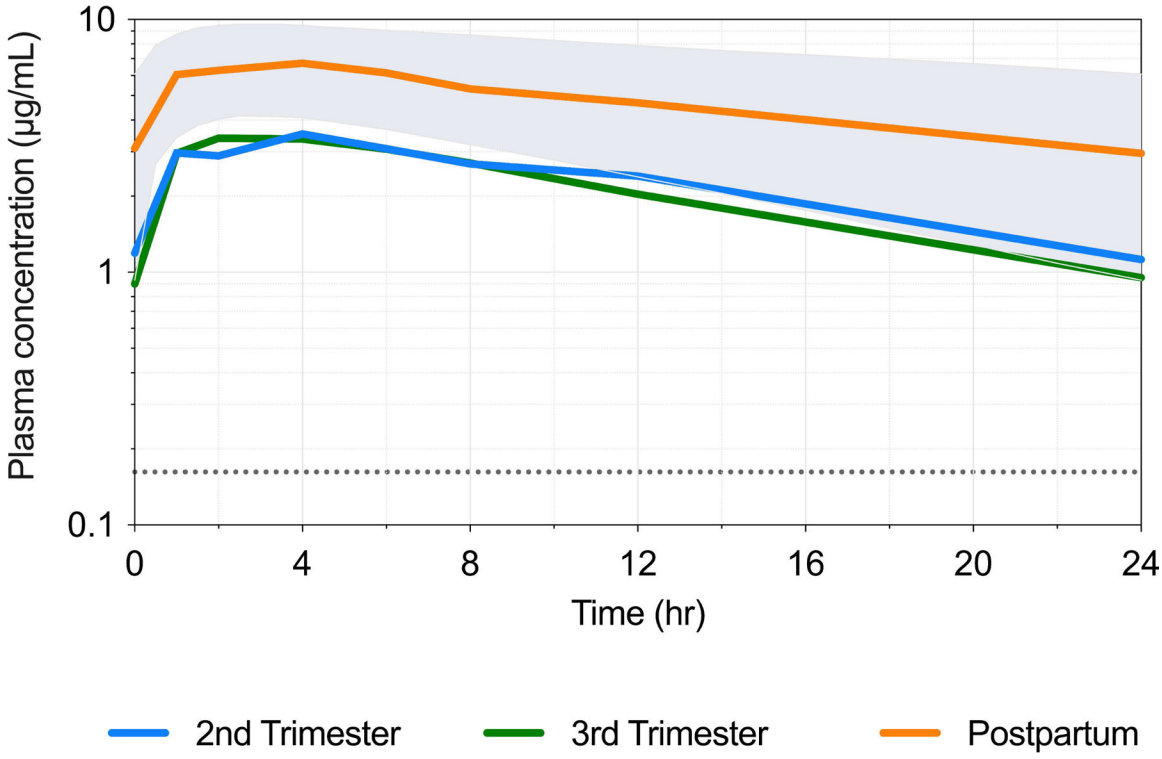

Fig 1:

Median antepartum and postpartum plasma bictegravir versus time profiles at steady state following once-daily dosing of 50 mg of bictegravir. The shaded area displays the 10th–90th percentile concentrations of bictegravir in nonpregnant adults. The dotted line indicates the bictegravir protein-adjusted EC_{95} (0.162 µg/mL).

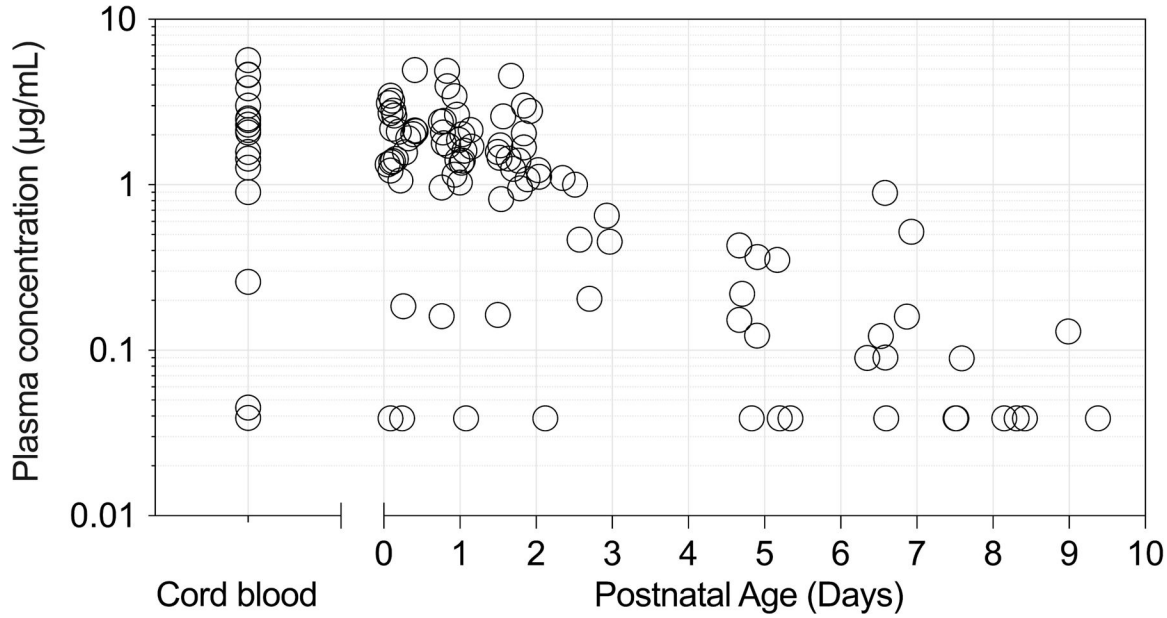

Fig 2:

Scatter plot of bictegravir plasma concentrations in cord blood and in infants after birth. Concentrations below the limit of quantitation (BLQ; 0.78 ng/mL) are displayed as half of the lower limit of quantitation (0.39 ng/mL). A total of 93 washout samples were obtained from 25 infants over the first 9 days of life. At 2–10 hours, 18–28 hours, and 36–72 hours post birth, 2, 1, and 1 infants had bictegravir concentrations BLQ At 5–9 days, 11 (44%) had bictegravir BLQ.

Table 1:

Maternal and Infant Sociodemographic and Clinical Characteristics

	N (%) or Median (Q1, Q3)
Maternal Demographics	
Age at delivery (Years)	31.6 (26.2, 36.7)
Weight at delivery (kg)	93.4 (79.5, 99.8)
Race[1]	
Black/African American	15 (68%)
White	4 (18%)
Asian	2 (9%)
Native American/Alaska Native	1 (5%)
Ethnicity	
Hispanic/Latinx	8 (30%)
Non-Hispanic/Latinx	19 (70%)
Country of Residence	
United States	26 (96%)
Thailand	1(4%)
Maternal Clinical Characteristics	
HIV-1 RNA (copies/mL)	
Proportion with HIV-1 RNA < 40 copies/mL	
2nd Trimester	11 (92%)
3rd Trimester	24 (89%)
Delivery	24 (92%)
6–12 Weeks Postpartum	22 (88%)
Median HIV-1 Viral Load for HIV-1 RNA ≥ 40 copies/mL	
2nd Trimester (n = 1)	553 (553, 553)
3rd Trimester (n = 3)	110 (88, 429)
Delivery (n = 2)	935 (668, 1,201)
6–12 Weeks Postpartum (n = 3)	59 (43, 10,300)
Infant Clinical Characteristics	
Gestational Age (Weeks)	39.4 (39.0, 39.9)
Preterm Birth (< 37.0 Weeks)	1 (4%)
Birth Weight (kg)	3.44 (3.15, 3.62)
Birth Length (cm)	50.4 (48.5, 52.0)
HIV Status	
Uninfected	15 (58%)
Probably Uninfected (Based on best available information)	9 (35%)
Insufficient HIV Testing Data for Determination	1 (<4%)
No Results Available	1 (<4%)

Abbreviations: Q1– 25th percentile; Q3– 75th perentile; kg – kilograms; cm - centimeters

[1] Missing Data: Race = 5

Table 2.

Bictegravir Pharmacokinetic Parameters During Pregnancy and Postpartum

Parameter	Second Trimester	Third Trimester	Postpartum	Non-pregnant Adults with HIV[1]	GMR[2] (90% CI) 2T/PP, n=12	GMR[2] (90% CI) 3T/PP, n=24[3]
	n = 12	n = 27	n = 24			
$AUC_{0–24}$ (μg*hr/mL)	53.4 (48.3, 71.9)	51.8 (38.8, 64.6)	118 (70.2, 132)	102 ± 26.9	0.54 (0.43, 0.69)*	0.48 (0.43, 0.55)*
C_{0h} (μg/mL)	1.13 (0.59, 1.37)	0.95 (0.55, 1,21)	2.92 (1.55, 3.78)	-	0.41 (0.30, 0.58)*	0.33 (0.28, 0.39)*
C_{max} (μg/mL)	4.16 (3.80, 5.27)	3.72 (3.07, 4.66)	7.13 (5.76, 8.88)	6.15 ± 22.9	0.65 (0.53, 0.80)*	0.56 (0.50, 0.62)*
T_{max} (hr)	1.50 (1.00, 4.00)	2.00 (1.00, 4.00)	2.00 (1.00, 2.00)	-	-	-
C_{24} (μg/mL)	1.13 (0.59, 1.37)	0.95 (0.69, 1.21)	2.96 (1.68, 3.78)	2.61 ± 0.1	0.38 (0.28, 0.52)*	0.32 (0.27, 0.38)*
C_{min} (μg/mL)	1.13 (0.59, 1.37)	0.95 (0.55, 1.21)	2.92 (1.55, 3.78)	-	0.41 (0.30, 0.58)*	0.33 (0.28, 0.39)*
CL/F (mL/hr)	937 (696, 1035)	965 (774, 1287)	424 (378, 714)	-	1.84 (1.45, 2.33)*	2.07 (1.82, 2.34)*
V/F (L)	13.3 (11.5, 17.2)	15.4 (12.9, 19.4)	11.6 (9.7, 16.6)	-	1.09 (0.89, 1.33)	1.30 (1.11, 1.52)*
$T_{1/2}$ (hr)	11.20 (9.02, 12.20)	11.10 (9.42, 12.00)	17.70 (13.70, 21.20)	-	0.59 (0.52–0.67)*	0.63 (0.56, 0.70)*

Data presented as median (Q1, Q3) unless otherwise indicated.

Abbreviations: $AUC_{0–24}$: area under the concentration-time curve from time 0 through 24 hours post-dose; C_{0h}: predose (time 0) concentration; C_{max}: maximum concentration; T_{max}: time to C_{max}; C_{24}: concentration at 24 hours post-dose; C_{min}: minimum concentration; CL/F: apparent oral clearance; V/F: apparent volume of distribution; $t_{1/2}$: half-life.

*p<0.10 compared to postpartum

1Historical data from Bictegravir® package insert, represented as mean (±S.D.)

2Paired comparisons

3For T_{max} and C_{max} n=25

Table 3:

Summary of Delivery Maternal and Cord Blood Bictegravir Pharmacokinetic Parameters

	Median (Q1, Q3)	**< Lower Limit of Quantitation [# (%)][1]**
Cord Blood Plasma Bictegravir (ng/mL) n=17	2310 (1440, 3010)	1 (6%)
Maternal Plasma Bictegravir (ng/mL) n = 17	1770 (994, 2100)	1 (6%)
Ratio Cord Blood/Maternal Blood Bictegravir Concentrations	1.38 (1.17, 1.63)	NA

Abbreviations: Q1– 25th percentile; Q3– 75th perentile.

[1]For concentrations below the lower limit of quantitation of 78 ng/mL, half the limit was substituted