Population Pharmacokinetics of ABC/DTG/3TC FDC to Support Dosing in Peds With HIV-1 (IMPAACT 2019)

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Introduction

- Once-daily fixed-dose combination (FDC) containing abacavir (ABC), dolutegravir (DTG), and lamivudine (3TC) have been approved in the US for adults and children with HIV weighing ≥6 kg[1].
- This analysis assessed the ability of previously developed ABC, DTG, and 3TC pediatric population pharmacokinetic (PopPK) models to describe and predict PK data in young children in the IMPAACT 2019 study[2] (Table 1).

Table 1. ABC/DTG/3TC FDC Dosing in IMPAACT 2019

Weight Band (kg)	Total Daily Dose (ABC/DTG/3TC)
≥6 to <10	180 mg/15 mg/90 mg DT
≥10 to <14	240 mg/20 mg/120 mg DT
≥14 to <20	300 mg/25 mg/150 mg DT
≥20 to <25	360 mg/30 mg/180 mg DT
≥25	600 mg/50 mg/300 mg Tablet

Note: DT = Dispersible Tablet

Methods

- IMPAACT 2019 was a Phase I/II study assessing the PK, safety, tolerability, and efficacy of ABC/DTG/3TC FDC in children with HIV-1[2]. Intensive and sparse PK samples were collected through 48 weeks in the IMPAACT 2019 study.
- Nonlinear mixed effects modeling was performed using NONMEM v7.3. Existing pediatric PopPK models for ABC (2-compartment)[3], DTG (1-compartment)[4], and 3TC (1-compartment)[3] were applied to the IMPAACT 2019 PK data without re-estimation. Individual post-hoc estimates were also compared with observed data.
- PK exposures were then simulated across weight bands for each drug and compared with pre-defined exposure target ranges[2].

This Model-based Approach Leveraged Existing Pediatric Data and Models to Confirm ABC/DTG/3TC FDC DT and Tablet Dosing Using PK Data Collected in IMPAACT 2019

Results

- A total of 55 subjects contributed 598 DTG, 590 ABC, and 597 3TC intensive and sparse PK samples in the current population PK analysis.
- Goodness of fit plots and visual predictive checks demonstrated good agreement between observed and predicted data. The model-based post-hoc PK parameter estimates were also comparable to the non-compartmental analysis (NCA) PK parameter estimates from intensive PK group in IMPAACT 2019 study (Figures 1 to 3).
- Thus, new PopPK models to describe the IMPAACT 2019 study data were not necessary.

Figure 1. NCA Calculated vs. Model Predicted Individual ABC Post-hoc AUC0-24 Values

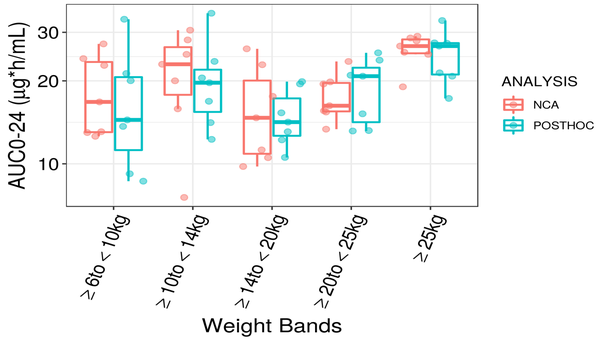

Figure 2. NCA Calculated vs. Model Predicted Individual DTG Post-hoc C24 Values

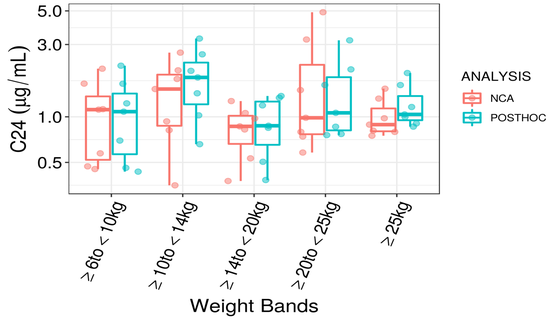

Figure 3. NCA Calculated vs. Model Predicted Individual 3TC Post-hoc AUC0-24 Values

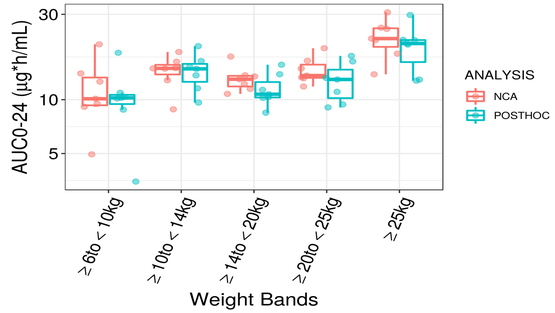

Table 2. Predicted ABC/DTG/3TC FDC Exposures in Pediatrics

Weight Band (kg)	Daily Dose (ABC/DTG/3TC)	ABC AUC0-24 (µg*h/mL)	DTG C24 (µg/mL)	3TC AUC0-24 (µg*h/mL)
≥6 to <10	180 mg/15 mg/ 90 mg DT	**17.36** (6.66 - 43.70)	**0.94** (0.13 - 4.60)	**11.57** (5.82 - 22.36)
≥10 to <14	240 mg/20 mg/ 120 mg DT	**16.66** (6.43 - 41.62)	**0.74** (0.10 - 3.54)	**11.40** (5.79 - 21.66)
≥14 to <20	300 mg/25 mg/ 150 mg DT	**15.47** (5.94 - 39.12)	**0.81** (0.11 - 3.78)	**10.78** (5.49 - 20.6)
≥20 to <25	360 mg/30 mg/ 180 mg DT	**14.89** (5.72 - 37.49)	**0.88** (0.13 - 4.03)	**10.50** (5.34 - 19.96)
≥25	600 mg/50 mg/ 300 mg Tablet	**18.50** (7.00 - 47.70)	**0.95** (0.15 - 4.11)	**13.20** (6.59 - 25.65)
Target GM Range		**6.3 to 50.4**	**0.697 to 2.26**	**6.3 to 26.5**

Note: AUC0-24, Cmax, and C24 presented as a Geometric Mean (90% Prediction Interval)

- The predicted geometric mean exposures were within the pre-defined target range for each drug (Table 2).
- These exposures were comparable to previously observed PK with adults and pediatric participants with individual drugs.

Conclusions

- The previously developed PopPK models were able to describe and predict DTG, ABC, and 3TC PK data in pediatric subjects at each weight band (≥6 kg to <40 kg) in the IMPAACT 2019 study without any clinically relevant bias between dose levels, formulations, or stratified weight bands.
- Overall, the modeling and simulation along with IMPAACT 2019 data support once-daily administration of ABC/DTG/3TC FDC to children living with HIV-1 weighing ≥6 kg.

Acknowledgments: The IMPAACT 2019 study was funded by ViiV Healthcare. Overall support for the IMPAACT network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References: 1. ViiV Healthcare and GlaxoSmithKline. TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension. Package Insert. Research Triangle Park, NC, USA. **2.** https://www.impaactnetwork.org/studies/impaact2019. **3.** https://fda.report/media/92051/N20-977S027-Abacavir-sulfate-Clinpharm-PREA.pdf. **4.** Chandasana et al. *Clin Pharmacokinet.* 2023;62:1445-1459.