Population Pharmacokinetics of Bictegravir in Pregnant and Postpartum Persons Living with HIV

Steven Sun[1], Mina Nikanjam[2], Mark Mirochnick[3,4], Kathleen M. Powis[5,6], Alice Stek[7], Kristina M. Brooks[8], Brookie M. Best[1], Edmund Capparelli[1], Jeremiah D. Momper[1]

[1]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA; [2]Division of Hematology-Oncology, University of California San Diego, La Jolla, CA; [3]Department of Pediatrics, Boston University Chobanian & Avedisian School of Medicine, Boston, MA; [4]Boston Medical Center, Boston, MA; [5]Massachusetts General Hospital, Boston, MA; [6]Harvard T.H. Chan School of Public Health, Boston, MA; [7]Department of Obstetrics and Gynecology, University of Southern California, Los Angeles, CA; [8]Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO

INTRODUCTION

- Bictegravir is a potent integrase strand transfer inhibitor that prevents HIV-1 viral replication and is widely used in combination with other antiretroviral drugs for HIV-1.[1]
- Bictegravir has demonstrated efficacy in non-pregnant populations, but reductions in bictegravir exposures during pregnancy necessitate a better understanding of changes in its pharmacokinetics (PK) during pregnancy.[2,3]
- While population pharmacokinetic (popPK) models have been developed for bictegravir in adults[4], the popPK of bictegravir in pregnant women living with HIV has not been described.
- Goal: To develop a popPK model of bictegravir to characterize its disposition throughout pregnancy and postpartum in women living with HIV.

METHODS

Study Data:

- IMPAACT 2026 is an open-label, multi-center phase-IV prospective study of antiretroviral PK in pregnant persons living with HIV. Pregnant persons living with HIV of at least 20 weeks gestational age, receiving oral bictegravir 50 mg once daily as part of standard of care, and who were not receiving tuberculosis medications were eligible to enroll. Participants were on therapy for at least 2 weeks prior to study entry.
- Intensive PK sampling was performed in the 2nd trimester, 3rd trimester, and postpartum visits.

Pharmacokinetic analysis:

- A popPK model was developed using nonlinear mixed effects modeling (NONMEM v. 7.5)
- Concentration-time data were fit using first-order conditional estimation (FOCE) method with interaction.
- A one-compartment PK structural model (ADVAN2, TRANS2 subroutine) with first order absorption was initially used to describe the data.
- Age, weight, HIV-1 RNA count, hematocrit, CD4 count, AST, ALT, total bilirubin, albumin, serum creatinine, pregnancy, race (Black/African American), and concomitant tenofovir alafenamide (TAF) were evaluated as potential covariates for apparent clearance (CL/F) and volume of distribution (V/F) using stepwise covariate modeling.
- A forward selection approach with a significance threshold of $p < 0.05$ and a backward selection process with the threshold of $p < 0.01$ was utilized for the multivariable assessment.

Monte Carlo Simulations:

- Monte Carlo simulations of the final model were performed using 2000 virtual subjects to compare the difference in bictegravir PK between pregnancy (3rd trimester) and postpartum.
- Simulated subjects were Black/African American on the FDA approved dosing of 50 mg orally daily.
- Concentration profiles were generated for 1000 subjects with median weight and albumin for the respective 3rd trimester and postpartum period.

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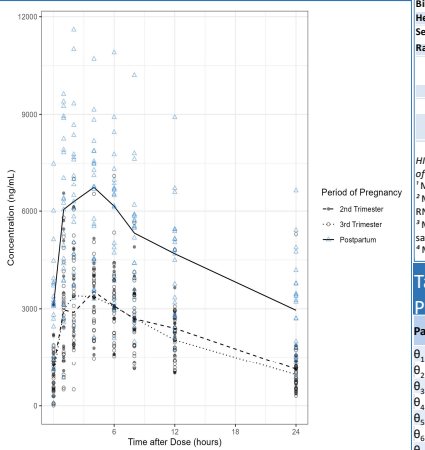
RESULTS

- Data for 27 participants, contributing a total of 508 bictegravir plasma concentrations across all visits were used for analysis.
- A summary of participant's baseline characteristics is summarized in **Table 1**.

Figure 1. Observed Steady-State Bictegravir Concentration vs. Time After Dose



Observed plasma bictegravir concentrations in pregnant and postpartum persons receiving bictegravir 50 mg daily. Dashed, dotted, and solid lines represent the observed median steady-state bictegravir concentrations in 2nd trimester, 3rd trimester, and postpartum, respectively. Shaded circles, open circles, and open triangles represent the raw observed steady-state bictegravir concentrations in 2nd trimester, 3rd trimester, and postpartum.

Table 1. Participant Characteristics

Characteristic	Period		
	2nd Trimester, N = 12[1]	3rd Trimester, N = 27[1]	Postpartum, N = 25[1]
Age (years)	31.1 (22.7, 39.8)	31.8 (17.8, 44.1)	32.1 (18.0, 43.2)
Weight (kg)	87 (56, 122)	90 (46, 149)	80 (44, 141)
HIV-1 RNA (copies/mL)[2]	<20 (<20, 553)	<20 (<20, 429)	<20 (<20, 10,300)
CD4 (cells/mm³)[3]	562 (27, 1,526)	692 (204, 1,814)	851 (817, 884)
AST (U/L)	17 (9, 27)	16 (8, 41)	23 (9, 116)
ALT (U/L)	9 (5, 23)	11 (6, 29)	18 (7, 187)
Albumin (g/dL)	3.60 (3.20, 4.00)	3.30 (2.90, 4.10)	4.50 (3.60, 4.80)
Bilirubin (mg/dL)	0.20 (0.15, 0.70)	0.20 (0.17, 0.90)	0.40 (0.16, 1.70)
Hematocrit (%)	33.5 (28.8, 35.9)	33.1 (25.8, 38.0)	37.8 (33.3, 42.9)
Serum Creatinine (mg/dL)	0.53 (0.40. 0.68)	0.53 (0.40, 0.70)	0.77 (0.56, 1.00)
Race[4]			
Black or African American	7/12 (58%)	15/27 (56%)	14/25 (56%)
White	2/12 (17%)	4/27 (15%)	4/25 (16%)
Asian	1/12 (8.3%)	2/27 (7.4%)	1/25 (4.0%)
American Indian or Alaska Native	0/12 (0%)	1/27 (3.7%)	1/25 (4.0%)
Missing	2/12 (17%)	5/27 (19%)	5/25 (20%)

HIV-1, human immunodeficiency virus type 1; LOD, limit of detection; RNA, ribonucleic acid; CD4, clusters of differentiation 4; AST, aspartate transaminase; ALT, alanine transaminase

[1] Median (Range); n / N (%)

[2] Many participant's HIV-1 RNA counts were below the assay's LOD (< 20 copies). 1 participant with HIV-1 RNA count of 10,300 copies was confirmed to be non-compliant with their treatment regimen.

[3] Missing 23 values from postpartum samples

[4] Most (96%) participants were enrolled in the United States; one was enrolled in Thailand.

Table 2. Final Population Pharmacokinetic Model Parameters and Bootstrap Estimates

Parameters	Final Parameter Estimates	Standard Error of Estimates	Bootstrap Estimates[a] Median (95% CI)
θ_1 (V/F; L)	12.6	0.897	12.5 (10.9 - 14.5)
θ_2 (CL/F; L/h)	0.549	0.0457	0.551 (0.457 - 0.661)
θ_3 (KA; h^{-1})	1.88	0.444	1.88 (1.22 - 3.13)
θ_4 (Pregnancy on CL)	1.61	0.166	1.62 (1.26 - 2.02)
θ_5 (Albumin on CL; g/dL)	-1.13	0.461	-1.12 (-2.12 - -0.22)
θ_6 (Weight on V; kg)	0.636	0.151	0.642 (0.297 - 0.940)
θ_7 (Race on V)	1.32	0.0938	1.33 (1.12 - 1.53)
Variability (η)	**CV (%)**	**Standard Error of Estimates**	**Bootstrap Estimates[a] Median (95% CI)**
Between-subject (V)	8.41	0.0502	6.00 (0.20 - 14.70)
Between-subject (CL)	28.5	0.0414	27.6 (19.2 - 35.2)
Error (ε)	**CV (%)**	**Standard Error of Estimates**	**Bootstrap Estimates[a] Median (95% CI)**
Proportional	28.7	0.0201	28.2 (24.7 – 32.1)

CI, confidence interval; V/F, apparent volume of distribution; CL/F, apparent clearance; KA, first-order absorption rate constant; CV, coefficient of variation

[a] Bootstrap successfully converged 99.3% of the time.

$$CL/F\ (L/hr) = 0.549 \times (Albumin/3.7)^{-1.13} \times (1.61\ if\ pregnant)$$

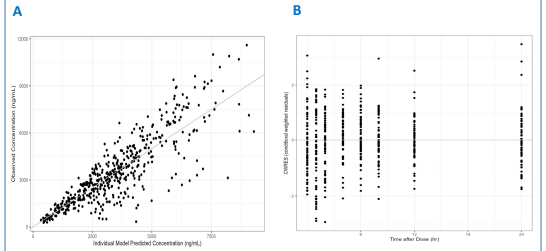
$$V/F\ (L) = 12.6 \times (Weight\ in\ kg/70)^{0.64} \times (1.32\ if\ Race\ is\ Black\ or\ African\ American)$$

CONCLUSIONS

- The current analysis represents the first popPK model of bictegravir in pregnancy.
- Bictegravir V/F is higher in Black/African American participants and those with higher body weight.
- Bictegravir CL/F increases during the 2nd and 3rd trimester of pregnancy and is inversely related to albumin concentration.
- Pregnancy was the most significant covariate in the model and a strong predictor for bictegravir CL/F.
- Monte Carlo simulations in participants receiving bictegravir 50 mg daily showed that >99% of participants in both the 3rd trimester of pregnancy and the postpartum period are anticipated to achieve adequate bictegravir concentrations for HIV-1 suppression, based on the in vitro antiviral activity.[1]
- Despite a higher bictegravir CL/F during pregnancy – leading to lower exposure – a 50 mg daily dose is predicted to achieve therapeutic levels both during pregnancy and postpartum.

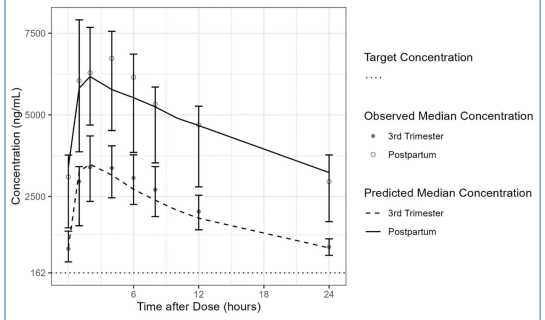
RESULTS

Figure 2. Final Model Diagnostic Plots



Diagnostic plots for the final model. A. Individual predicted bictegravir concentrations vs observed concentrations. Grey line represents the line of unity (y=x). B. Conditional weighted residual values vs time (hr) after dose. Grey line represents y = 0.

Figure 3. Observed Steady-State Bictegravir Concentration and Final Model Monte Carlo Simulation Results



Observed median steady-state bictegravir concentrations and simulated median steady-state bictegravir concentrations. Post-dose Monte Carlo simulations (n = 2000) using the final model of bictegravir PK for pregnant and postpartum persons living with HIV. All simulated participants were Black/African American and received the FDA-approved 50 mg oral dose daily. Shaded circles and open circles represent the median observed steady-state bictegravir concentrations, respectively. The error bars represent the interquartile ranges (25% - 75%) of the observed data. The dashed line and solid line represent the median simulated steady-state bictegravir concentrations. The horizontal dotted line at 162 ng/mL represents the protein-adjusted EC95 pharmacodynamic target for wild-type HIV-1.[1] Despite lower drug levels in pregnancy, bictegravir concentrations are maintained above the therapeutic target.

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