

Population Pharmacokinetic Analysis of Emtricitabine (FTC) in Adolescents and Children With HIV-1

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Conclusions

- A population pharmacokinetic (PK) model was developed to describe FTC (F) PK in adolescents and children with HIV-1
- Body weight and select treatment regimens (boosted atazanavir [ATV] + F/tenofovir alafenamide [TAF], boosted darunavir [DRV] + F/TAF, elvitegravir [E]/cobicistat [C]/F/TAF, lopinavir/ritonavir [LPV/r] + F/TAF, and bictegravir [B]/F/TAF) were identified as significant covariates on FTC PK
- Simulations of FTC steady-state exposures following weight band–based dosing of FTC-containing regimens (120 mg once daily [QD; 14-< 25 kg] or 200 mg QD [≥ 25 kg]) support the proposed FTC doses for these combination regimens

Introduction

- FTC is a nucleoside reverse transcriptase inhibitor that has demonstrated potent and selective inhibition of HIV
- It is usually co-formulated with TAF or tenofovir disoproxil fumarate (TDF)
- In adults with HIV, FTC is administered as a 200-mg QD dose concurrently with other antiretroviral drugs

Objective

- To develop a population PK model of FTC in children and adolescents with HIV-1
- To evaluate the effects of intrinsic and extrinsic factors on FTC PK
- To simulate steady-state exposures of FTC using the final models in children with HIV-1 aged ≥ 2 years and weighing ≥ 14 kg, treated with various FTC-containing combination regimens

Methods

- Data were pooled from six Phase 2/3 studies of FTC-containing regimens in children and adolescents with HIV-1 aged 2 to <18 years
- The population PK analysis was conducted in NONMEM v7.5¹
- Population and individual model parameters were estimated using the stochastic approximation expectation maximization method followed by Monte Carlo importance sampling
- A full covariate modeling approach was implemented to evaluate covariate effects
- Monte Carlo simulations were conducted using the final model parameters
 - Steady-state exposure metrics were evaluated over 1000 simulation replicates in a virtual population sampled from the NHANES database,² stratified by sex and weight groups of interest (i.e., 14-< 25 kg, 25-< 35 kg, ≥ 35 kg)
 - Simulated FTC doses were 120 mg QD (14-< 25 kg) or 200 mg QD (≥ 25 kg)

Results

Data Disposition

- The FTC PK analysis dataset included 4597 PK observations from 437 pediatric participants
- Continuous and categorical covariates of the analysis population are summarized in **Table 1**

Table 1. Summary of baseline covariates in analysis dataset

	Summary (N = 437)		Summary (N = 437)
Body weight, n (%)		Race, n (%)	
≥ 35 kg	252 (57.7)	White	9 (2.1)
25 to < 35 kg	106 (24.3)	Black or African American	333 (76.2)
14 to < 25 kg	79 (18.1)	Asian	66 (15.1)
Patient status, n (%)		Other	29 (6.6)
HIV treatment naïve	337 (77.1)	Body weight, kg	
HIV treatment experienced and virologically suppressed	100 (22.9)	Mean (SD)	40.2 (17.5)
eGFR,^a mL/min/1.73m²		Median (Range)	37.6 (14.1, 123)
Mean (SD)	155 (28.3)	Treatment, n (%)	
Median (Range)	152 (89.0, 283)	B/F/TAF	122 (27.9)
Sex, n (%)		E/C/F/TAF	176 (40.3)
Female	238 (54.5)	E/C/F/TDF	50 (11.4)
Male	199 (45.5)	ATV/co + F/TAF	29 (6.6)
Age, years		DRV/co + F/TAF	22 (5.0)
Mean (SD)	11.6 (3.83)	ATV/r + F/TAF	1 (0.2)
Median (Range)	12.0 (3, 17)	DRV/r + F/TAF	1 (0.2)
		LPV/r + F/TAF	23 (5.3)
		F/TAF + other (unboosted)	13 (3.0)

^aeGFR: estimated glomerular filtration rate calculated by Schwartz equation.

Model Development

- FTC PK were characterized by a two-compartment model with five transit compartments followed by first-order absorption and first-order elimination. Fixed and random effect parameter estimates are presented in **Table 2**
- FTC exposure decreased with increasing body weight for weight band–based dosing
- There was a trend of higher FTC exposure from boosted ATV + F/TAF or boosted DRV + F/TAF, relative to a reference subject receiving B/F/TAF (**Figure 1**)
- Exposure from E/C/F/TAF was also slightly higher than the reference. Exposure from LPV/r + F/TAF was slightly lower than B/F/TAF (**Figure 1**)

References: 1. Beal S.L., Sheiner L.B., Boeckmann A.J. & Bauer R.J. (Eds). NONMEM 7.4 users guides (ICON plc, Gaithersburg, MD, 1989-2018). 2. National Center for Health Statistics. National Health and Nutrition Examination Survey (NHANES) 2017-2020. Retrieved from <https://www.cdc.gov/nchs/nhanes>.

Acknowledgments: These studies were sponsored by Gilead Sciences. We thank all study participants and all participating study investigators and staff. **Abbreviations:** AUCtau, area under the concentration time curve in the dosing interval; ATV, atazanavir; B, bictegravir; Cmax, maximum concentration in the dosing interval; co/C, cobicistat; CV, coefficient of variation; DRV, darunavir; EVG/E, elvitegravir; eGFR, estimated glomerular filtration rate; EU, European Union; F/FTC, emtricitabine; HIV, human immunodeficiency virus; LPV, lopinavir; r, ritonavir; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic(s); QD, once daily; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Disclosures: XW, SK, AW, VAV and YZ: employees of Gilead and own stocks/shares in Gilead.

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Plain Language Summary

- Emtricitabine (FTC) is a drug that effectively inhibits HIV-1
- Researchers combined data from six studies to understand how FTC levels in blood change over time in children and teenagers with HIV-1
- They found that body weight and specific treatment plans affect FTC levels
- Researchers used simulations to predict how FTC levels would stabilize over time when given in doses based on different weight groups
- These simulations showed that the proposed FTC doses for different weight groups are safe, effective, and appropriate for combination treatments

Results

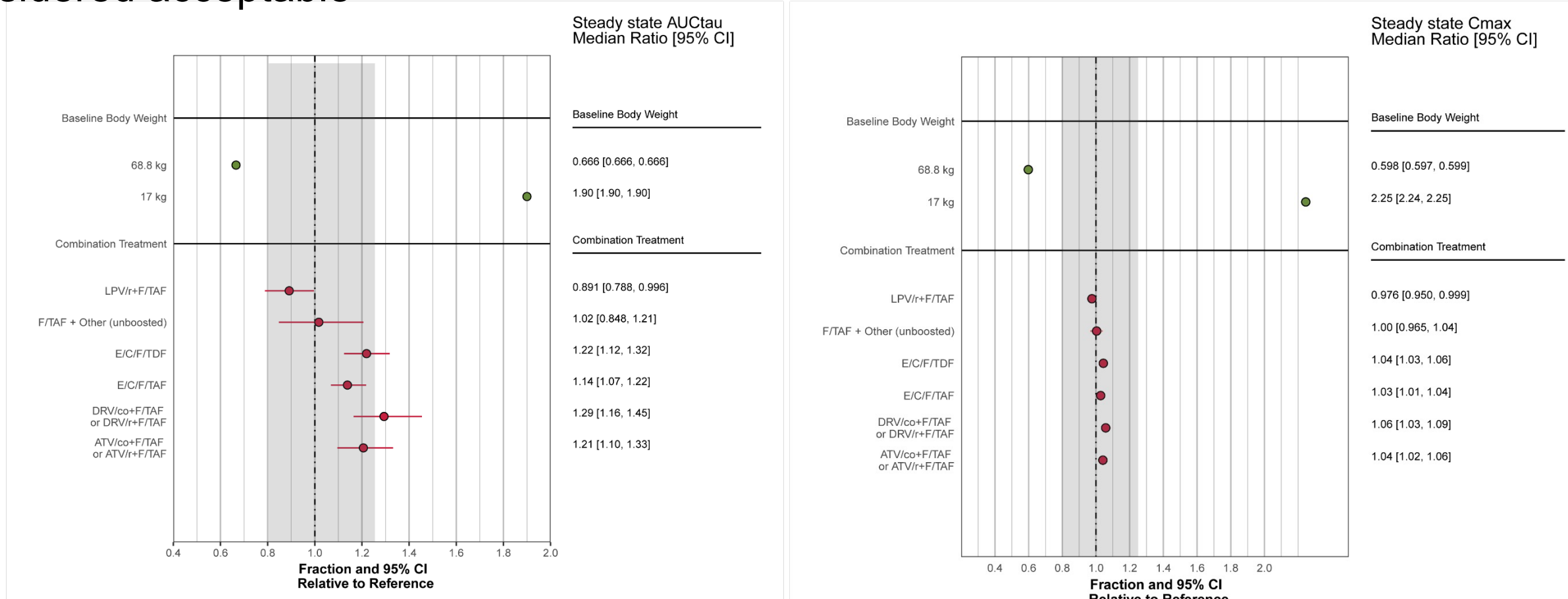
Table 2. Final FTC model fixed and random effect parameter estimates

Parameter	Description	Fixed Effect		Random Effect			Shrinkage
		Value	95% CI ^b	SD	CV% ^a	95% CI	
CL/F	Apparent clearance (L/hr)	12.1	11.6, 12.7	0.0464	21.8%	0.0367, 0.0561	9.25%
Vc/F	Apparent central volume (L)	64.4	61.4, 67.5	0.0496	22.5%	0.0222, 0.0770	37.4%
Q/F	Apparent intercompartmental clearance (L/hr)	1.80	1.63, 1.98				
Vp/F	Apparent peripheral volume (L)	133	102, 173				
MTT	Mean transit time (hr)	0.696	0.586, 0.826	1.36	170%	1.07, 1.64	16.1%
KA	First-order absorption rate (1/hr)	3.75	2.76, 5.11				
CL/F ~ B/F/TAF	B/F/TAF effect on clearance	1.14	1.07, 1.22	-	-	-	-
CL/F ~ E/C/F/TDF	F/TDF effect on clearance	0.934	0.859, 1.01	-	-	-	-
CL/F ~ boosted ATV + F/TAF	ATV/co + F/TAF or ATV/r + F/TAF effect on clearance	0.945	0.865, 1.03	-	-	-	-
CL/F ~ boosted DRV + F/TAF	DRV/co + F/TAF or DRV/r + F/TAF effect on clearance	0.879	0.787, 0.982	-	-	-	-
CL/F ~ LPV/r + F/TAF	LPV/r + F/TAF effect on clearance	1.28	1.15, 1.42	-	-	-	-
CL/F ~ other treatment + F/TAF	F/TAF with other (unboosted) treatment effect on clearance	1.12	0.958, 1.32	-	-	-	-
σ	Proportional residual error	-	-	0.458		0.436, 0.480	-

^aCV% is derived from SD: $\sqrt{\exp(SD^2)-1} \times 100\%$. ^bCI = estimate $\pm 1.96 \times$ standard error. Parameters and CIs estimated in the log-domain were back-transformed for clarity. Allometric scaling with fixed exponents (0.75 for clearances and 1 for volumes) was included in the model. Categorical covariate effects were modeled as proportional. The reference treatment is E/C/F/TAF with an FTC dose of 200 mg.

Figure 1. Forest plot for final model estimated covariate effects on FTC steady-state AUCtau and Cmax

- Although FTC exposure changed ~2 fold across the body weight range, simulations indicated that the exposure was largely contained within the range of adult exposure and, therefore, considered acceptable

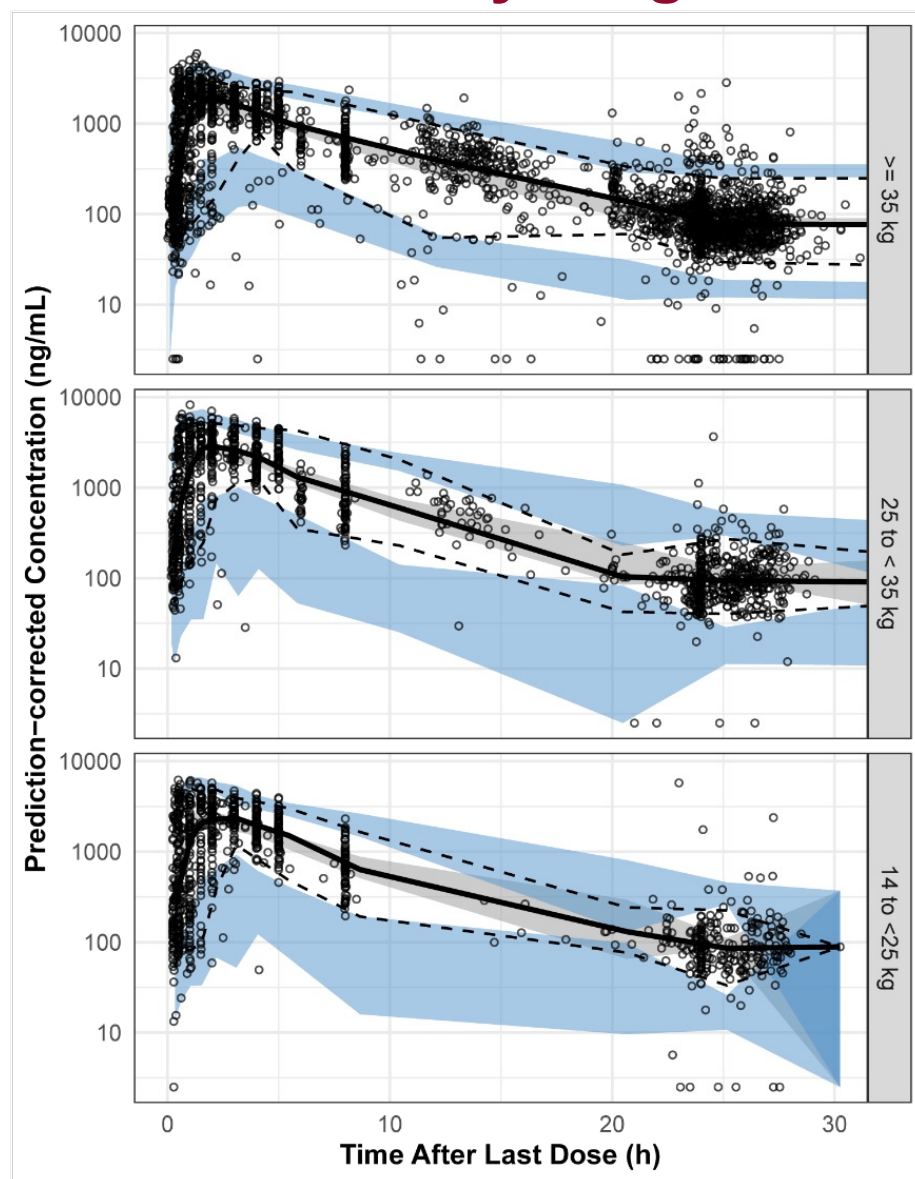


The reference subject is an individual weighing 40 kg and treated with B/F/TAF at an FTC dose of 200 mg. Points represent the estimated median effect. Horizontal bars represent the 95% CIs of the estimated effects. An FTC dose of 120 mg was simulated for a subject with a body weight of 17 kg.

Model Evaluation

- Prediction-corrected visual predictive checks (pcVPCs) (**Figure 2**) indicated adequate performance of the FTC model across pediatric body weight bands

Figure 2. Final FTC model pcVPCs by baseline body weight bands

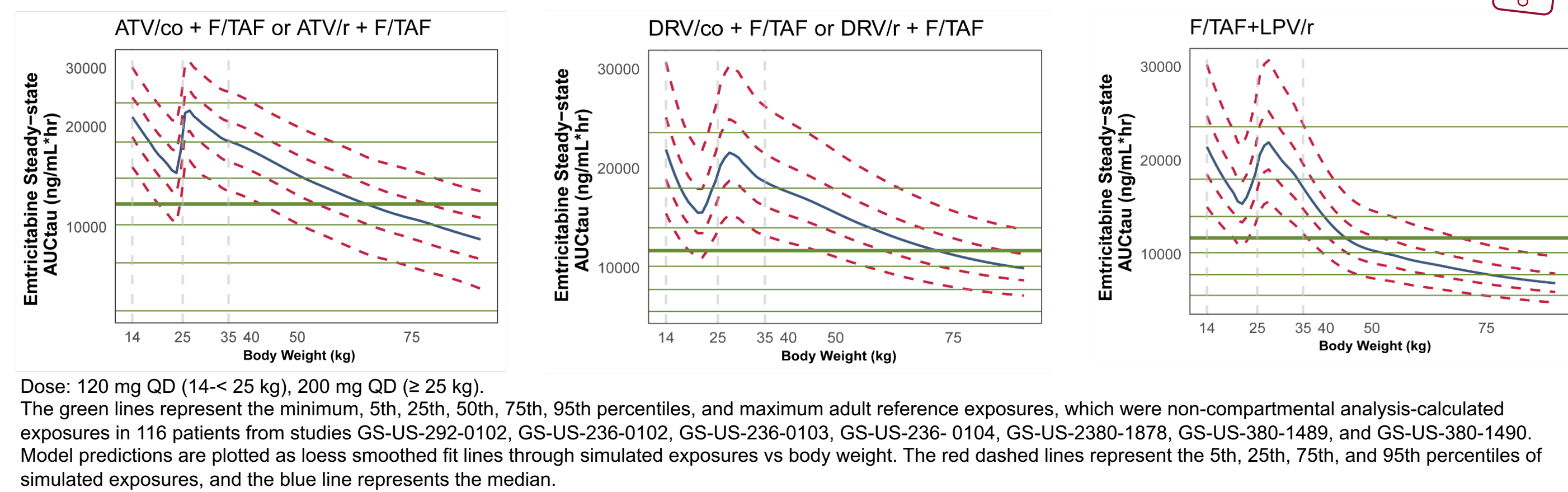


Black points represent the observed data. Observed data are summarized as the median (solid black line) and 5th and 95th percentiles (dashed black lines). Percentiles are overlaid by the simulated 95% CIs from the final model (shaded areas).

Simulations

- Simulated FTC steady-state exposures for children with HIV-1 aged ≥ 2 years and weighing ≥ 14 kg, treated with various FTC-containing combination regimens (E/C/F/TAF, boosted ATV + F/TAF, boosted DRV + F/TAF, LPV/r + F/TAF, and B/F/TAF) were largely contained within the range observed in the adult reference (**Figure 3**)

Figure 3. Population simulations for steady-state FTC AUCtau following administration of various FTC treatment regimens



Dose: 120 mg QD (14-< 25 kg), 200 mg QD (≥ 25 kg). The green lines represent the minimum, 5th, 25th, 50th, 75th, 95th percentiles, and maximum adult reference exposures, which were non-compartmental analysis-calculated exposures in 116 patients from studies GS-US-292-0102, GS-US-236-0102, GS-US-236-0103, GS-US-236-0104, GS-US-2380-1878, GS-US-380-1489, and GS-US-380-1490. Model predictions are plotted as loess smoothed fit lines through simulated exposures vs body weight. The red dashed lines represent the 5th, 25th, 75th, and 95th percentiles of simulated exposures, and the blue line represents the median.