

PBPK modelling of drug-drug interactions between long-acting cabotegravir and rilpivirine with oral rifabutin

Sandra Grañana-Castillo¹, Maiara Montanha-Camotti¹, Fazila Bunglawala¹, Nicolas Cottura¹, Hannah Kinvig¹, Andy Lloyd¹, Saye Khoo¹, Rachel Bearon¹, Marco Siccardi¹

¹University of Liverpool, UK

✉ s.granana-castillo@liverpool.ac.uk

Background

- Tuberculosis** remains the primary cause of death among people living with **HIV**.
- Cabotegravir** (UGT1A1) and **rilpivirine** (CYP3A4) in combination are two antiretrovirals newly available as **long-acting intramuscular injections**.
- Rifabutin** is an antituberculosis drug that elicits a **moderate induction effect on CYP3A4 and UGT1A1 enzymes**.
- Current target minimum concentrations for cabotegravir are 0.664 mg/L (4x protein adjusted IC₉₀), and 0.050 mg/L for rilpivirine.

The aim was to simulate the administration of long-acting cabotegravir/rilpivirine with rifabutin.

Methodology

- 100 adult individuals (50% female, 18-60 of age) were simulated using a whole-body physiologically based pharmacokinetic (PBPK) model built in **Simbiology (Matlab R2018a)**.
- The model was validated using oral and intramuscular clinical data for the drugs alone, and oral clinical studies for each drug-drug interaction (DDI) at steady state at the commonly prescribed dose.
- The model was assumed to be verified if the simulated values were within 2-fold of the reported clinical values and if the absolute average-fold error (AAFE) was <2. The model yielded an **AAFE of 1.21** (1.00-1.84) average (min-max).

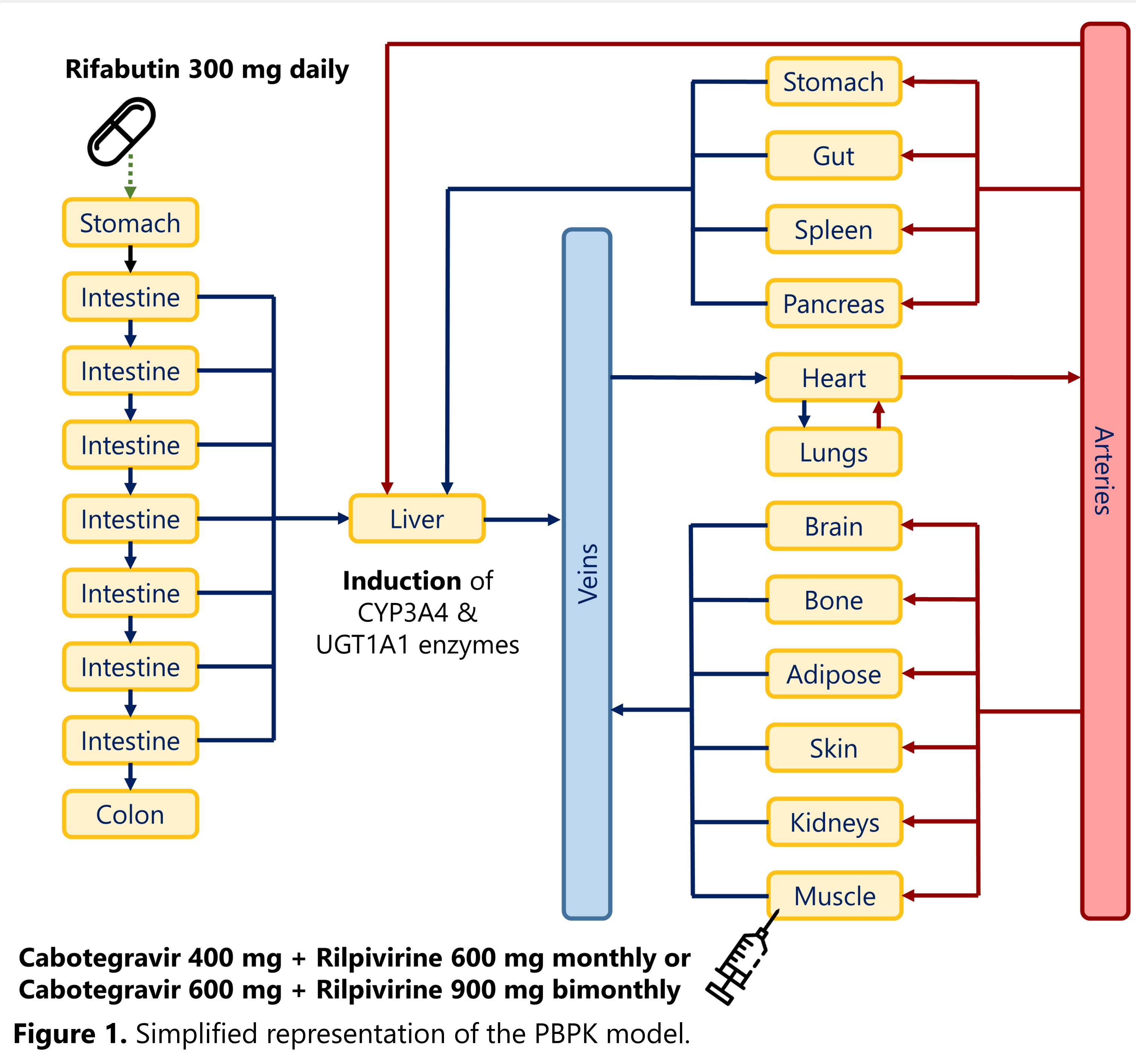


Table 1. Summary of physicochemical and in vitro data.

Parameter	Rilpivirine	Cabotegravir	Rifabutin
Log P _{ow}	4.86 [1]	1.04 [2]	4.1 [3]
f _u	0.003 [4]	0.007 [2]	0.29 [5]
pK _a	5.6 [1]	10.04 [2]	6.9 [3]
R	0.7 [4]	0.44 [2]	0.6 [5]
Caco-2 permeability (10 ⁻⁶ cm/s)	12 [4]	NA	NA
K _a (h ⁻¹)	NA	2.16 [6]	0.201 [7]
K _{im} (h ⁻¹)	9 · 10 ⁻⁴ [2]	4.5 · 10 ⁻⁴ [2]	NA
CL _{int} CYP3A4 liver (uL/min/pmol)	6* [8]	NA	19.2** [9]
CL _{int} CYP3A4 gut (uL/min/pmol)	NA	NA	8.24** [9]
CL _{int} UGT1A1 liver (uL/min/mg)	NA	4.5 [2]	NA
CL _{int} UGT1A9 liver (uL/min/mg)	NA	2.2 [2]	NA
EC ₅₀ CYP3A4 (mg/L)	NA	NA	0.254 [10]
E _{max} CYP3A4 (fold)	NA	NA	4.75 [10]
UGT1A1 increase (fold)	NA	NA	1.75 [11]

CL_{int}, intrinsic clearance; CYP, cytochrome P450; EC₅₀, half maximum effect concentration; E_{max}, maximum attainable effect; f_u, fraction unbound in plasma; K_a, oral absorption rate; K_{im}, intramuscular release rate; log P_{ow}, partition coefficient between octanol and water; NA, not applicable; pK_a, logarithmic value of the dissociation constant; R, blood-to-plasma drug ratio; UGT, UDP-glucuronosyltransferase. *retrograde calculation; **adjusted to twice the reported values.

Results

Table 2. Predictions of long-acting cabotegravir and rilpivirine with and without rifabutin for the monthly regimen at steady state.

PK parameter (mean)	Monthly regimen			Monthly regimen		
	Cabotegravir 400 mg			Rilpivirine 600 mg		
	alone	with rifabutin	% change	alone	with rifabutin	% change
AUC _{0-τ} (mg/L·h)	2710	1843	-32.0	91.83	52.42	-42.9
C _{trough} (mg/L)	3.82	2.62	-31.3	0.10	0.06	-42.1
C _{max} (mg/L)	4.15	2.85	-31.2	0.16	0.10	-39.2

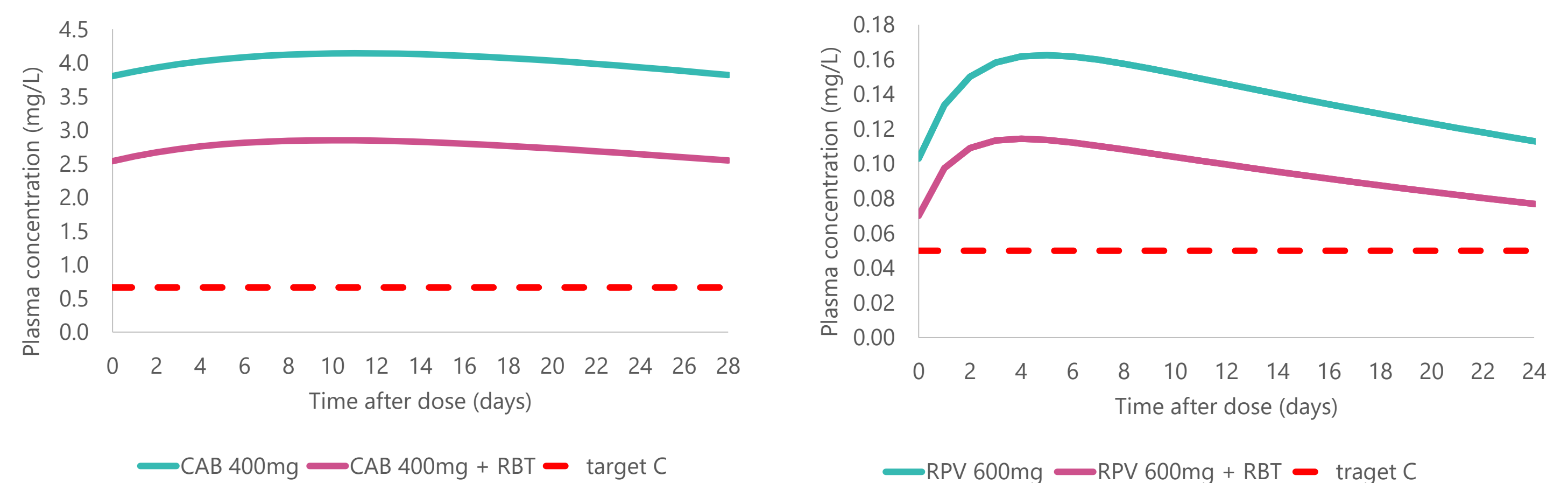


Figure 2. Monthly cabotegravir 400 mg (left); monthly rilpivirine 600 mg (right). Cabotegravir and rilpivirine alone (green) and with rifabutin (purple) at steady state. The dashed red line represents the target minimum concentration.

Table 3. Predictions of long-acting cabotegravir and rilpivirine with and without rifabutin for the bimonthly regimen at steady state.

PK parameter (mean)	Bimonthly regimen			Bimonthly regimen		
	Cabotegravir 600 mg			Rilpivirine 900 mg		
	alone	with rifabutin	% change	alone	with rifabutin	% change
AUC _{0-τ} (mg/L·h)	4111	2778	-32.4	135.21	78.99	-41.6
C _{trough} (mg/L)	2.54	1.67	-34.3	0.05	0.03	-40.9
C _{max} (mg/L)	3.38	2.35	-30.3	0.15	0.10	-37.6

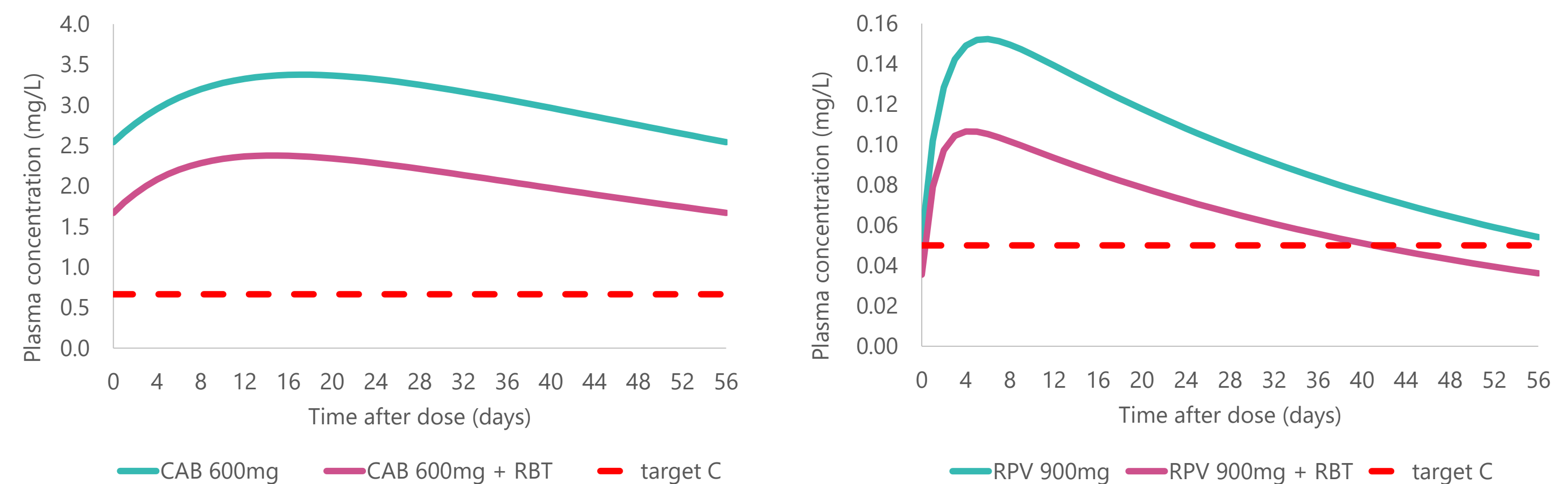


Figure 3. Bimonthly cabotegravir 600 mg (left); bimonthly rilpivirine 900 mg (right). Cabotegravir and rilpivirine alone (green) and with rifabutin (purple) at steady state. The dashed red line represents the target minimum concentration.

The PBPK model suggested a significant decrease on key PK parameters, with the mean C_{trough} for rilpivirine 900 mg bimonthly below the minimum target concentration.

Conclusion

Therefore, a clinical evaluation of this potential interaction might be required to fully evaluate the safety of concomitant use with moderate enzymatic inducers.

References

- DrugBank. Rilpivirine. 2. Rajoli, R.K.R., et al. J Infect Dis, 2019. 219(11): p. 1735-1742. 3. Drugbank, Rifabutin. 4. FDA. Rilpivirine: clinical pharmacology and biopharmaceutics review(s). 5. Gertz, M., et al. Drug Metab Dispos, 2010. 38(7): p. 1147-58. 6. Ford, S.L., et al. ICAAC 2014. Washington, DC. 7. Gatti, G., et al. Antimicrob Agents Chemother, 1998. 42(8): p. 2017-23. 8. Aouri, M., et al. Antimicrob Agents Chemother, 2017. 61(1). 9. Iatsimirskaja, E., et al. Clin Pharmacol Ther, 1997. 61(5): p. 554-62. 10. McGinnity, D.F., et al. Drug Metab Dispos, 2009. 37(6): p. 1259-68. 11. Brainard, D.M., et al. J Clin Pharmacol, 2011. 51(6): p. 943-50.

