

What is the effective concentration of dolutegravir? A pharmacokinetic/pharmacodynamic analysis

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Background & objectives

The **minimum effective concentration (MEC)** of dolutegravir is not **well defined** and putative trough concentration (C_{trough}) targets have been suggested for efficacy.

While the in-vitro protein-adjusted 90% inhibitory concentration (PA-IC₉₀) is 0.064 mg/L^{1,2}, an **often-referenced value is the C_{trough} of 0.3 mg/L**³. This is derived from a phase 2b dose-ranging trial (SPRING-1) and corresponds to a geometric mean from 15 participants receiving 10 mg of dolutegravir daily. However, **10, 25, and 50 mg doses had comparable rates of virological suppression** in the same study³.

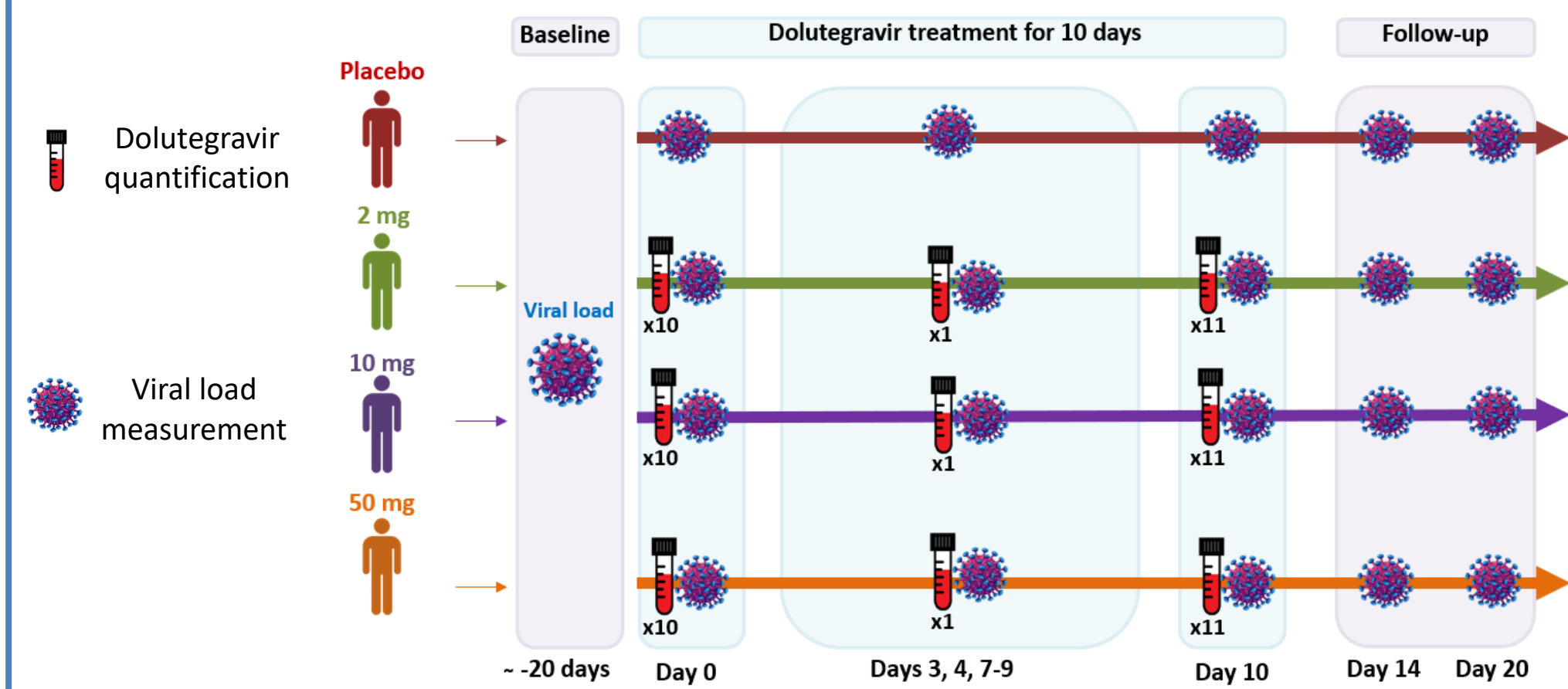
We aimed to:

1. Develop a pharmacokinetic/pharmacodynamic (PK/PD) model to characterize the relationship between dolutegravir exposure and participant viral load dynamics.

2. Used the final model to evaluate the current dolutegravir regimen with and without rifampicin co-administration.

Methods

Figure 1. Study protocol The PK/PD model was developed using data from the phase 2a, placebo-controlled, dose-ranging VIIV-ING11521 study of dolutegravir monotherapy².



The PK/PD analysis was performed in NONMEM®, and the uncertainty of parameter estimates was evaluated using the Sampling Importance Resampling (SIR) method.

We simulated the standard regimen of dolutegravir 50 mg with and without co-administration of 600 mg of rifampicin to assess the impact on viral load.

Results

Table 1. Participant baseline characteristics

Parameter	Dolutegravir once-daily dose			
	Placebo (n=7)	2 mg (n=9)	10 mg (n=9)	50 mg (n=10)
Male (n)	7 (100)	9 (100)	9 (100)	10 (100)
Age (years)	41 (21-54)	41 (20-55)	40 (32-45)	34 (22-53)
Weight (kg)	85.8 (60.0-121)	81.7 (67.5-113)	86.0 (69.5-106)	77.9 (60.5-100)
Plasma HIV-1 RNA (log10 copies/mL)	4.25 (4.03-4.74)	4.40 (4.03-4.85)	4.58 (4.25-5.54)	4.47 (3.85-5.17)

Data is expressed as number and percentage or mean and range.

Figure 2. Dolutegravir concentrations

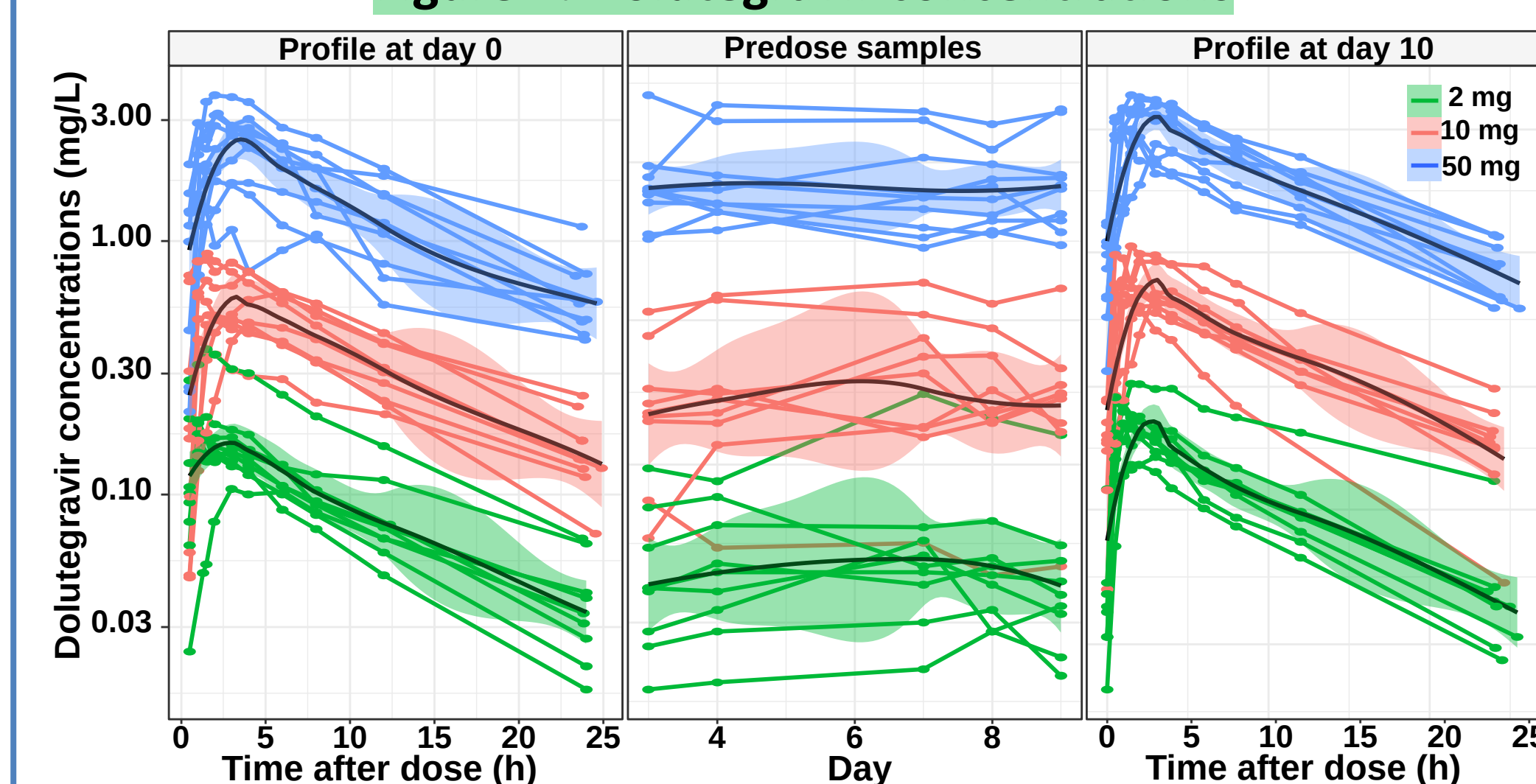
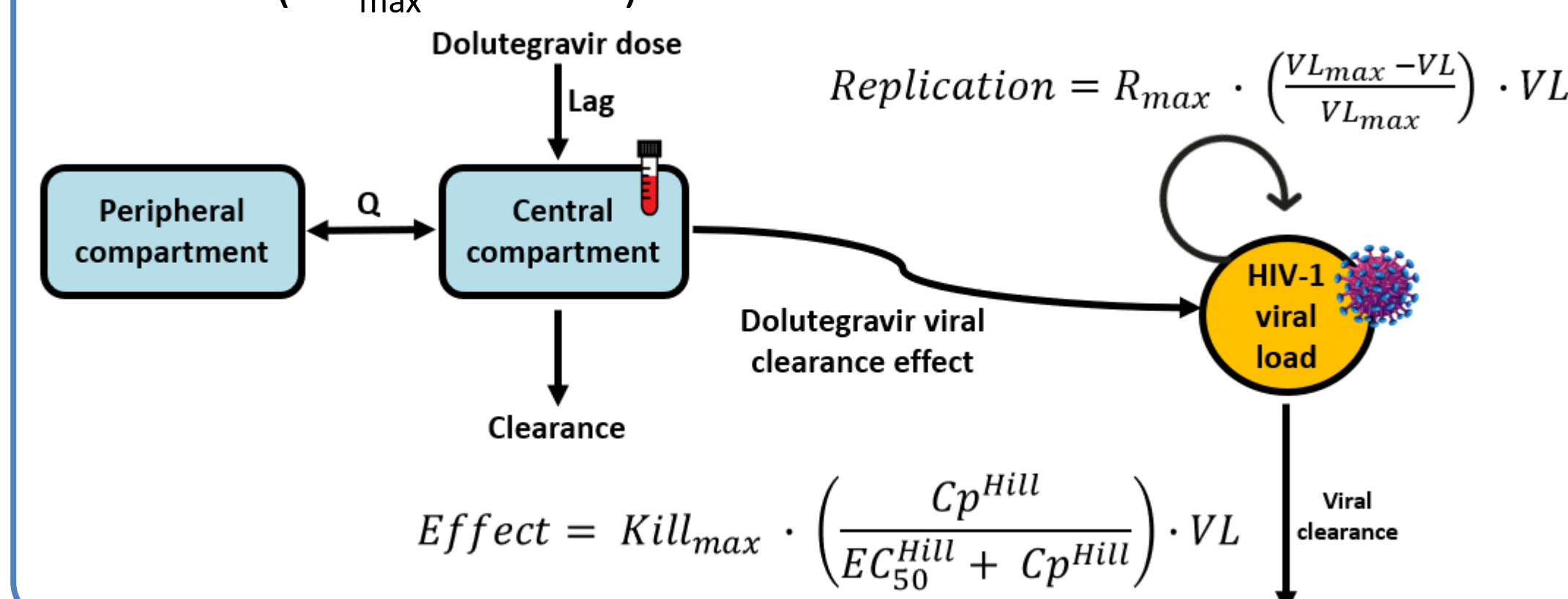


Figure 3. Final PK/PD model The PK two-compartment model appropriately described the data and the parameter estimates were in line with the literature⁴.

Dolutegravir concentrations determined the viral load described as the equilibrium between viral replication (modelled using a growth rate R_{max} and carrying capacity VL_{max}) and drug-mediated viral clearance ($Kill_{max}$ function).



Results

Table 2. Final parameter estimates

Parameter	Typical value	95% CI from SIR	Variability (% CV)	95% CI from SIR
Clearance (L/h)	1.26	1.14-1.39	BSV: 21.0	16.8-26.7
Central volume of distribution (L)	18.2	16.8-19.8	-	-
Intercompartmental clearance (L/h)	0.319	0.186-0.483	-	-
Peripheral volume of distribution (L)	3.14	1.79-4.66	-	-
Absorption constant rate (1/h)	2.51	1.86-3.38	BOV: 99.1	79.6-125
Absorption lag time (h)	0.238	0.179-0.289	BOV: 59.3	42.8-86.1
Bioavailability with 50 mg dolutegravir (.)	1 FIX	-	BOV: 24.9	21.8-28.3
Change in bioavailability with 2 mg dolutegravir (%)	+75.0	+57.0 - +94.0	-	-
Change in bioavailability with 10 mg dolutegravir (%)	+23.0	+10.0 - +40.0	-	-
Proportional error for dolutegravir (%)	10.4	9.71-11.7	-	-
Additive error for dolutegravir (mg/L)	0.001 (fixed to 20% of LLOQ)	-	-	-
HIV-1 Maximum replication, R_{max} (copies/h)	0.0284	0.0256 - 0.0316	-	-
HIV-1 Maximum viral load, VL_{max} (log10 copies/mL)	4.45	4.34 - 4.56	BOV: 74.4	59.0 - 99.1
Kill _{max} (copies/h)	0.0517	0.0478 - 0.0566	BOV: 5.20	2.41 - 7.23
EC ₅₀ (mg/L)	0.0632	0.0427 - 0.0932	BOV: 61.9	44.4 - 79.4
Hill coefficient (.)	1.58	1.07 - 2.45	-	-
Proportional error for viral load (%)	22.1	20.4 - 24.0	-	-
Additive error for viral load (log10 copies/mL)	0.876	0.419 - 1.11	-	-

Allometric scaling was used to estimate PK clearances and volumes for the typical male patient with a body weight of 78.1 kg. CI: confidence interval. SIR: Sampling Importance Resampling. LLOQ: Lower limit of quantification. BSV: between-subject variability. BOV: between-occasion variability.

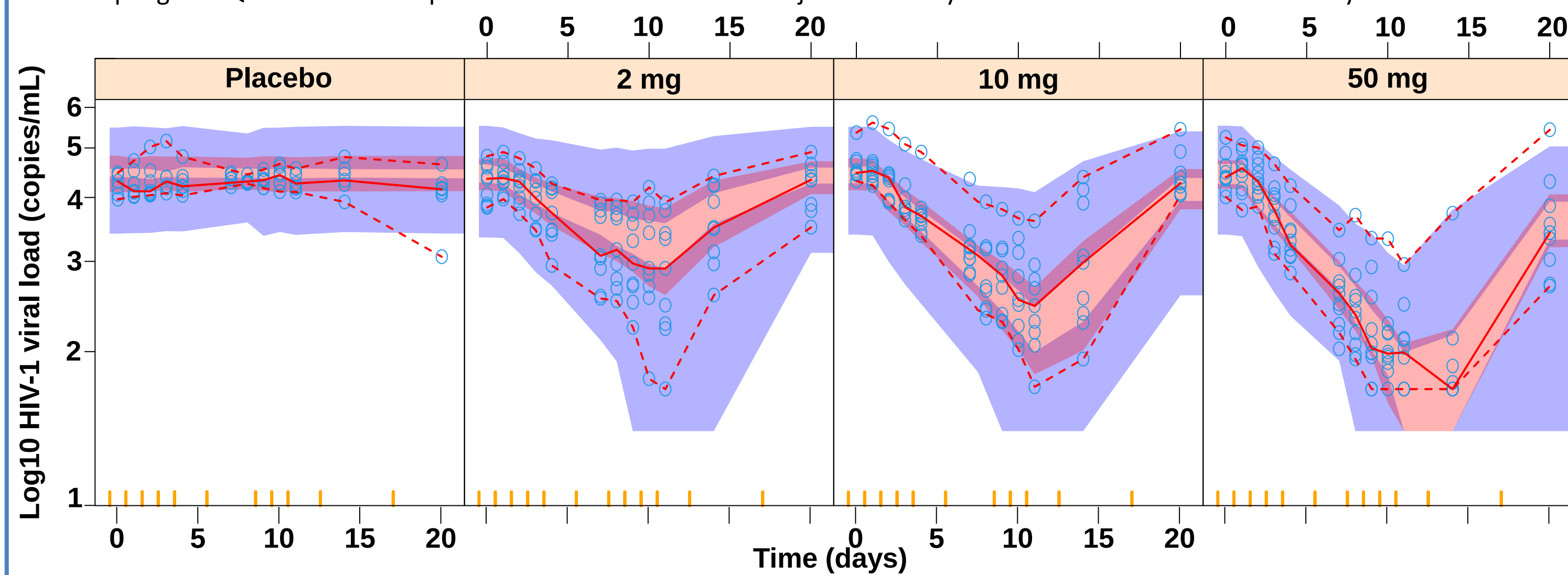


Figure 4. VPC of the final PK/PD model The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observed data. The shaded areas represent the 95% CI for the same percentiles of the model predictions.

Figure 5. Simulations

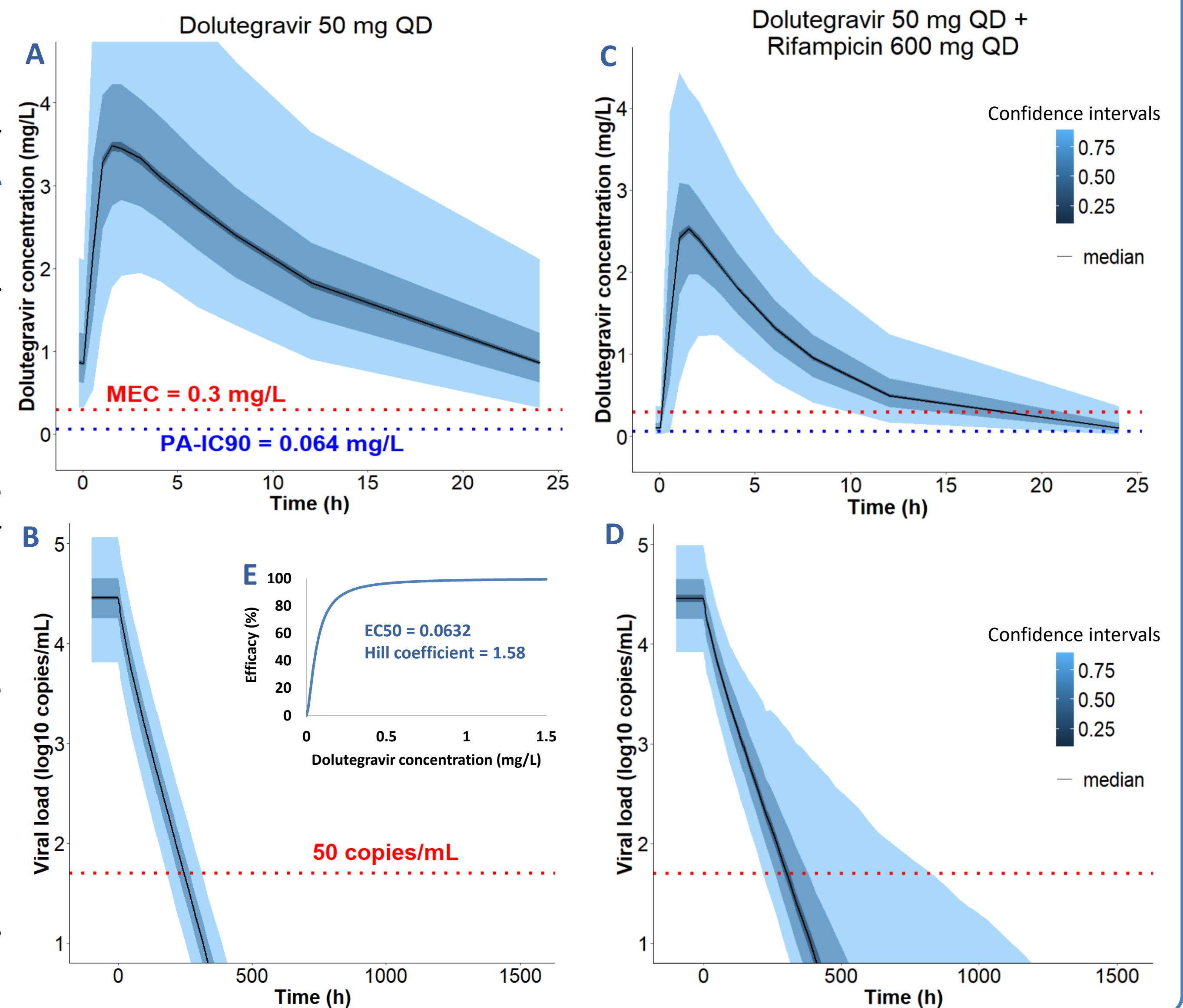
Scenario 1: Standard dolutegravir dose (predicted concentrations **Fig 5A** and viral load **Fig 5B**).

Scenario 2: Standard dolutegravir dose co-administered with rifampicin (predicted concentrations **Fig 5C** and viral load **Fig 5D**).

With administration of rifampicin, the concentrations of dolutegravir drastically decreased (**Fig 5C**).

However, viral suppression is still predicted to be achieved despite the interaction between rifampicin and dolutegravir (**Fig 5D**).

The dolutegravir efficacy plot (**Fig 5E**) shows the interplay between dolutegravir concentrations and its efficacy.



Conclusion

We developed a PK/PD model for dolutegravir in male participants with HIV that allowed us to explore the impact of different dosing regimens on viral load.

Our simulations showed that using only the C_{trough} **does not adequately describe the effect of dolutegravir on viral load**.

Simulated **viral suppression was achieved even when dolutegravir C_{trough} levels were lower than the often-referenced target of 0.3 mg/L**. This is consistent with the findings in RADIANT-TB⁵, which investigated the un-adjusted standard dose of dolutegravir in people receiving rifampicin.

These results demonstrate that the current dolutegravir targets are not reliable, and limiting its efficacy solely to C_{trough} may be oversimplistic.

References

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