# MECHANISTIC PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING TO PREDICT BICTEGRAVIR DISPOSITION IN PREGNANCY

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## BACKGROUND

Bictegravir (BIC), is a potent HIV-1 integrase strand transfer inhibitor, used in a fixed dose combination (50 mg once a day (QD), orally, with tenofovir alafenamide and emtricitabine (B/F/TAF) [1]. BIC is metabolized by CYP3A4 and UGT1A1 and is highly plasma protein bound (~99.7%) [1]. Pregnancy can affect drug disposition compared to non-pregnant state due to temporal physiological and metabolic changes, including increased CYP3A4 and UGT1A1 activity, as well as varied fraction unbound ($f_u$) [2] leading to altered metabolism and total and unbound plasma concentrations of BIC (Fig 1). Indeed, in the study conducted to investigate steady state pharmacokinetics (PK) of B/F/TAF during pregnancy and postpartum [3], BIC plasma PK parameters ($AUC_{tau}$, $C_{max}$ and $C_{tau}$) were lower during pregnancy compared to postpartum. Higher mean unbound fractions for BIC were observed during second and third trimesters of pregnancy compared to 6 and 12-weeks postpartum.

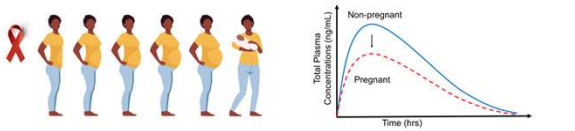


**Fig 1:** Graphical Abstract. (Left) Schematic of HIV-infected women through pregnancy. (Right) Simplified single dose administration representation for visualization of BIC plasma concentration-time profile overlaid for non-pregnant and pregnant women.

## AIMS

1. Develop a BIC PBPK model and validate it with observed study data, to further predict maternal BIC steady-state plasma concentrations at various gestational ages.
2. Gain mechanistic understanding of BIC disposition during pregnancy.

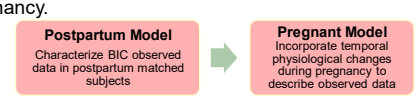


**Fig 2:** Schematic representation of workflow of BIC PBPK model development and validation across gestational ages

## METHODS

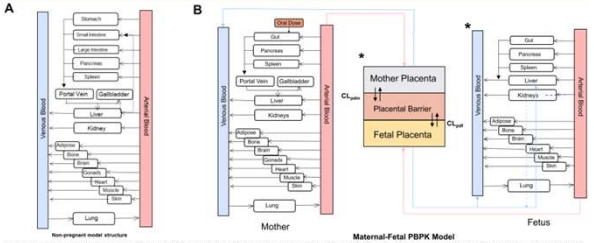


**Fig 3:** Schematic diagram of PBPK Model Structure in Simcyp Simulator v22 (A) Postpartum Model Structure (B) Maternal-Fetal Model Structure along with Permeability-limited Placental Model. Solid arrows indicate tissue blood flows, whereas dashed arrows indicate clearances. f/F, fetal; pd, passive diffusion; m, maternal; p, placental. *Placental Model was not parameterized, and Fetal Predictions were not carried out in this work.

1. The PBPK models were developed using Simcyp Simulator V22
2. BIC physicochemical properties were used to first predict exposures in "Healthy Volunteer" population which was qualified against clinical PK data from postpartum women-12 weeks after delivery. Postpartum PK was assumed to have returned to non-pregnant state [4].
3. All drug-specific parameters, except the $f_u$ were fixed ($f_u$ increases during pregnancy) and the Simcyp Pregnancy model parameters (for eg. pregnancy-specific changes in metabolic enzyme levels/distribution) were used to make predictions in pregnant population in the second and third trimesters.
4. PBPK models were considered qualified if the predicted values were within ±50% deviation from the observed values [5].

## RESULTS

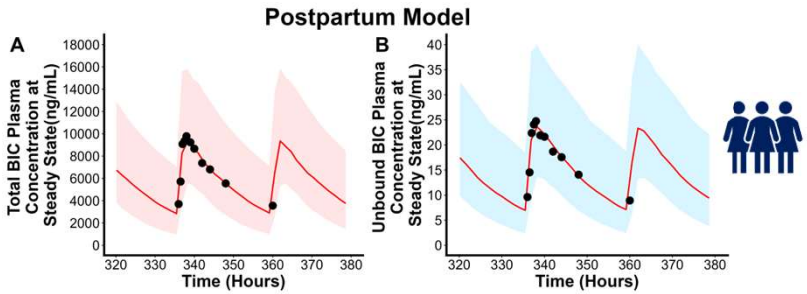


**Fig 4**: Observed and Simulated BIC Plasma concentration-time profiles at Steady State following once-daily administration of BIC 50 mg (as a component of B/F/TAF). Total Plasma concentration-time profiles presented in (A). Unbound Plasma concentration-time profiles presented in (B) Population simulations (n=200) were conducted where red line indicates model-predicted median, the shaded region is the predicted 5th-95th percentile range. Black dots are the observed data medians [3].

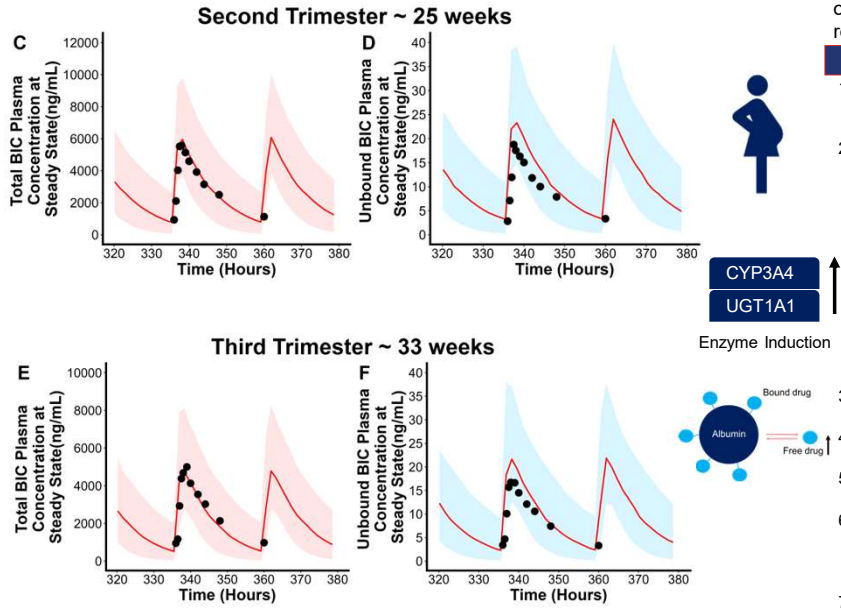


**Fig 5:** Observed and Simulated BIC Plasma concentration-time profiles at Steady State following once-daily administration of BIC 50 mg (as a component of B/F/TAF). Total Plasma concentration-time profiles presented in (C) & (E). Unbound Plasma concentration-time profiles presented in (D) & (F). Observed and simulated data are presented as described for Fig 4.

## RESULTS

**Total BIC Plasma PK Parameters at Steady State (ng/mL)**

| Model | Observed Median | | | Simulated Median (Predicted/Observed) | | |
|---|---|---|---|---|---|---|
| | Tmax (hr) | Cmax (ng/mL) | $AUC_{0\text{-}tau}$ (ng/mL.hr) | Tmax (hr) | Cmax (ng/mL) | $AUC_{0\text{-}tau}$ (ng/mL.hr) |
| Postpartum (12 weeks post delivery) | 1.5 | 10500 | 146,978 | 1.73 (1.15) | 9262.5 (0.88) | 133,647.9 (0.91) |
| Second Trimester (25 weeks Gestation) | 2 | 6090 | 64,108.5 | 1.73 (0.87) | 6092 (1.00) | 63,599.4 (0.99) |
| Third Trimester (33 Weeks Gestation) | 2 | 5340 | 58,575.1 | 1.73 (0.87) | 4759.3 (0.89) | 49,434.9 (0.84) |
| **Unbound BIC Plasma PK Parameters at Steady State (ng/mL)** | | | | | | |
| Postpartum (12 weeks post delivery) | 1.73 | 27 | 359.1 | 1.73 (1.00) | 26.5 (0.98) | 345 (0.96) |
| Second Trimester (25 weeks Gestation) | 1.73 | 19.3 | 205.1 | 1.73 (1.00) | 24.16 (1.25) | 252.8 (1.23) |
| Third Trimester (33 Weeks Gestation) | 1.73 | 19.2 | 199.8 | 1.73 (1.00) | 21.67 (1.12) | 221.8 (1.11) |

**Table 1: Model Validation** (Top) PBPK Predictions of total BIC steady state plasma concentrations in postpartum individuals, pregnant women at 25 weeks gestation followed by pregnant women at 33 weeks gestation. Observed/Predicted ratios for each PK parameter are in parenthesis under "Simulated Median" (Bottom) PBPK predictions of unbound BIC steady state plasma concentrations in the same groups listed previously. All predicted PK parameters met our *a priori* acceptance criteria (within 50% deviation of the observed values). Observed PK parameters were estimated from previously reported data [3].

## DISCUSSION & CONCLUSIONS

1. BIC, as a component of B/F/TAF, is included in international guidelines as first-line therapy for patients living with HIV (PWH). PWH need chronic antiretroviral therapy and may become pregnant, while on a BIC containing regimen [6].
2. Significant physiological and enzymatic changes occur during pregnancy, and the unique binding characteristics of BIC to plasma proteins and its metabolism by CYP3A4 and UGT1A1 enzymes, along with the HIV disease condition, warranted further investigation[3]. Clinical study conducted found lowered BIC plasma concentrations during pregnancy versus postpartum, however all the pregnant women remained virologically suppressed and there was no perinatal transmission to neonates [3]. This was consistent with findings from another study (IMPAACT 2026) [7].
   - Based on the observed data and overall cumulative findings, BIC use as a component of B/F/TAF in the pregnant PWH subpopulation was approved recently by the FDA and the EMA and recommended as an alternative option per the US DHHS guidelines [8]
3. To gain additional mechanistic insight into BIC disposition during pregnancy, PBPK models were built using Simcyp V22 to describe the observed clinical data.
4. Developed pregnancy PBPK model successfully predicted total plasma concentration time profiles of BIC in the second and third trimester.
5. Median unbound plasma exposures were overpredicted by up to +23% from the observed values.
6. While this modeling work assumes 12-week postpartum status as return to normal (non-pregnant) baseline, the clinical study had observed that postpartum exposures of BIC were higher than the historical data in non-pregnant adults with HIV [3]. This phenomenon has been noted with other antiretrovirals [9].
7. Future work will address this knowledge gap by exploration of a "rebound" cytokine effect observed in inflammatory conditions postpartum.

## REFERENCES

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