

Population Pharmacokinetic Modelling of Plasma and Intracellular Bictegrovir in People Living with HIV

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Objectives

Bictegravir is a second-generation human immunodeficiency virus (HIV) integrase strand transfer inhibitor (INSTI) widely used in first-line antiretroviral therapy[1]. In routine care, clinically relevant interindividual variability persists, including virologic non-suppression and treatment discontinuation, as well as reported body weight gain and neuropsychiatric adverse effects with INSTI-based regimens[2,3]. Variability in drug exposure may contribute to these differences. While plasma exposure has previously been modelled[4], bictegravir exposure in peripheral blood mononuclear cells (PBMCs), the intracellular site of viral integration, remains poorly characterized. Developing a joint plasma–PBMC description may therefore provide a quantitative basis for evaluating intracellular exposure variability and future exposure–response relationships.

The aims were to (i) develop a population pharmacokinetic (popPK) model to characterize bictegravir plasma exposure in clinical practice and (ii) link plasma to PBMC concentrations to derive model-based estimates of intracellular exposure and its variability between individuals.

Methods

A retrospective, single-centre study was performed using data from a longitudinal clinical trial (NCT04805944) including bictegravir-treated adults living with HIV. Plasma and PBMC concentrations were collected at scheduled follow-up visits. All participants were genotyped for selected *ABCG2* and *NR1I2* polymorphisms.

The bictegravir pharmacokinetics were characterized using popPK modelling in NONMEM v7.5. One- and two-compartment plasma model structures, different residual error models, and parameter correlations were evaluated. To describe PBMC concentrations, two approaches were evaluated: an intracellular compartment model vs. an effect-compartment model. The influence of demographics (body weight, sex, age) and polymorphisms on structural PK parameters was assessed using stepwise covariate modelling (forward $p \leq 0.05$; backward $p \leq 0.01$). Model selection was based on objective function value comparisons, diagnostic plots, and visual predictive checks. Parameter uncertainty was evaluated by nonparametric bootstrap ($n = 2,000$).

Results

Data from 51 patients yielded 138 plasma and 42 PBMC bictegravir concentrations. Plasma pharmacokinetics were best described by a one-compartment model with linear elimination, a lagged linear absorption and proportional residual error (35%). For a typical patient, clearance was 425 mL/h (relative standard error [RSE]: 6%; interindividual variability [IIV]: 20%), volume of distribution 10,600 mL (RSE: 18%), the absorption rate constant was 2.60 h^{-1} (fixed)[5], and the lag time was 0.24 h (fixed)[5]. PBMC concentrations were best linked to plasma using an effect-compartment model, yielding a steady-state intracellular-to-plasma concentration ratio of 0.04 (RSE: 14%, IIV: 89%), with the effect-compartment rate constant fixed at 0.90 h^{-1} [5]. None of the evaluated demographic or genetic covariates provided statistically significant evidence for reducing interindividual variability, and no covariate effects were retained in the final model.

Conclusion

A plasma popPK model with an effect-compartment link to PBMC concentrations was developed to characterize intracellular bictegravir exposure in routine care. Intracellular exposure exhibited substantial interindividual variability, and no demographic or *ABCG2*/*NR1I2* genetic predictors of PK variability were identified in this cohort. This work provides a quantitative framework for future studies evaluating bictegravir exposure–response relationships and the clinical implications of intracellular drug levels.

References: [1] Gandhi RT et al. JAMA. (2025) 333, 609–628. [2] Rolle C-P et al. Medicine (Baltimore). (2025) 104, e41728. [3] Pérez-Valero I et al. Expert Rev Anti Infect Ther. (2023) 21, 655–665. [4] Sun S et al. J Clin Pharmacol. (2026) 66(1), e70134. [5] U.S. FDA (CDER). Uni-Review – NDA 210251: Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) FDC (BIKTARVY®). (2018). Reference ID: 4217839.