



A semi-mechanistic population pharmacokinetic model of tenofovir alafenamide fumarate and tenofovir in children living with HIV

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Background and Objectives

- Tenofovir alafenamide (TAF) is a prodrug of tenofovir (TFV), a nucleoside analogue that inhibits human immunodeficiency virus (HIV) replication.
- TFV is activated intracellularly to tenofovir-diphosphate (TFV-DP).
- TAF is always combined with other drugs in the treatment for HIV.

Objective: Build a semi-mechanistic model describing TAF and TFV pharmacokinetics (PK) in children that also take ritonavir-boosted(/r) protease inhibitors (PIs) or dolutegravir.

Methods

- TAF and TFV concentrations were available from a sub-study nested within the CHAPAS-4 study (#ISRCTN22964075), evaluating practical TAF dosing in weight bands combined with dolutegravir or ritonavir boosted atazanavir, darunavir or lopinavir.
- PK sampling at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 h after dose was performed at least 6 weeks after treatment initiation with a daily 15 or 25 mg TAF dose.
- TAF and TFV were quantified using a validated liquid chromatography-tandem mass spectrometry assay with a lower limit of quantification of 0.0005 mg/L.

Table 1: Demographics

	Dolutegravir (N=20)	Atazanavir/r (N=31)	Darunavir/r (N=34)	Lopinavir/r (N=21)	Total (N=106)
Age (years)					
Median	10.9	9.85	10.9	11.2	10.7
[Min - Max]	[5.46 - 14.2]	[4.79 - 14.9]	[3.83 - 14.7]	[4.27 - 14.6]	[3.83 - 14.9]
Sex					
Male	9 (45.0%)	15 (48.4%)	16 (47.1%)	10 (47.6%)	50 (47.2%)
Female	11 (55.0%)	16 (51.6%)	18 (52.9%)	11 (52.4%)	56 (52.8%)
Height (cm)					
Median	131	129	133	136	131
[Min - Max]	[94.0 - 170]	[105 - 162]	[97.8 - 161]	[97.1 - 169]	[94.0 - 170]
Weight (kg)					
Median	25.9	25.5	24.0	26.0	25.3
[Min - Max]	[15.9 - 53.0]	[14.5 - 50.0]	[14.5 - 47.0]	[14.2 - 48.5]	[14.2 - 53.0]
Creatinine Clearance (ml/min)					
Median	118	127	124	113	120
[Min - Max]	[72.4 - 247]	[84.1 - 206]	[72.6 - 217]	[86.4 - 183]	[72.4 - 247]
Missing	0 (0%)	3 (9.7%)	4 (11.8%)	0 (0%)	7 (6.6%)

Results

Table 2: Final Parameter Estimates

Parameter description	Typical value (95% CI) ^a	Parameter variability (% CV) (95%CI)
Bioavailability	1 FIX	49.5 (39.5 – 53.3)
Atazanavir/r effect (%) ^c	+51 (+35 – +79)	
Darunavir/r effect (%) ^c	+12 (+1.7 – +32)	
Lopinavir/r effect (%) ^c	+4.1 (-6.1 – +32)	
Lag time (h)	0.437 (0.380 – 0.467)	69.9 (57.3 – 80.2)
Absorption rate constant (/h)	1.63 (1.55 – 1.73)	76.4 (69.4 – 91.9)
Volume of distribtution TAF (L) ^b	33.0 (33.0 – 40.5)	
Clearance TAF Slow (L/h) ^b	40.5 (37.4 – 48.3)	52.7 (47.2 – 63.0)
Atazanavir/r effect (%) ^c	-19 (-29 – +13)	
Darunavir/r effect (%) ^c	+58 (+43 – +105)	
Lopinavir/r effect (%) ^c	+24 (+16 – 134)	
Clearance TAF Fast (L/h) ^b	20.9 (15.7 – 21.9)	152 (117 – 178)
Atazanavir/r effect (%) ^c	-6.8 (-48 – +14)	
Darunavir/r effect (%) ^c	+22 (+3.3 – +134)	
Lopinavir/r effect (%) ^c	+22 (+1.9 – +120)	
Volume “intracellular” (L) ^b	680 (529 – 700)	
Q “intracellular” (L/h) ^b	227 (210 – 266)	
Volume central TFV (L) ^b	146 (130 – 177)	
Clearance TFV (L/h) ^b	28.8 (27.2 – 30.3)	28.8 (23.5 – 29.8)
Renal function effect ^d	0.425 (0.349 – 0.503)	
Atazanavir/r effect (%) ^c	-33 (-40 – -21)	
Darunavir/r effect (%) ^c	-42 (-48 – -28)	
Lopinavir/r effect (%) ^c	-51 (-57 – -35)	
Q TFV (L/h) ^b	190 (173 – 234)	
Volume peripheral TFV (L) ^b	1140 (1043 – 1414)	
Proportional error TAF (%)	57.4 (53.4 – 0.580)	
Additive error TAF (ug/L)	0.158 (0.147 – 0.177)	
Proportional error TFV (%)	11.7 (10.9 – 12.4)	
Additive error TFV (ug/L)	0.067 (0.035 – 0.067)	

^a95% confidence intervals got by non-parametric bootstrap; ^bAllometric scaling with weight (reference individual of 25 kg); ^cChildren on dolutegravir are the reference; ^d($Creatinine\ clearance_{121}$)^{0.425}

Results

- 106 children contributed 957 TAF and 954 TFV concentrations.
- A one-compartment TAF and a two-compartment TFV disposition model best described the data linked via an “intracellular” compartment.
- The CL TAF fast path describes the immediate appearance of TFV.
- The CL TAF slow path describes a slow release of TFV into the plasma.
- The model describes the data reasonably well.
- The absorption model of TAF when co-administered with dolutegravir and atazanavir/r can still be improved. The observed absorption seems to be somewhat slower than model predictions.
- Antiretroviral treatments influence bioavailability and TAF and TFV clearance.

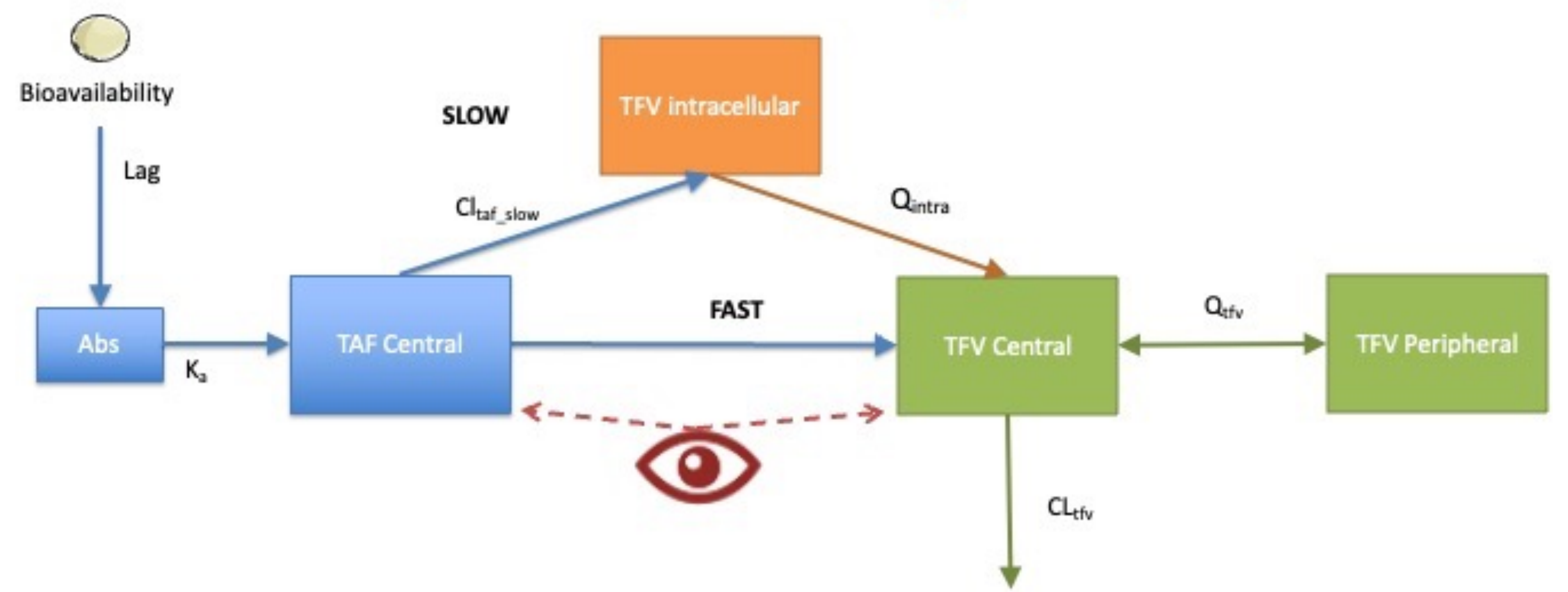


Figure 1: Model structure

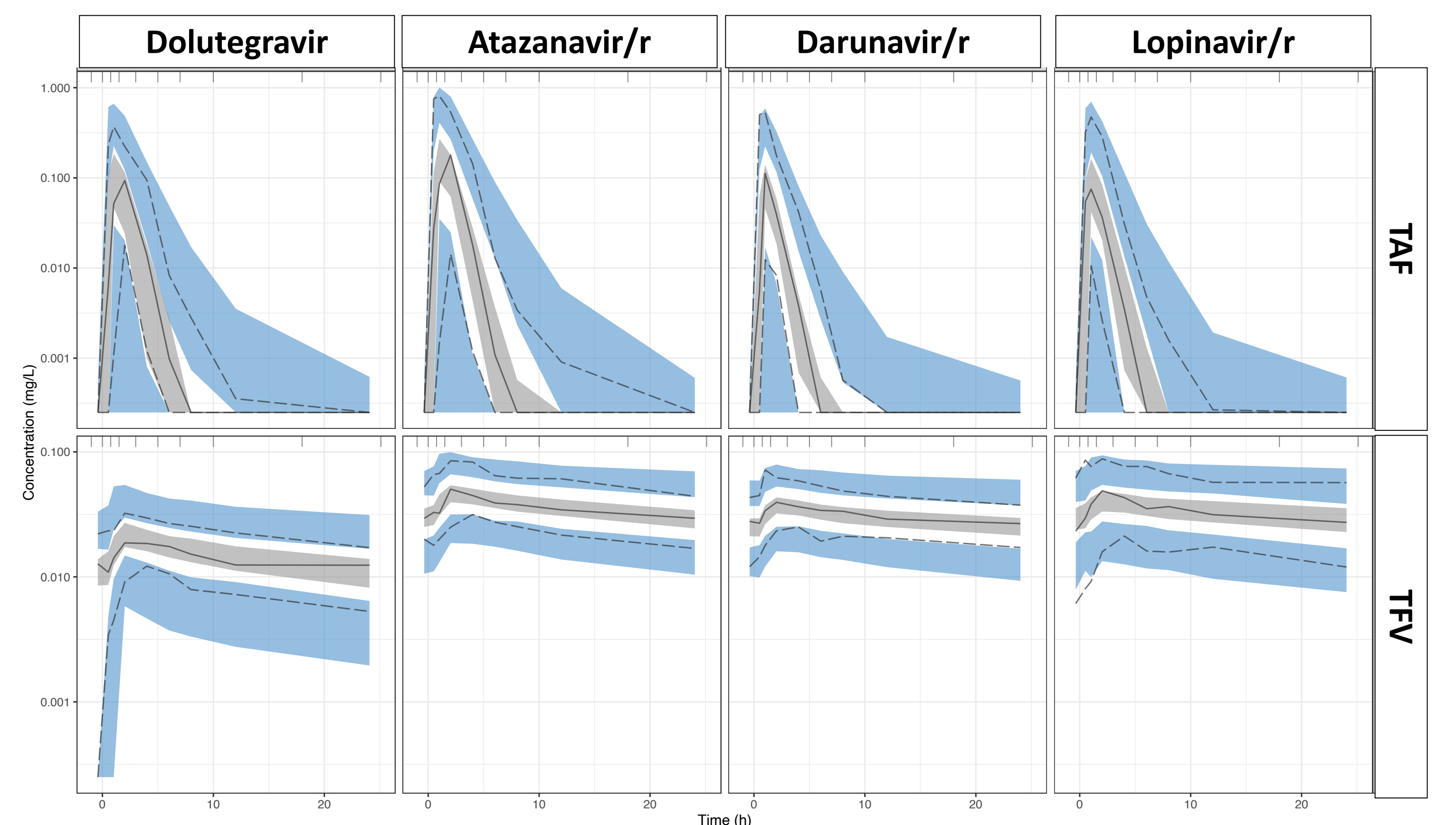


Figure 2: Visual predictive check of the TAF and TFV model, stratified by antiretroviral treatment arm. The solid and dashed lines are the 10th, 50th, and 90th percentiles of the observations, while the shaded areas represent the 95% model-predicted confidence intervals for the same percentiles.

Discussion and Conclusions

- We developed a semi-mechanistic model that describes the disposition of TAF and TFV after TAF administration in children living with HIV.
- This model allows for a more detailed investigation of drug-drug interactions with dolutegravir, and ritonavir boosted PIs.
- Antiretroviral treatments have a strong effect on TAF and TFV pharmacokinetics most likely caused by ritonavir
- The higher TFV concentrations in children with a PIs are cause by an interplay of a higher bioavailability, a mostly increased TAF clearance to TFV, and finally a lower TFV clearance.
- The large proportional error for TAF might be due to molecule instability
- This model will be extended by adding ritonavir exposure as a covariate

References

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