

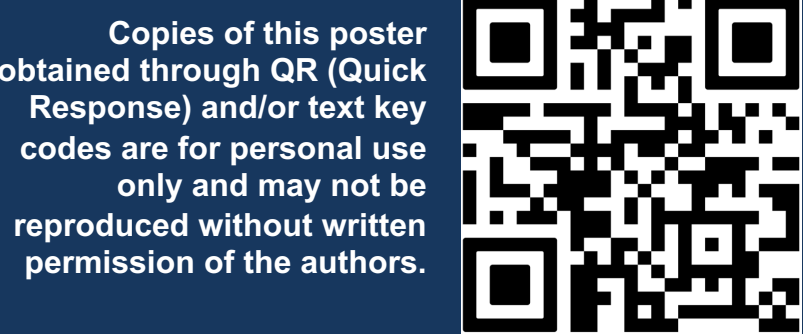
Population Pharmacokinetic Analysis of Tenofovir Alafenamide (TAF) and Tenofovir (TFV) in Adolescents and Children With HIV-1

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Conclusions

- A sequential population pharmacokinetic (PK) model was developed to describe TAF and TFV PK following administration of TAF-containing regimens in adolescents and children with HIV-1
- Body weight and select treatment regimens (elvitegravir [E]/cobicistat [C]/emtricitabine [F]/TAF and boosted atazanavir [ATV] + F/TAF for TAF; lopinavir/ritonavir [LPV/r] + F/TAF, E/C/F/TAF, boosted darunavir [DRV] + F/TAF, boosted ATV + F/TAF, unboosted F/TAF + other for TFV) were identified as significant covariates on TAF and TFV PK
- Simulations of TAF and TFV steady-state exposures following weight band-based dosing of TAF-containing regimens support the proposed TAF doses for these combination regimens

Introduction

- TAF is an oral prodrug of TFV, a nucleotide analog that inhibits HIV-1 reverse transcription
- TAF has been evaluated in a broad range of adult and pediatric participants (e.g., treatment naïve, virologically suppressed, etc.)
- In the US, F/TAF 200/25 mg is indicated for the following uses:
 - In combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in adults and pediatric patients weighing ≥ 35 kg (approved dose is 200/25 mg)
 - In combination with other ARV agents other than protease inhibitors that require a cytochrome P450 (CYP)3A inhibitor for the treatment of HIV-1 infection in pediatric participants weighing ≥ 14 kg and < 35 kg (approved dose is 200/25 mg for body weight of 25- < 35 kg and 120/15 mg for body weight of 14- < 25 kg)
- In the EU, F/TAF 200/25 mg is approved for use with unboosted ARV agents in adults and adolescents aged ≥ 12 years and weighing ≥ 35 kg; F/TAF 200/10 mg is approved for use with boosted ARV agents in adults and adolescents aged ≥ 12 years and weighing ≥ 35 kg

Objective

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

Methods

- Data were pooled from five Phase 2/3 studies 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 TAF doses were 6 mg once daily (QD; 14- < 25 kg) or 10 mg QD (≥ 25 kg) for E/C/F/TAF, and 15 mg QD (14- < 25 kg) or 25 mg QD (≥ 25 kg) for all other regimens

Results

Data Disposition

- The TAF PK analysis dataset included 2507 PK observations from 382 pediatric participants
- The TFV PK analysis dataset included 3904 observations from 395 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 = 488)
Sex, n (%)	
Female	221 (57.4)
Male	164 (42.6)
Race, n (%)	
White	8 (2.1)
Black	297 (77.1)
Asian	52 (13.5)
Other	28 (7.3)
Patient status, n (%)	
HIV treatment experienced and virologically suppressed	335 (87.0)
HIV treatment naïve	50 (13.0)
Treatment, n (%)	
ATV/co + F/TAF	29 (7.5)
ATV/r + F/TAF	1 (0.3)
B/F/TAF	122 (31.7)
DRV/co + F/TAF	22 (5.7)
DRV/r + F/TAF	1 (0.3)
E/C/F/TAF	174 (45.2)
F/TAF + Other (unboosted)	13 (3.4)
LPV/r + F/TAF	23 (6.0)
Age, years	
Mean (SD)	11.1 (3.8)
Median (Range)	11.0 (3.0, 17.0)
Body weight, kg	
Mean (SD)	38.0 (16.7)
Median (Range)	35.0 (14.1, 123)
eGFR,^a mL/min/1.73m²	
Mean (SD)	156 (28.6)
Median (Range)	153 (89.0, 284)

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

References: 1. Beal S.L., Sheiner L.B., Boeckmann A.J. & Bauer R.J. (Eds). NONMEM 7.4 user 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>.

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Abbreviations: AUC_{tau}, area under the concentration time curve in the dosing interval; ARV, antiretroviral; ATV, atazanavir; B, bictegravir; co/C, cobicistat; CV, coefficient of variation; CYP3A, cytochrome P450 3A; DRV, darunavir; E, elvitegravir; eGFR, estimated glomerular filtration rate; EU, European Union; F, emtricitabine; HIV-1, human immunodeficiency virus type 1; LPV, lopinavir; r, ritonavir; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic(s); QD, once daily; SD, standard deviation; TAF, tenofovir alafenamide; TFV, tenofovir; TDF, tenofovir disoproxil fumarate.

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Results

Model Development

TAF

- TAF PK were characterized by a one-compartment model with lag-time, sequential zero-order release, first-order absorption, and first-order elimination (**Figure 1**). Fixed and random effect parameter estimates are presented in **Table 2**
- The M3 method was implemented given the large proportion of samples below the limit of quantification
- TAF exposure decreased with increasing body weight for weight band-based dosing. Compared to a reference subject receiving bictegravir (B)/F/TAF at the same TAF dose, combination treatments of E/C/F/TAF and boosted ATV + F/TAF were associated with increased TAF exposures, while other combination treatments (LPV/r + F/TAF, boosted DRV + F/TAF, unboosted F/TAF + other) had a small or no effect on TAF exposures (**Figure 3**)

TFV

- TFV PK were characterized by a two-compartment model with input from the TAF central compartment and first-order elimination (**Figure 1**). Individual empirical Bayes estimates from the TAF final model were used to generate inputs for this sequential TAF-TFV model. Fixed and random effect parameter estimates are presented in **Table 3**
- TFV exposure decreased with increasing body weight for weight band-based dosing of TAF. Compared to the reference subject receiving B/F/TAF at the same TAF dose, combination treatments of LPV/r + F/TAF, E/C/F/TAF, boosted DRV + F/TAF, and boosted ATV + F/TAF were associated with increased TFV exposures, while unboosted F/TAF + other treatment resulted in decreased TFV exposures (**Figure 3**)

Figure 1. Sequential TAF-TFV model scheme

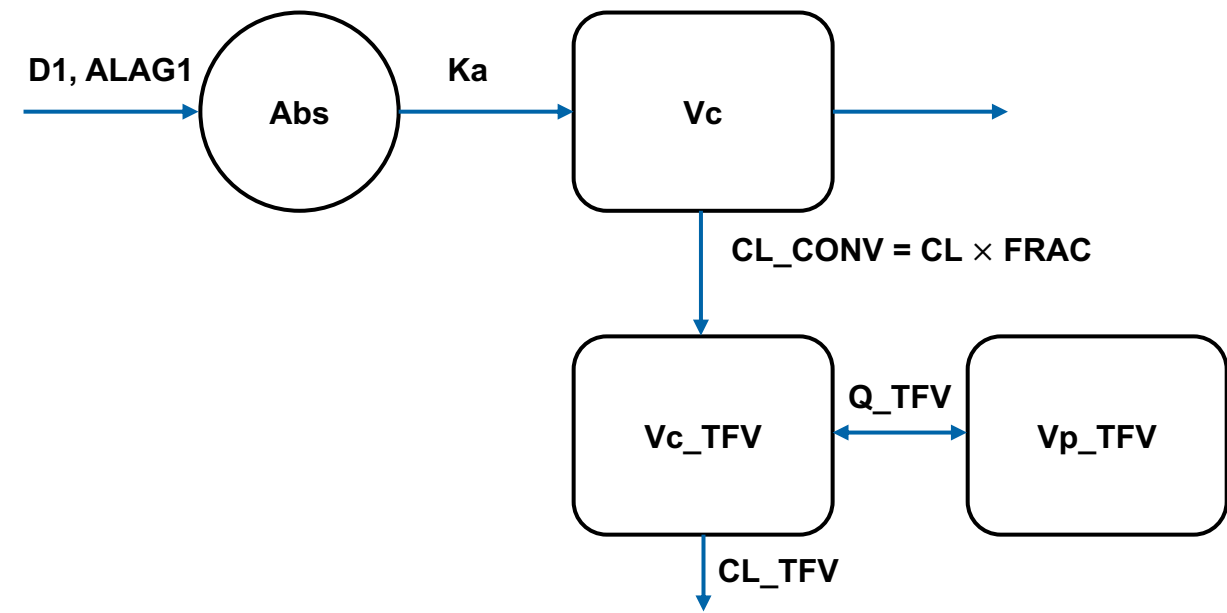


Table 2. Final TAF model fixed and random effect parameter estimates

	Fixed Effect		Random Effect		Shrinkage
	Value	95% CI	Variance	95% CI	
Apparent clearance, CL/F (L/h)	30.8	27.2, 34.9	0.281 [CV%=58.0]	0.205, 0.358	28.1%
Apparent central volume, V/F (L)	28.0	22.9, 34.1	1.30 [CV%=163]	0.893, 1.70	25.5%
First-order absorption rate, KA (1/h)	1.94	1.75, 2.16	0.0250 [CV%=15.9]	FIXED	64.3%
Zero-order release duration to depot, D1 (h)	0.104	0.0943, 0.115	0.0250 [CV%=15.9]	FIXED	86.1%
Absorption lag time, ALAG1 (h)	0.151	0.124, 0.184	1.05 [CV%=136]	0.689, 1.41	27.5%
D1 multiplier for LPV/r + F/TAF	6.67	4.67, 9.54	-	-	-
D1 multiplier for B/F/TAF	7.31E-04	6.29E-04, 8.50E-04	-	-	-
D1 multiplier for F/TAF + other (unboosted)	1.34	0.667, 2.69	-	-	-
CL/F multiplier for boosted DRV + F/TAF	2.58	1.96, 3.39	-	-	-
CL/F multiplier for boosted ATV + F/TAF	0.883	0.719, 1.08	-	-	-
CL/F multiplier for LPV/r + F/TAF	4.09	3.01, 5.55	-	-	-
CL/F multiplier for B/F/TAF	2.93	2.44, 3.53	-	-	-
CL/F multiplier for F/TAF + other (unboosted)	3.12	2.42, 4.02	-	-	-
CL/F multiplier for treatment-naïve health status	1.34	0.997, 1.81	-	-	-
Clearance-central volume correlation	-	-	0.0895 [Corr=-0.148]	-0.0157, 0.195	-
Proportional residual error, σ	-	-	0.943	0.882, 1.00	-
Additive residual error	-	-	0.500	FIXED	-

Allometric scaling with fixed exponents (0.75 for clearances and 1 for volumes) was included in the model. Covariates were parameterized with treatment-experienced and virologically suppressed health status and E/C/F/TAF as the reference.

Table 3. Final TFV model fixed and random effect parameter estimates

	Fixed Effect		Random Effect		Shrinkage
	Value	95% CI	Variance	95% CI	
Apparent TFV clearance, CL _{TFV} /F _{TFV} (L/h)	10.5	10.1, 10.9	0.0654 [CV%=26.0]	0.0462, 0.0846	8.72%
Apparent TFV peripheral volume, V _{TFV} /F _{TFV} (L)	871	799, 950	0.223 [CV%=50.0]	0.0417, 0.405	43.7%
Apparent TFV intercompartmental clearance, Q _{TFV} /F _{TFV} (L/h)	3780	2240, 6370	-	-	-
Fraction of TAF converted to TFV, FRAC	0.593	FIXED	-	-	-
CL _{TFV} /F _{TFV} multiplier for boosted DRV + F/TAF	1.07	0.888, 1.29	-	-	-
CL _{TFV} /F _{TFV} multiplier for boosted ATV + F/TAF	0.931	0.846, 1.02	-	-	-
CL _{TFV} /F _{TFV} multiplier for LPV/r + F/TAF	0.846	0.732, 0.978	-	-	-
CL _{TFV} /F _{TFV} multiplier for B/F/TAF	2.35	-	-	-	-
CL _{TFV} /F _{TFV} multiplier for F/TAF + other (unboosted)	3.93	3.31, 4.67	-	-	-
Additive residual error (log scale)	-	-	0.0932 [SD=0.305]	0.0752, 0.111	-

Allometric scaling with fixed exponents (0.75 for clearances and 1 for volumes) was included in the model. Covariates were parameterized with E/C/F/TAF as the reference. $F_{TFV} = F_{TAF} \times FRAC$ where F_{TFV} is the relative bioavailability of TFV, F_{TAF} is the relative bioavailability of TAF, FRAC is the fraction of TAF converted to TFV.

Plain Language Summary

- Tenofovir alafenamide (TAF) is a drug used to treat children and adults with HIV-1. It is given together with other drugs to treat HIV
- TAF is called a pro-drug and needs to be broken down by the body to turn into tenofovir (TFV), which is the active form of the drug
- Information from five clinical studies was combined to make a model that explains how much TAF and TFV is found in the body over a certain time in children and adolescents with HIV-1
- In the model, body weight and the type of treatment regimens were found to affect how much TAF and TFV were found in the body over time
- Models showed that proposed doses of TAF based on weight should be used in children and adolescents with HIV-1

Model Evaluation

- Prediction-corrected visual predictive checks (pcVPCs) (**Figure 2**) indicated adequate performance of the TAF and TFV models overall and by baseline body weight bands

Figure 2. Final TAF and TFV model pcVPCs by baseline body weight bands

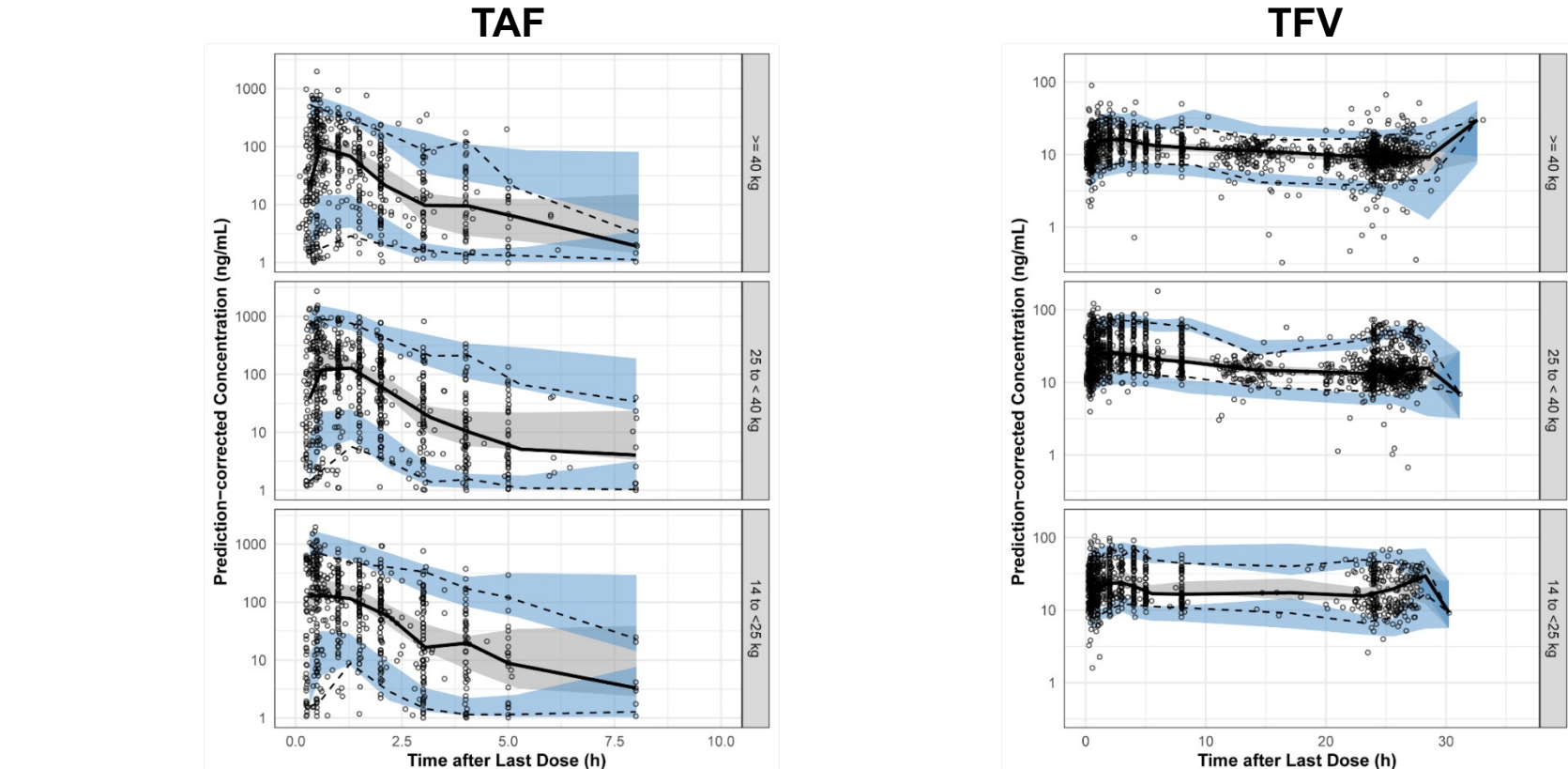
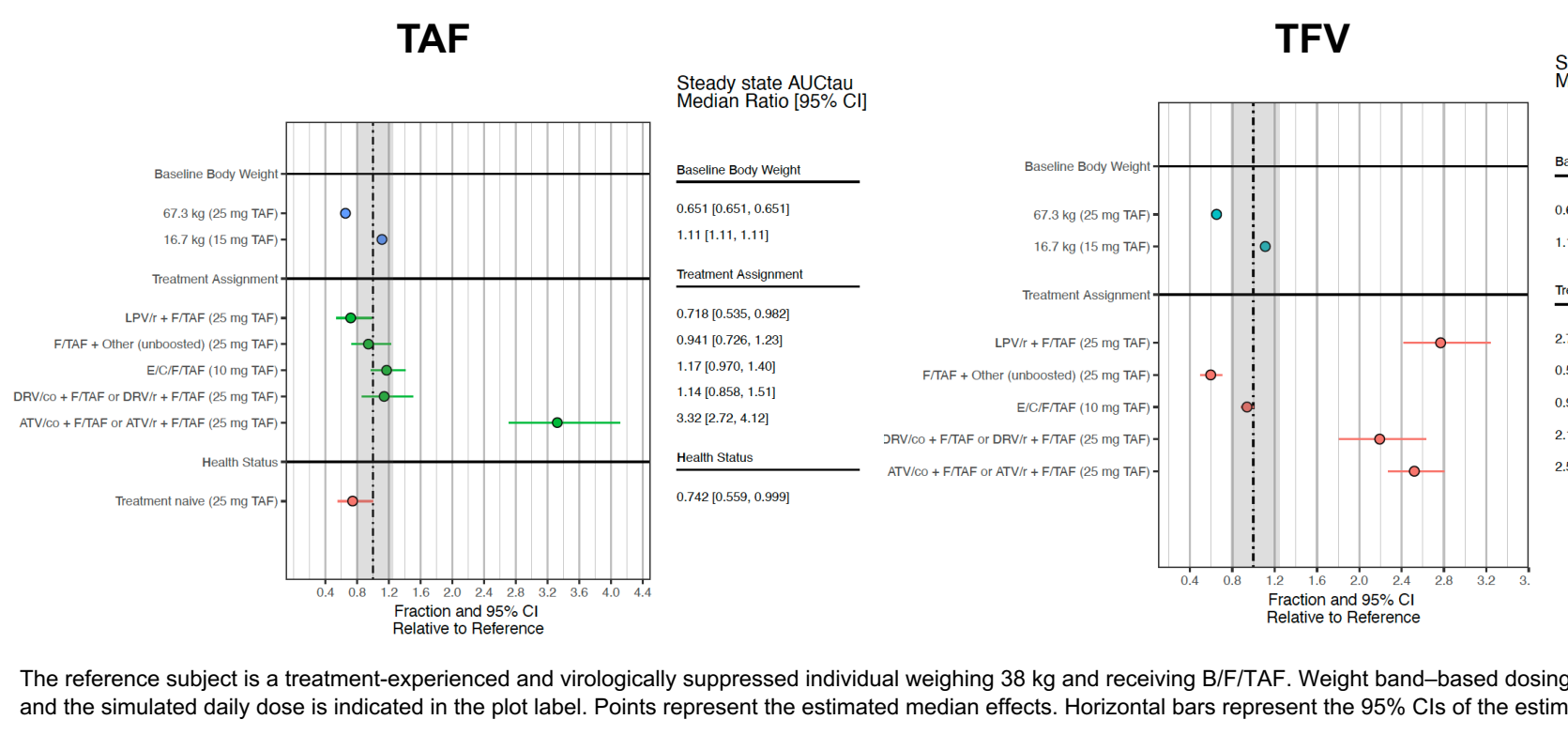


Figure 3. Forest plot for final model estimated covariate effects on steady-state TAF and TFV AUC_{tau}



Simulations

- Simulated TAF steady-state exposures for children with HIV-1 aged ≥ 2 years and weighing ≥ 14 kg, treated with various TAF-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 4**)
- Simulated TFV steady-state exposures for children with HIV-1 aged ≥ 2 years and weighing ≥ 14 kg, treated with various TAF-containing combination regimens, were largely contained within the range observed in the adult reference and well below the observed TFV exposures in adults treated with E/C/F/tenofovir disoproxil fumarate (TDF) and children treated with TDF (**Figure 5**)

Figure 4. Population simulations for TAF steady-state AUC_{tau} following administration of various TAF-containing treatment regimens

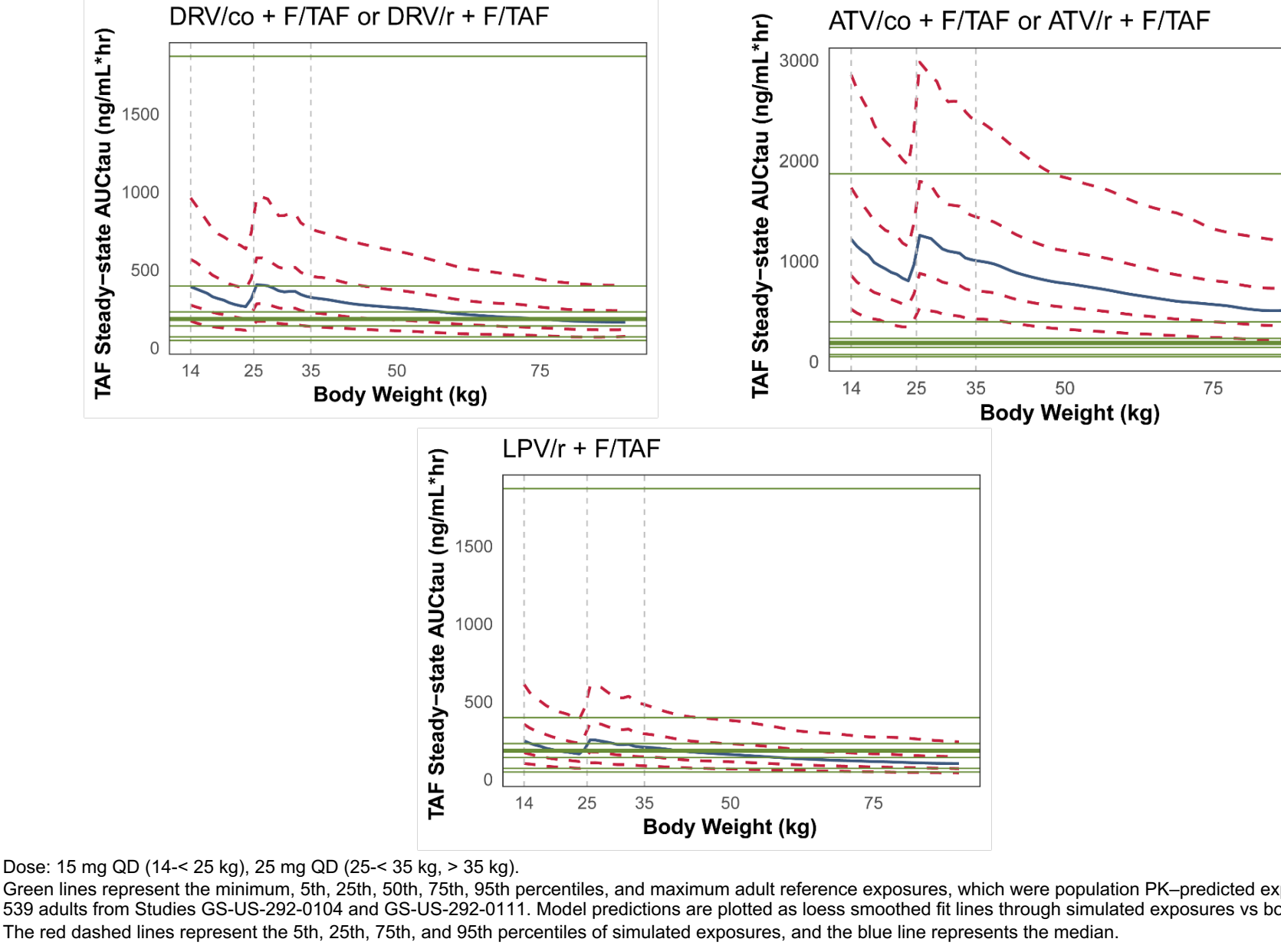
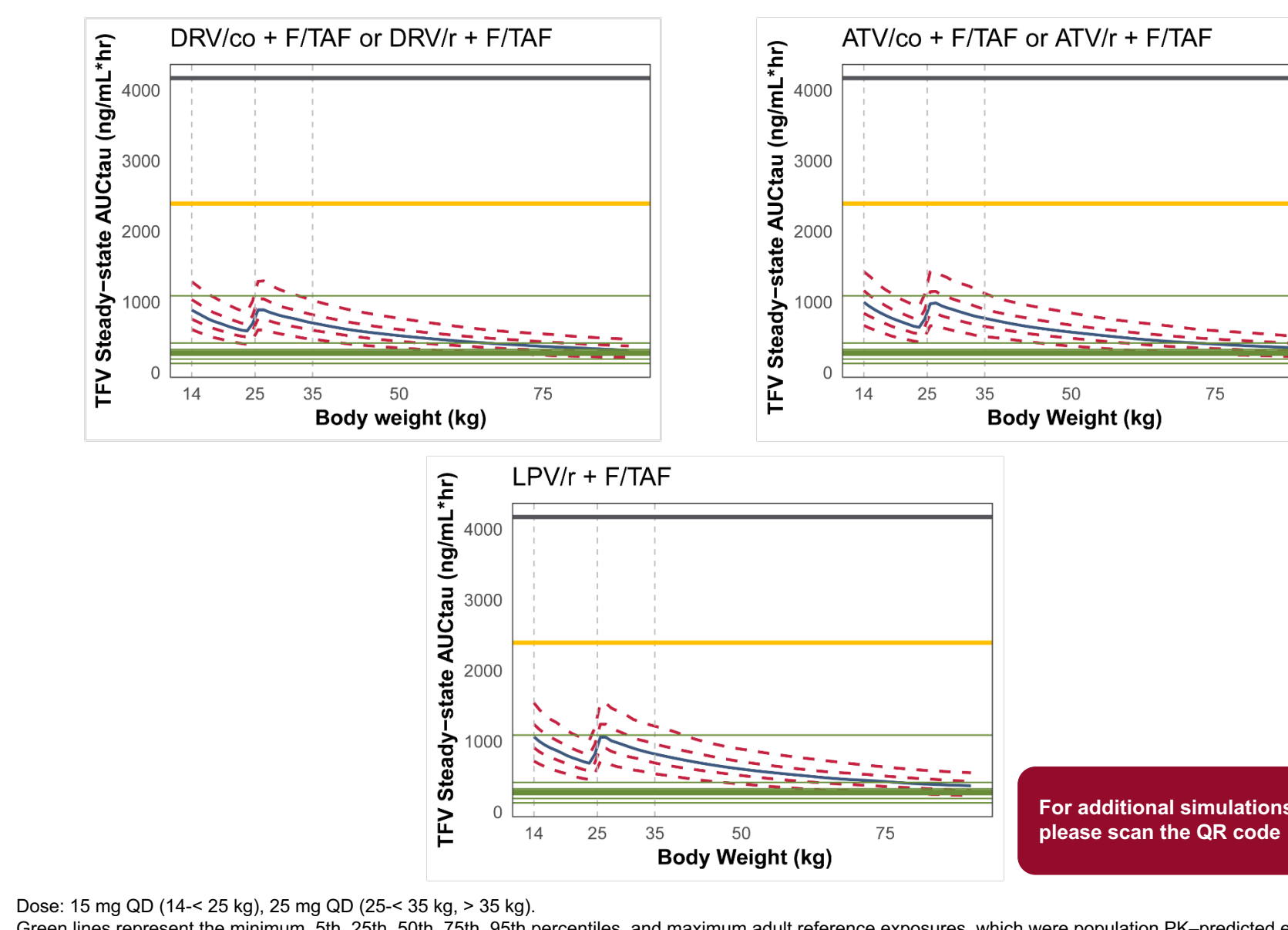


Figure 5. Population simulations for TFV steady-state AUC_{tau} following administration of various TAF treatment regimens



Dose: 15 mg QD (14- < 25 kg), 25 mg QD (25- < 35 kg, ≥ 35 kg). Green lines represent the minimum, 5th, 25th, 50th, 75th, 95th percentiles, and maximum adult reference exposures, which were population PK-predicted exposures in 539 adults from Studies GS-US-292-0104 and GS-US-292-0111. Model predictions are plotted as least 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. The grey line represents the median exposure from the E/C/F/TDF Phase 2/3 program in adults, and the yellow line represents the median exposure for TDF powder (8 mg/kg TDF) in children aged ≥ 2 years (GS-US-154-0352).

