

Population pharmacokinetics of tenofovir given as either tenofovir disoproxil fumarate or tenofovir alafenamide

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Background and Objectives

- Tenofovir is a nucleoside analogue that inhibits HIV replication.
- Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are prodrugs of tenofovir.
- TDF leads to high plasma tenofovir concentrations associated with kidney and bone toxicity.^{1–4}
- TAF is more stable in plasma and efficiently delivers tenofovir to HIV target cells, leading to lower plasma tenofovir concentrations.
- HIV treatment guidelines recommend TAF for adults with osteoporosis and/or impaired kidney function.

Objective: We aimed to use a single model to jointly describe the population pharmacokinetics of tenofovir, given as TAF or TDF, in Africans living with HIV.

Methods

- Tenofovir pharmacokinetic data were available from a sub-study nested within the ADVANCE study (NCT03122262), an open-label, phase 3, randomized non-inferiority trial in Southern African adults.⁵
- PK sampling at steady state at 0, 1, 2, 4, 6, 8, and 24-hours post-dose was done.
- Tenofovir quantified using a validated liquid chromatography-tandem mass spectrometry assay.⁶ lower limit of quantification was 0.0005 mg/L
- Release of tenofovir after TAF was described by two absorption pathways; an estimated fast fraction available for immediate absorption into systemic circulation while a slow fraction was modelled as if it was first absorbed intracellularly and then slowly transitioned to the systemic circulation
- This was to mimic the intracellular conversion of TAF to TFV-DP and its decay back to tenofovir.

Table 1: Patient information

Characteristic	Median (interquartile range) or no. (% of volunteers (n=41))
Age (years)	31.0 (29.0, 36.0)
Weight (kg)	73.1 (67.2, 85.2.0)
Height (cm)	167 (161, 174)
Creatinine clearance at baseline	120(96, 140)
Sex, n (%) Male/Female	27 (65.9)/ 14 (34.1)
TDF/FTC/DTG regimen	21 (51.2%)
TAF/FTC/DTG regimen	20 (48.8%)

Model Building

-NONMEM 7.5(FOCE-I)
-Pirana
-PsN
-Xpose

Results

- 41 participants with 279 tenofovir concentrations contributed to the model.
- A two-compartment disposition model ($\Delta\text{OFV}=-47$, $p<0.001$ compared to one-compartment) best described the pharmacokinetics of tenofovir.
- The half-life of transition of intracellular tenofovir to systemic circulation was fixed to 6.8 days; the half-life previously reported for intracellular TFV-DP to decay.⁷

Table 2: Final parameter estimates (95% CI)*

Parameter description	Typical value (95% CI) ^a	Parameter variability (% CV) ^c (95%CI)
CL (L/h) ^b	44.7 (40.2 – 49.5)	20.1 (16.1 – 24.7)*
V _c (L) ^b	378 (319 – 459)	
Q (L/h) ^b	157 (103 – 233)	
V _p (L) ^b	356 (298 – 438)	
Relative bioavailability; TDF arm	1 Fixed	23.9 (18.2 – 30.3) [#]
Relative bioavailability; TAF arm	0.822 (0.723 – 0.939)	
k _a (/h); TDF arm	3.04 (2.11 – 3.88)	114.5 (68.4 – 162) [#]
k _a (/h); TAF arm	1.45 (0.924 – 2.60)	66.3 (31.0 – 91.6) [#]
T _{1/2} (transition) (days)	6.83 Fixed	
F _{Fast} (%)	32.4 (27.0 – 37.7)	
Proportional error (%)	11.9 (10.8 – 13.4)	
Additive error (mg/L)	Fixed to 20% LLOQ	

^a95% confidence intervals got by sampling importance resampling.

^bAllometric scaling with weight (reference individual of 70 kg) for (CL, Q, V_c, and V_p)

The half-T_{1/2} (transition) is the life of the first-order process by which tenofovir leaves the intracellular compartment to the central compartment. F_{fast} is the percentage of tenofovir that is immediately available for absorption into the systemic circulation

*Between-subject variability (BSV) and [#]between-occasion variability (BOV) were assumed to be log-normally distributed and calculated by $\text{CV}\% = \sqrt{\omega^2} \cdot 100$

^dlower limit of quantification (LLOQ) was 0.0005 mg/L.

Results

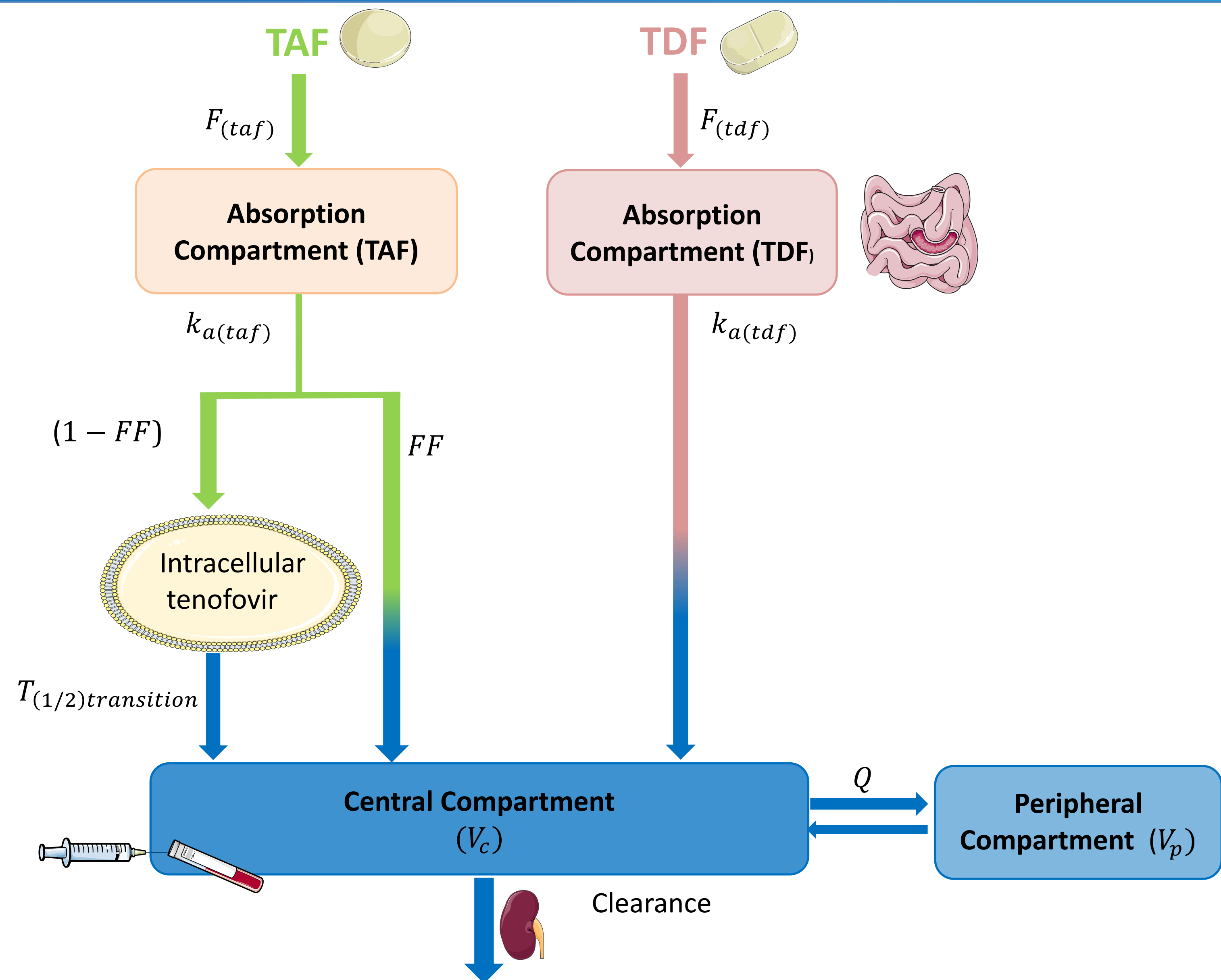


Figure 1: Final model structure

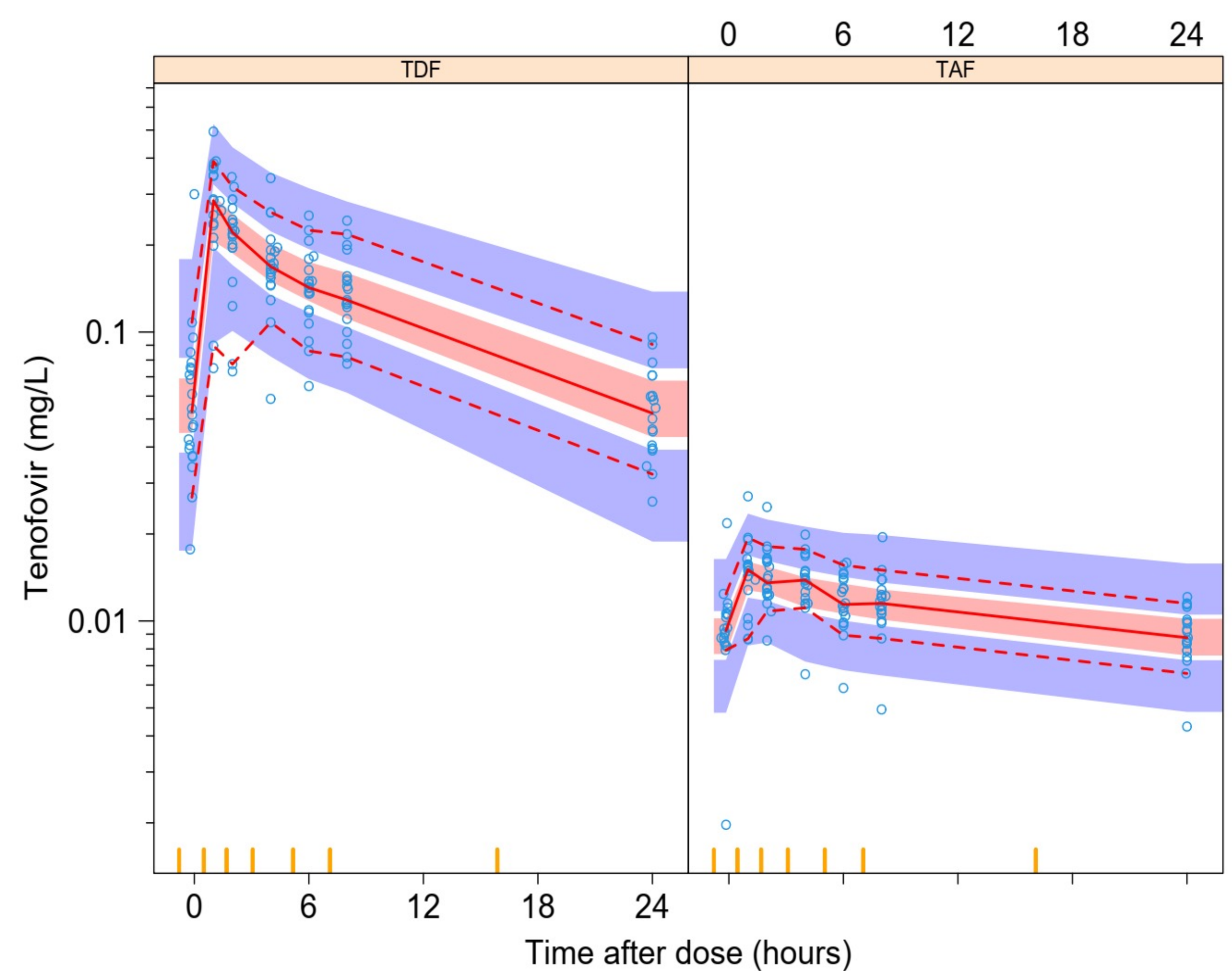


Figure 2: Visual predictive check of the tenofovir model, stratified by study arm.

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 jointly described tenofovir disposition when dosed as either TDF or TAF unlike previous reports in which two separate models have been reported for tenofovir; based on the prodrug administered.⁸
- A key strength of our approach is that we estimate a single clearance value for tenofovir, strengthening the idea that once tenofovir is in systemic circulation, its excretion is the same regardless of how it was administered. In contrast, its appearance in systemic circulation is a function of the prodrug administered.
- This model can be used as a tool for exposure prediction in patients, for simulation of alternative regimens, and for sample size calculations for further clinical trials that may increasingly involve the use of TAF as it replaces TDF.
- These findings further contribute to our understanding of the disposition of tenofovir from the two prodrugs

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