Pharmacokinetics and Virologic Outcomes of Bictegravir in Pregnancy and Postpartum

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Kathleen M. Powis, MD, MPH[1,2], Mauricio Pinilla, MS[2], Lauren Bergam, MS[2], Alice Stek, MD[3], Kristina M. Brooks, PharmD[4], David E. Shapiro, PhD[2], Kevin Knowles[5], Kathleen George, MPH[6], Renee Browning, MSN[7], Nahida Chaktoura, MD, MsGH[8], A. Gretchen Buckler, MD, MPH[8], Priyanka Arora, PhD[9], Brookie M. Best, PharmD, MAS[10], Mark Mirochnick, MD[11,12], Jeremiah D. Momper, PharmD, PhD [10] on behalf of the IMPAACT 2026 Protocol Team

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Harvard T.H. Chan School of Public Health, Boston, MA USA. [3]University of Southern California, Los Angeles, CA, USA, [4]University of Colorado Anschutz Medical Campus, Aurora, CO, USA, [5]Frontier Science & Technology Research Foundation, Inc, Buffalo, NY, USA, [6]FHI 360, Durham, NC, USA, [7]National Institute of Allergy and Infectious Diseases, Rockville, MD, USA [8] National Institute of Child Health and Human Development, Bethesda, MD, USA [9]Gilead Sciences, Inc Foster City, CA, USA, [10] University of California San Diego, San Diego, CA, USA, [11]Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA, [12] Boston Medical Center, Boston, MA, USA

BACKGROUND

Bictegravir (BIC) is a potent HIV-1 integrase strand transfer inhibitor. It is highly protein bound (~99.7%) and eliminated by UGT1A1 and CYP3A metabolism, with these processes altered in pregnancy. Limited data exist on BIC pharmacokinetics (PK) in pregnancy. We describe preliminary BIC PK in pregnancy compared to postpartum, and associated clinical outcomes.

METHODS

- IMPAACT 2026 is an ongoing, nonrandomized, open-label, parallel-group, multi-center phase-IV prospective study of antiretroviral PK in pregnant women living with HIV.
- Intensive steady-state 24-hour PK sampling of oral BIC 50 mg once-daily was performed during the 2nd and 3rd trimesters (2T, 3T) of pregnancy and 6-12 weeks postpartum (PP).
- Total BIC concentrations were measured by a validated LC-MS/MS assay, quantitation limit of 0.078 mcg/mL.
- Geometric mean ratios (GMR) with 90% confidence intervals (CI) were calculated for 2T and 3T vs. PP. Wilcoxon signed rank tests compared PK parameters in 2T and 3T to PP, with p<0.10 considered statistically significant.

TABLE 1. Maternal and Infant Characteristics

Maternal Characteristics	N (%) or Median (Q1, Q3)
2nd Trimester Visit (N = 12)	
Gestational Age (in weeks)	23.9 (21.8, 24.9)
HIV-1 RNA < LLoQ	10 (83%)
Maternal Weight (kg)	87.5 (75.4, 90.5)
Albumin < Lower Limit of Normal Range	4 (33%)
3rd Trimester Visit (N = 26)	
Gestational Age (in weeks)	32.0 (30.9, 33.9)
HIV-1 RNA < LLoQ	23 (88%)
Maternal Weight (kg)	90.8 (75.2, 97.2)
Albumin < Lower Limit of Normal Range	19 (73%)
Delivery Visit (N = 23)	
Gestational Age (in weeks)	39.3 (39.0, 39.7)
HIV-1 RNA < LLoQ	19 (90%)
Maternal Weight (kg)	94.9 (79.5, 101.0)
Albumin < Lower Limit of Normal Range	10 (63%)
Postpartum Visit (N = 19)	
Weeks After Delivery	8.29 (7.29, 10.1)
HIV-1 RNA < LLoQ	13 (76%)
Maternal Weight (kg)	81.7 (67.4, 92.9)
Albumin < Lower Limit of Normal Range	0 (0%)
Infant Outcomes (N = 22)	
Birth Weight (grams)	3408 (3130, 3620)

Abbreviations: kg – kilograms; LLoQ – Lower Limit of Quantitation

Total bictegravir (BIC) exposure was lower in pregnancy than postpartum, but all C24 concentrations were above the estimated BIC protein-adjusted EC_{95} value of ~0.162 mcg/mL and 90% of participants were virally suppressed at delivery.

RESULTS

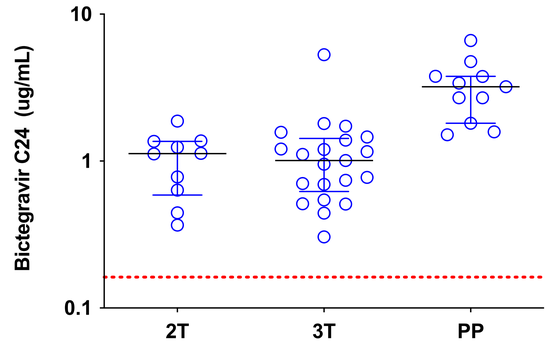
- 27 mother-infant pairs enrolled into the BIC study arm between 1-Sep-21 and 27-Oct-22 (Table1); 12 (44%) enrolled in 2T and 15 (56%) in 3T, with follow-up ongoing and data presented through 30-Jan-23.
- 22 participants reported race/ethnicity, 15 (68%) Black, 4 (18%) white, 2 (9%) Asian, and 1 (5%) American Indian/Alaskan Native. 19 (70%) were non-Hispanic/Latinx; 3 (11%) were Hispanic/Latinx.
- Compared with paired postpartum data, BIC AUC_{tau} was 49% and 56% lower and Cmax was 39% and 50% lower at the 2T and 3T study visits, respectively. (Table 2).
- 6 (60%) and 13 (62%) in 2T and 3T, respectively, had BIC AUC_{tau} < the 10th percentile for non-pregnant adults (58.7 µg*hr/mL), while no PP BIC AUC_{tau} was below the target. No participant with a BIC AUC_{tau} in pregnancy < the10th percentile target had a detectable viral load.
- Of participants with detectible HIV viral loads at any timepoint, only one had a viral load > 200 copies/mL.
- All C24 concentrations were above the estimated BIC protein-adjusted EC_{95} value of ~0.162 mcg/mL.
- Seven grade 3 adverse events were reported (preeclampsia (2), anemia (2), post-op wound infection, hernia pain, and proteinuria). None were deemed related to BIC.
- No infant has been confirmed to have acquired HIV as of 25-Jan-23.

TABLE 2. Median (IQR) Bictegravir Pharmacokinetic Parameters by Noncompartmental Analysis

Parameter	2nd Trimester (N = 10)	3rd Trimester (N = 21)	Postpartum (N = 11)	GMR (90% CI): 2nd Trimester/ Postpartum (N = 4)	GMR (90% CI): 3rd Trimester/ Postpartum (N = 11)
AUC_{tau} (mcg*hr/mL)	53.4 (49.4, 70.3)	51.8 (38.8, 66.9)	126.0 (80.3, 140.0)	0.51 (0.37, 0.70)	0.44 (0.37, 0.53)[1]
C_{24} (mcg/mL)	1.13 (0.59, 1.37)	1.01 (0.69, 1.21)	3.30 (1.81, 3.78)	0.28 (0.19, 0.40)[1]	0.29 (0.23, 0.37)[1]
CL/F (mL/hr)	937 (712, 1013)	965 (747, 1287)	396 (358, 623)	1.97 (1.43, 2.72)	2.27 (1.91, 2.70)[1]
$T_{1/2}$ (hr)	11.2 (9.6, 11.7)	11.3 (9.4, 12.0)	18.3 (15.2, 22.8)	0.48 (0.38, 0.59)	0.58 (0.49, 0.69)[1]
C_{max} (mcg/mL)	4.02 (3.69, 4.90)	3.70 (3.07, 4.66)	8.18 (6.40, 9.39)	0.61 (0.44, 0.84)	0.50 (0.43, 0.58)[1]

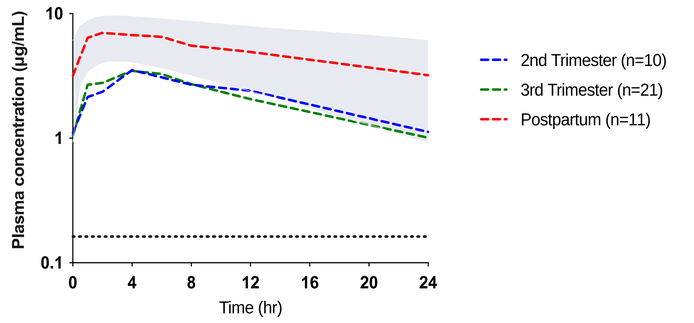
[1]A two sided p-value less than 0.10 was considered statistically significant.
Abbreviations: AUC_{tau}: Area under plasma concentration-time curve over the 24 hour dosing interval; C_{24}: Plasma concentration 24 hours post dose; CL/F: Apparent oral clearance; C_{max}: Maximum observed concentration; GMR (90% CI): Geometric Mean Ratio (90% Confidence Interval); IQR: Interquartile Range; $T_{1/2}$: Elimination half-life

Figure 1: Median Observed BIC Concentration 24 Hours After Dosing by Study Visit



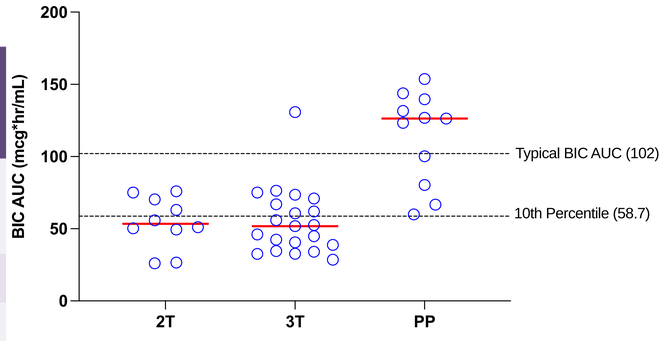
Legend: Red dashed line displays the protein-adjusted EC95 value 361 nM (~0.162 mcg/mL)

Figure 2: Median Concentration vs Time Profiles by Study Visit



Legend: Shaded area displays 10th-90th percentile concentrations in non-pregnant adults. Black dashed line displays the protein-adjusted EC95 value 361 nM (~0.162 mcg/mL)

Figure 3: Bictegravir Participant AUC Results by Study Visit



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