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In Silico Drug Interaction of Long-acting Rilpivirine and Cabotegravir With Rifampin

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Introduction

- Co-administration of anti-TB drugs and many antiretrovirals (ARVs) result in important drug-drug interactions (DDIs)
- Investigation of DDIs between ARVs and anti-TB drugs in individuals can be complicated by numerous clinical, logistical barriers and also due to the risk of treatment failure
- Physiologically-based pharmacokinetic (PBPK) modelling represents a mathematical tool to predict DDI magnitude through a detailed understanding of mechanisms underpinning pharmacokinetics
- The objective of this study was to simulate the effect of rifampicin on the pharmacokinetics of cabotegravir and rilpivirine long-acting injectable (LAI) intramuscular (IM) formulations using PBPK modelling

Results

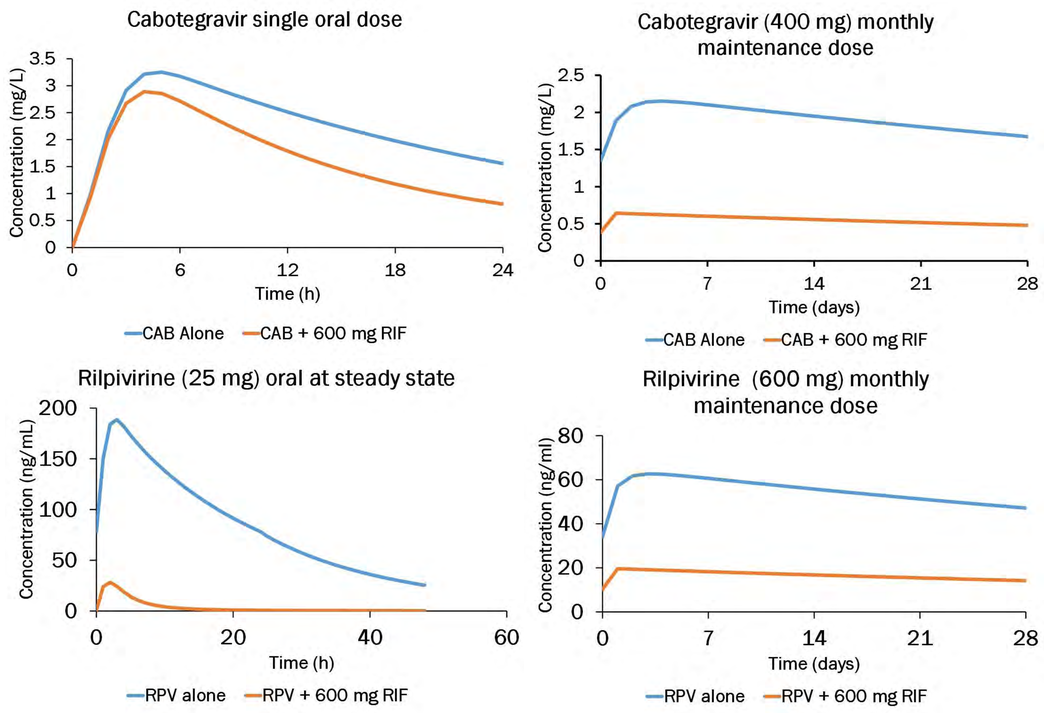

Figure 1 – Cabotegravir and rilpivirine oral OD and intramuscular maintenance doses alone and with 600 mg OD rifampicin administered through the dosing interval

- PBPK models were successfully qualified against oral rifampicin, oral and IM cabotegravir and rilpivirine
- Plasma AUC decreased by 40% and 80% for cabotegravir and rilpivirine when co-administered with 600 mg oral rifampicin (Figure 1)
- Co-administration of rifampicin at steady state LA IM cabotegravir lead to plasma concentrations below minimum effective concentration of 1.2 mg/L (Figure 2)

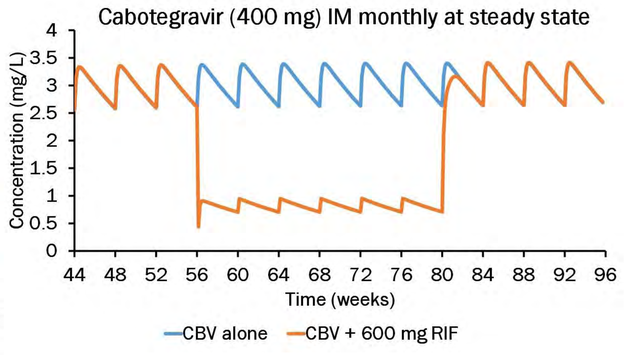

Figure 2 – Steady state LA cabotegravir alone and with oral 600 mg rifampicin OD administered from week 56 to week 80

Table 2 – Comparison of pharmacokinetics between drug administered alone and with rifampin (600 mg once daily) for maintenance doses of cabotegravir and rilpivirine 4-weekly and 8-weekly intramuscular formulations

	Drug Alone		Drug + 600 mg OD rifampin		% difference (alone vs. DDI)		Half-life (days)	
	AUC	C_{trough}	AUC	C_{trough}	AUC	C_{trough}	Alone	Drug + Rif
Cabotegravir 400 mg MD (4-weekly)	1340 ± 295	1.40 ± 0.31	794 ± 186	0.8 ± 0.2	-40.7%	-42.8%	68	65
Cabotegravir 800 mg MD (8-weekly)	2291 ± 541	1.42 ± 0.33	1247 ± 319	0.77 ± 0.2	-45.6%	-45.8%	69	64
Rilpivirine 600 mg MD (4-weekly)	39313 ± 22724	37.3 ± 22.3	7128 ± 3128	6.7 ± 2.9	-81.9%	-82.1%	62	59
Rilpivirine 900 mg MD (8-weekly)	59219 ± 28134	37.4 ± 17.9	10175 ± 4464	6.6 ± 2.9	-82.8%	-82.4%	62	59

LD – loading dose, MD – maintenance dose. C_{trough} is computed at the end of the dosing interval (4/8 weeks). Cabotegravir C_{max}, C_{trough} are expressed as µg/ml and AUC in µg.h/ml; Rilpivirine C_{max}, C_{trough} are expressed as ng/ml and AUC in ng.h/ml. Intramuscular maintenance dose was preceded by 4-weeks of daily oral dose (30 mg- cabotegravir, 25 mg – rilpivirine) and 4-weeks of intramuscular loading dose (800 mg- cabotegravir, 900 mg – rilpivirine)

Methods

- 100 virtual individuals were simulated using Simbiology v.4.3.1, a product of MATLAB (version 2013b)
- PBPK models were qualified against literature data for oral formulations of rifampicin (600 mg OD, at day 6 & 14), cabotegravir and rilpivirine (oral, single dose & steady state and IM compared to LATTE-2 studies)[1-4]
- Loading doses of 800 mg, 900 mg and maintenance doses of 400/800 mg, 600/900 mg were used for cabotegravir and rilpivirine respectively as four/eight weekly doses.[3]
- PBPK models were assumed to be qualified if the difference between mean simulated values and observed mean values was less than 2-fold[1,2,7]
- Effect of oral 600 mg rifampicin against IM cabotegravir and rilpivirine LAI formulations was studied for 84 days

Table 1 Drug specific parameters used in the PBPK model[5,6]

	Cabotegravir	Rilpivirine	Rifampicin
log P	2.2	4.32	2.7
pKa	4.14	3.26	1.7
Protein binding	99.3%	99.7%	80%
Blood-to-plasma ratio	0.441	0.67	0.9
Clint CYP3A4 (µL/min/pmol)	-	2.04	-
Clint UGT1A1 (µL/min/pmol)	4.5	-	-
Clint UGT1A9 (µL/min/pmol)	2.2	-	-
IM release rate (h^{-1})	4.54×10^{-4}	9×10^{-4}	-
Ind_{max}/ Ind_{50} CYP3A4	-	-	15/ 0.715[7]
UGT clearance	-	-	↑2.4 fold[1]

Conclusions

- These simulations suggest that co-administration of cabotegravir and rilpivirine with rifampicin is likely to result in suboptimal exposure
- Drug plasma half-lives of LA formulations during these DDI are not predicted to change even though decrease in plasma concentrations were observed due to flip-flop kinetics

References

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