Unexpectedly low drug exposures among Ugandan patients with TB and HIV receiving high-dose rifampicin.

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Background and objectives

Higher doses of rifampicin have been shown to improve tuberculosis (TB) treatment outcomes [1] and possibly reduce the risk of developing drug resistance.

Rifampicin induces its own metabolism at standard doses. Little is known of the extent of this induction when higher doses are administered to patients with TB.

Objective: To characterize the pharmacokinetics of standard- and high-dose rifampicin in adults with TB and HIV.

Methods

Data was available from the SAEFRIF study (NCT03982277) carried out in Kampala, Uganda.

Participants with TB and HIV were randomized to receive TB treatment with either standard 10 mg/kg (10RHZE) or 35 mg/kg (35RHZE) rifampicin-dose containing TB regimen.

A different rifampicin-only formulation (Rif_caps) was used to top up the dose of the fixed dose combination (FDC) in the 35RHZE cohort. Pharmacokinetic sampling was done >4 weeks after starting treatment; at pre-dose, 1-, 2-, 4-, and 8-h after the dose.

Population pharmacokinetic analysis was done using SAEM method in NONMEM v7.5.0. One- and 2-compartment models with 1st order absorption (with lag or transit compartments) and elimination were tested. A previous model with saturated hepatic extraction was also tested [2].

Results

A total of 533 samples from 111 adult participants (characteristics in **Table 1**) were used to fit the rifampicin model.

Table 1: Participant characteristics

Characteristic	Rifampicin regimen		Total
	10RHZE	35RHZE	
Number (%)	57 (51)	54 (49)	111 (100)
Male (%)	35 (51)	34 (49)	69 (62)
Age (yr)	38 (32 – 43)	34 (30 – 42)	36 (31 – 43)
Weight (kg)	52 (46 – 60)	54 (48 – 54)	53 (47 – 60)

Data are presented as a number (%) or median (range).

A previous rifampicin model **Figure 1** with saturable hepatic extraction [2] best fit the 10RHZE data but it over predicted the 35RHZE exposures, and indeed, the concentrations were lower than those reported in previous studies.

The best way to adjust for this was to include a formulation effect for the top up formulation, after which the model fit both arms as shown by the VPC in **Figure 2.** Final rifampicin model parameters are presented in **Table 2.**

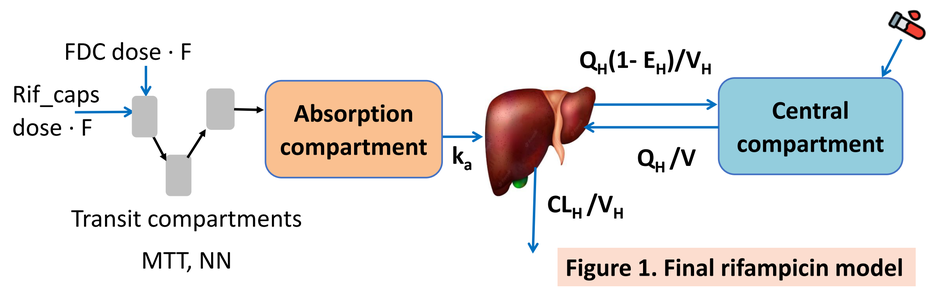

Figure 1. Final rifampicin model

$$CL_H = Q_H \cdot E_H, \qquad E_H = \frac{CL_{int} \cdot fu}{CL_{int} \cdot fu + Q_H}, \qquad CL_{int} = \frac{CL_{int,max} \cdot k_m}{C_H + k_m}$$

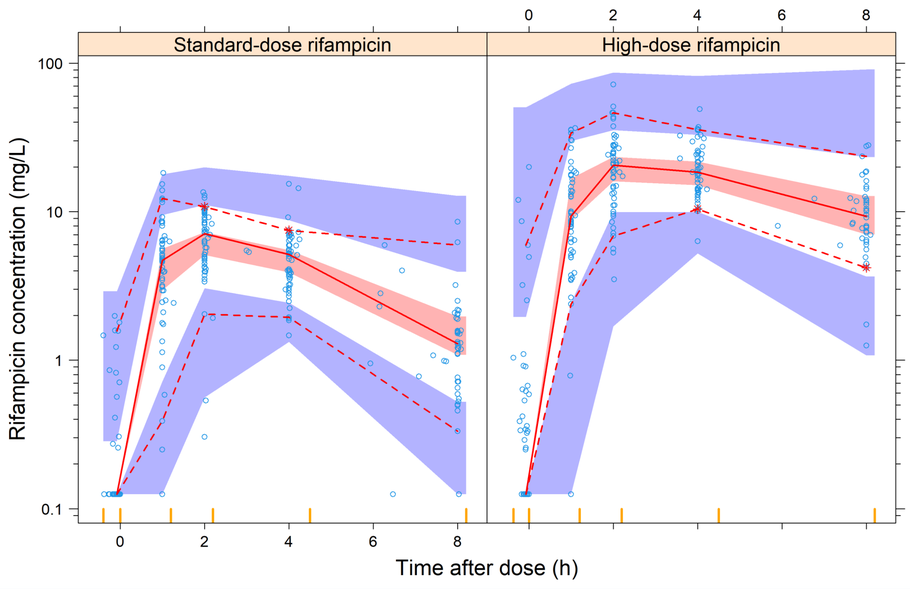

Figure 2. VPC stratified by rifampicin regimen. The solid and dashed lines represent the 50th, 5th, and 95th percentiles of the observed data (open circles), while the shaded areas represent the model-predicted 95% confidence intervals for the same percentiles

Results

Table 2. Parameter estimates

Parameter	Typical value (95% CI) [c]	Variability as CV% [b] (95% CI) [c]
Maximum intrinsic clearance, $CL_{int,max}$ (L/h) [a]	133 (109 – 165)	BSV: 25.0 (12.2 – 31.9)
Michaelis-Menten constant, k_m (mg/L)	8.00 (5.32 – 10.9)	
Volume of distribution, V (L) [a]	45.2 (38.6 – 48.7)	
Hepatic volume, V_H (L) [a]	1 fixed	
Hepatic blood flow rate, Q_H (L/h) [a]	90 fixed	
Unbound fraction of rifampicin, *fu* (fraction)	0.2 fixed	
Absorption rate constant, ka (/h)	1.76 (1.04 – 2.39)	BOV: 85.0 (49.6 – 110)
Mean transit time (h)	0.505 (0.299 – 0.669)	BOV: 88.1 (59.0 – 121)
Number of transit compartments (n)	16.8 (11.4 – 21.5)	
Relative bioavailability, F (fraction)	1 fixed	BOV: 27.0 (20.8 – 32.1)
Change in F of top-up rifampicin capsules (%)	-38.4 (-48.6 – -26.0)	
Scaling factor for BOV of data from dosing (fold)	2.82 (1.71 – 3.29)	
Proportional error (%)	21.3 (18.0 – 25.0)	
Additive error (mg/L)	0.05, fixed to 20% of LLOQ	

All the parameters refer to a typical 53 kg person in the study whereas the hepatic flow and liver volume are for a typical 70 kg adult.
[a] Disposition parameters were allometrically scaled by fat-free mass.
[b] Variability was included either as between-subject variability (BSV) or between-occasion variability (BOV), assuming a lognormal distribution. It is reported here as the percent coefficient of variation (CV) calculated as %CV= $\sqrt{(\omega^2)} \times 100$.
[c] The values in the parentheses are empirical 95% confidence interval (CI) generated by sampling importance resampling.
LLOQ, lower limit od quantification.

Of note, the increase in rifampicin AUC_{0-24} (**Table 3**) of the high- versus standard-dose participants in our study was lower than what was reported from other studies.

We simulated what the exposures of our participants would be with a bioequivalent top up formulation and the resulting AUC_{0-24} and C_{max} were in line with previous studies.

Table 3. Comparative exposures of high-dose rifampicin reported by different studies

Characteristic	STUDY											
	RifT [6]		LASER-TBM [5]		Boeree [4]		Boeree [1]		Chirehwa [2]	Current study		
Day of pharmacokinetic sampling	Day 2		Day 3		Day 14		Week 4		Week 4	Week 6		
Rifampicin dose (mg/kg)	10	**35**	10	**35**	10	**35**	10	**35**	10	10	**35**	***35****
Number of participants (n)	21	**20**	17	**15**	8	**15**	123	**63**	61	54	**57**	-
Median weight (kg)	50	**51**	64	**60**	57	**57**	54	**52**	55	51.7	**53**	-
Median age (yr)	34	**33**	38	**41**	27.5	**37**	34	**33**	32	38	**34**	-
Median AUC_{0-24} (mg·h/L)	42.9	**327**	42.9	**295**	26.3	**235**	24.2	**170**	39.3	32.3	**153**	***230***
Fold-change in AUC_{0-24}	-	**7.6**	-	**6.9**	-	**8.9**	-	**7.0**	-	-	**4.7**	***7.1***
C_{max} (mg/L)	6.04	**29.3**	6.9	**34.7**	7.4	**35.2**	5.8	**26.7**	6.9	8.07	**25**	***38.2***
Fold-change in C_{max}	-	**4.9**	-	**5.0**	-	**4.8**	-	**4.6**	-	-	**3.2**	***4.7***

*High-dose exposure after simulating equal bioequivalence of FDC and top-up rifampicin regimen. C_{max}, maximum concentration.

Discussion and conclusions

Whereas the data initially showed lower-than-expected high-dose rifampicin exposures, pharmacokinetics modeling revealed that indeed rifampicin had saturable hepatic extraction and that the bioavailability of the top up rifampicin-only formulation used in the high-dose cohort was 38% lower than that of the fixed dose combination.

It is known that rifampicin can adhere to other excipients in some formulations [3], and this may be the reason for lower bioavailability and resultant lower-than-expected high-dose exposures observed in this study.

More stringent bioequivalence-based assays are recommended to ensure good quality of rifampicin containing formulation.

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