BRIEF REPORT

Population Pharmacokinetics of Dolutegravir in African Children: Results From the CHAPAS-4 Trial

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We characterized population pharmacokinetics in 42 African children receiving once-daily 25 mg (14 to <20 kg) or 50 mg (>20 kg) dolutegravir. Coadministration with emtricitabine and tenofovir alafenamide reduced dolutegravir bioavailability by 19.6% (95% confidence interval: 8.13%–30.8%) compared with zidovudine or abacavir with lamivudine. Nevertheless, concentrations remained above efficacy targets, confirming current dosing recommendations.

Key words. children; dolutegravir; HIV; pharmacokinetic; population pharmacokinetics.

INTRODUCTION

The CHAPAS-4 trial evaluated dolutegravir pharmacokinetics in children weighing >14 kg taking dolutegravir with a 250-kcal breakfast combined with emtricitabine/tenofovir alafenamide (FTC/TAF) or a standard of care (SOC) backbone of either lamivudine/abacavir (3TC/ABC) or lamivudine/zidovudine (3TC/ZDV) [1]. We previously reported non-compartmental

pharmacokinetic analysis results, confirming overall concentrations align with reference values of adults and children taking dolutegravir without food, but also showed a reduction in dolutegravir area under the concentration curve (AUC) in children receiving FTC/TAF compared with the other backbones [1, 2]. This did not relate to suppression rates in our study that were higher for TAF-based regimens than for SOC [3]. Previous reports have shown dolutegravir bioavailability with the dispersible tablet (DT) to be 76% higher than the adult film-coated tablet (FCT) of dolutegravir [4], and that food intake facilitates bioavailability of dolutegravir leading to a 41% increase in dolutegravir AUC [5]. Our non-compartmental analysis had limited power to account for differences in body weight and fat-free mass between children, or the overlapping effects of factors such as formulation between groups, leaving some questions for further exploration.

In this secondary analysis, we describe dolutegravir pharmacokinetics using nonlinear mixed-effects modeling and investigate the potential interaction between backbone regimen and dolutegravir, as well as the use of 2 dolutegravir formulations administered with food. We then simulate the probability of maintaining trough concentrations above target thresholds when accounting for covariate effects and parameter variability.

METHODS

In CHAPAS-4 (Children with HIV in Africa—Pharmacokinetics and Acceptability of Simple second-line antiretroviral regimens; #ISRCTN22964075), children received once-daily dolutegravir according to World Health Organization (WHO) recommendations: 25 mg as five 5-mg DT if weighing 14 to <20 kg and one 50-mg FCT if >20 kg [6]. Children were randomized to receive either FTC/TAF or SOC backbone (3TC/ABC or 3TC/ZDV), with daily doses as per Supplementary Table 1. On the day of the pharmacokinetic assessment, at steady state and observed by study staff, dolutegravir was taken with a standardized low-fat breakfast (250 kcal, 5% fat). Blood samples were collected pre-dose, and at 1, 2, 4, 6, 8, 12, and 24 hours post-dose, with an additional sample at 0.5 hours for children taking TAF. Dolutegravir samples were analyzed using a validated liquid chromatography with tandem mass spectrometry method with a lower limit of quantification (LLOQ) of 0.05 mg/L [7].

We developed a population pharmacokinetic model using principles of statistical significance and parsimony (more details in the Supplementary Materials) [8]. We used allometry with either total body weight or fat-free mass to adjust for clearance and disposition parameters. The effects of the 3 backbone drug combinations were tested both as categorical and continuous covariates using TAF or tenofovir (TFV) AUC.

Dolutegravir formulation effects on absorption parameters and biomarkers, including liver enzymes alanine transaminase and aspartate transaminase and creatine clearance (calculated using the Schwartz formula) on elimination were also tested. We used visual predictive checks (VPC) to diagnose both intermediate and final models, and sampling importance resampling to quantify the uncertainty in parameter estimates.

The final model was used to simulate (n = 3000) dolutegravir AUC and 24-hour post-dose plasma concentration (C_{trough}) for children taking dolutegravir with food and with FTC/TAF or SOC backbone, following study dosing guidelines and formulations.

Geometric mean (GM) AUC and C_{trough} were compared with historical references. For AUC, GM was compared with reference values of adults taking 50 mg FCT dolutegravir with food (GM AUC_{0-24}: 53.6 mg·h/L) [9]. GM C_{trough} values were compared with 0.32 mg/L (calculated 90% effective concentration [EC90] of 50 mg dolutegravir FCT obtained in a 10-day adult monotherapy study [10]). The minimal target value for individual dolutegravir concentrations was the protein-adjusted concentration achieving 90% viral suppression in vitro (IC90: 0.064 mg/L) [10]. The percentage of children above the efficacy target in each group is reported.

RESULTS

Between January 2019 and March 2021, 42 children from Uganda, Zambia, and Zimbabwe receiving dolutegravir contributed 358 blood samples (2 below the LLOQ). The children in the study were evenly distributed to receive FTC/TAF or SOC (21 each), 10 weighing 14 to <20 kg received 25 mg dolutegravir DT, 32 above 20 kg received a 50 mg FCT (Supplementary Table 2).

Dolutegravir pharmacokinetics was best described by a 2-compartment model (P < .001) with first-order elimination and absorption, following a series of transit compartments. Incorporating allometric scaling on disposition parameters improved the model fit, with total body weight as the best body size descriptor.

Backbone regimens 3TC/ABC and 3TC/ZDV were combined into SOC after testing the regimens separately revealed no significant difference in effect on dolutegravir bioavailability (Supplementary Table 4). The clearance of a typical child weighing 30 kg taking dolutegravir with SOC backbone, was 0.722 L/h. Children receiving FTC/TAF had 19.6% [95% confidence interval: 8.13%–30.8%] lower bioavailability (and therefore AUC) compared with children on SOC (P < .001). Including TAF or TFV AUC as a continuous covariate did not further improve the model compared with using the backbone regimen as a categorical covariate. Other backbone drug concentrations were not available. Dolutegravir formulation (DT vs FCT) was tested on absorption parameters, including bioavailability, but did not significantly improve the

model fit, nor did biomarkers for liver and kidney function on clearance.

We found moderate between-subject variability in clearance (21.1%) and high between-occasion variability in dolutegravir absorption (98.3%). Allowing the model to estimate larger between-occasion variability in bioavailability when the dose was not observed by study staff (the dose on the day before pharmacokinetic assessment) significantly improved the model fit (P < .001), resulting in 22.1% variability for samples from observed doses to about 75% for the pre-dose samples coming from an unobserved dose.

Final model parameters are in Supplementary Table 3, and diagnostic plots confirming a good fit to the data are in Supplementary Figure 1.

The effect of the backbone combination on expected C_{trough} and AUC was simulated using the final model (Figure 1). GM AUC and C_{trough} values of each subgroup are in Supplementary Table 5. Compared with adults taking 50 mg dolutegravir with food, most subgroups had comparable or higher GM AUC values. However, children weighing 14 to <20 kg taking dolutegravir with FTC/TAF exhibited a 21% lower GM AUC than the adult reference.

In all subgroups, GM C_{trough} consistently exceeded the efficacy target of 0.32 mg/L, with over 99% of individuals in each subgroup above the predefined minimal efficacy target of 0.064 mg/L.

DISCUSSION

In this secondary analysis, we characterized dolutegravir's population pharmacokinetics when taken with food and report that children with FTC/TAF backbone had 19.6% reduced bioavailability (8.13%–30.8% 95% confidence interval) compared with SOC backbone regimens. Simulations showed that the current dosing regimen achieves effective concentrations, with more than 99% of individual C_{trough} values exceeding the minimal efficacy target of 0.064 mg/L, also in children taking FTC/TAF. These results align with the main trial results of CHAPAS-4, which showed over 90% viral suppression with dolutegravir, regardless of backbone combination, and better viral suppression of children on FTC/TAF compared with children on SOC (89% vs 83%) [3].

The cause of decreased dolutegravir bioavailability in combination with FTC/TAF is unclear. Both TAF and dolutegravir are substrates of the transporter P-glycoprotein, with intestinal expression, but this is unlikely to play a role, as TAF is not reported to induce P-glycoprotein and high membrane permeability to dolutegravir should limit the effect transporters have on its intestinal absorption [11]. Moreover, previous studies combining dolutegravir and FTC/TAF in adults didn't observe reduced dolutegravir exposures [9, 12]. Reduced absorption due to a chemical interaction between
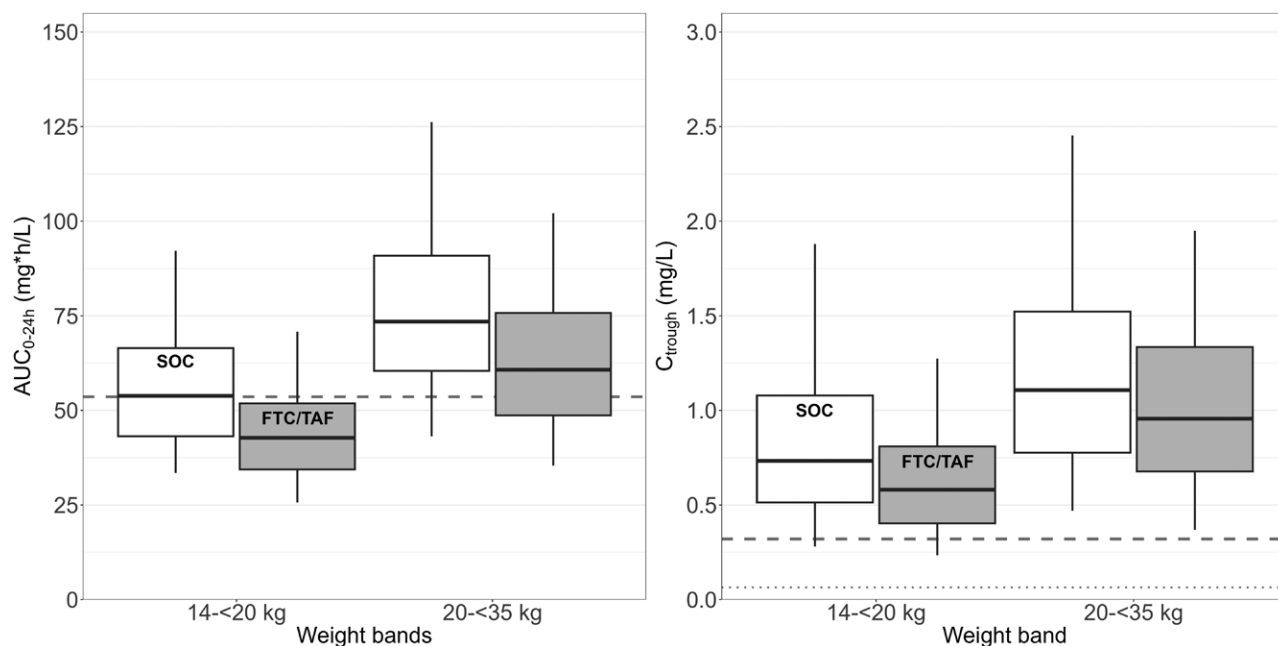
Figure 1. Simulated dolutegravir exposure, area under the concentration curve 0–24 hours (AUC_{0-24h}, left panel) and concentration at 24 hours (C_{trough}, right panel) for children taking dolutegravir with standard of care (SOC; white boxes) or emtricitabine/tenofovir alafenamide (FTC/TAF; gray boxes) in dose and formulation 25 mg dispersible tablet for children 14 to <20 kg and 50 mg film-coated tablet for children weighing more than 20 kg. The boxes represent the 25th, 50th, and 75th percentiles, while the whiskers show the 5th and 95th percentiles. The dashed line in the AUC panel indicates the adult geometric mean AUC_{0-24h} of adults taking 50 mg dolutegravir film-coated tablet with food of 53.6 h·mg/L [8]. The dashed line in the C_{trough} panel indicates the reported 90% effective concentration (EC90) of 0.32 mg/L [9]. The dotted line in the C_{trough} panel indicates the in vitro protein-adjusted dolutegravir IC90 of 0.064 mg/L, the minimal target for efficacy.

the drugs or excipients in the formulation at the absorption site cannot be ruled out.

We observed no difference in bioavailability between the FCT and the DT. Chandasana et al reported higher bioavailability of DT compared with FCT in a cohort of young children who mostly took dolutegravir without food [13]. This aligns with the 76% increased DT bioavailability compared with FCT in children without food in the ODYSSEY trial [4]. In our analysis, this formulation effect was not observed. We hypothesize that food intake may be 1 potential explanation for this observation, since children in our study all took dolutegravir with breakfast. While food might facilitate the dissolution of the FCT, enhancing absorption, DT might fully dissolve even without food, possibly negating any difference seen between the formulation taken on an empty stomach. Our values of CL/F for dolutegravir in combination with SOC (0.722 L/h) were similar to those of Chandasana's 1-compartment model (0.700 L/h at 30 kg), despite our model structure identifying 2-compartment disposition. The difference in model structure may be due to differences in the sampling schedule between the studies and or our handling of the additional uncertainty in the pre-dose samples. These samples, after an unobserved dose, may suffer from additional uncertainty and variability arising from imprecisely reported dosing times and varying dosing conditions at home (eg, food intake). By including extra variability for the pre-dose

sample in our model, we were able to better characterize the kinetics based on the more "reliable" samples collected after the observed dose. Furthermore, 2-compartment kinetics has been reported in adult dolutegravir models [12].

CONCLUSION

In this analysis, we characterized dolutegravir population pharmacokinetics in children weighing >14 kg taking dolutegravir with food. We report a modest decrease in dolutegravir bioavailability when combined with a backbone of FTC/TAF vs SOC, but concentrations remain in the therapeutic range. Of note, we did not observe the large reduction in bioavailability previously observed for the FCT compared with DT, possibly due to dosing with food. Our results support the current recommendations on dolutegravir use in children.

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Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

Notes

Author Contributions

HW managed the pharmacokinetic studies, modeled the pharmacokinetic data, and wrote the paper. PD and RW oversaw the modeling process and contributed to manuscript writing. HM, AC, and DMB supervised the conduction of the pharmacokinetic studies, providing valuable input on the project and manuscript writing. AB served as the pediatrician for the trial and provided valuable insights for the manuscript. DG acted as the trial's principal investigator, providing valuable input on the manuscript.

Data Availability

MRC CTU at UCL supports a controlled access approach based on the completion of a data request proforma available from the corresponding author.

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