Population pharmacokinetic modeling of rifampicin at standard and high doses in adults with tuberculous meningitis

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Background and Objectives[1-3]

Tuberculous meningitis (TBM) is the most fatal form of tuberculosis (TB) with high morbidity and mortality, especially in people living with HIV.
Rifampicin (RIF), an antibiotic, is the cornerstone of TB treatment. **RIF standard dose is 10 mg/kg/day**. **Higher doses (up to 35 mg/kg/day**) are being investigated.

RIF pharmacokinetics (PK):

- Mainly **metabolized by liver** esterases and excreted in bile.
- **Saturable elimination** observed at higher doses.
- **Induces its own clearance (CL)** with repeated dosing (via Pregnane X Receptor-mediated mechanisms that induces the esterases).
- CL expected to double after ~2 weeks due to autoinduction.

We aimed to describe RIF PK in plasma, including CL autoinduction, and compare exposures for intravenous vs oral RIF administration and for high-dose vs standard-dose RIF.

Methods

Study population: HIV-1 infected adults with TBM enrolled from 4 public hospitals in South Africa as part of the LASER-TBM study.
Study design: for the PK sub-study is shown below.

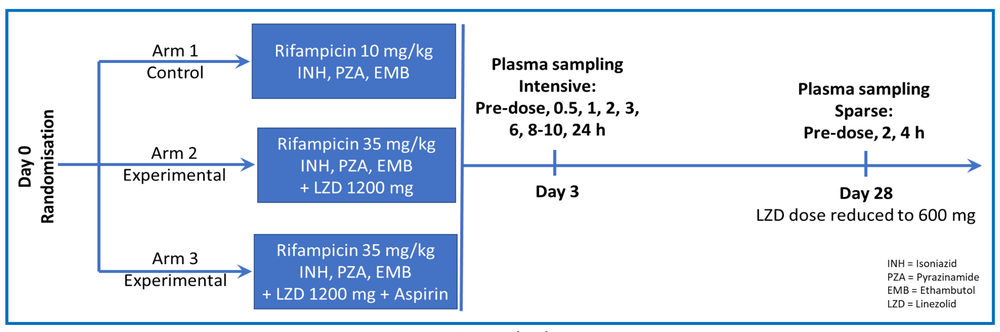

Figure 1: Study design

A second randomization was done for the experimental arms to receive RIF either as oral or intravenous (IV) infusion for ~1 hour dose.

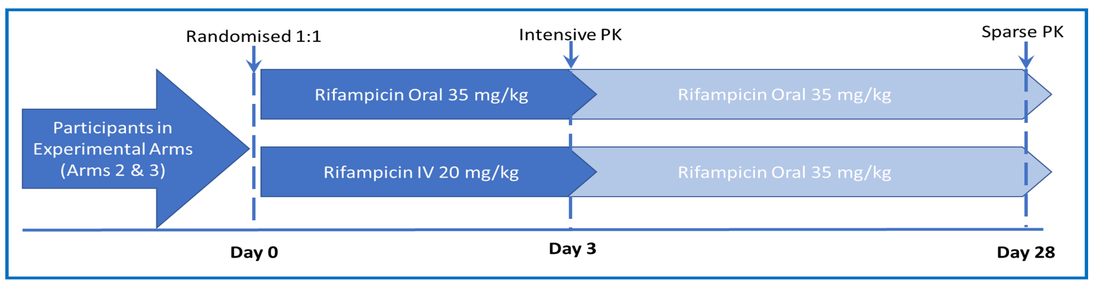

Figure 2: Second randomization

Total RIF concentrations were quantified in the plasma samples using liquid chromatography with mass spectrometry.
The concentrations were modelled with nonlinear mixed-effects modelling in NONMEM® 7.5 using first-order conditional estimation with eta-epsilon interaction.

Results

We enrolled 49 participants for PK sampling on Day 3, 40 of whom had a second PK visit on day 28 contributing to 415 total RIF plasma observations.

Table 1: Participant characteristics

	Day 3	Day 28
	Median (Min – Max)	
Number	49	40
Sex	Males: 27 (55%) Females: 22 (45%)	Males: 22 (55%) Females: 18 (45%)
Age (years)	39 (25 – 78)	38 (25 – 57)
Weight (kg)	60.0 (30.0 – 107)	62.2 (37.4 – 105)
Height (m)*	160 (148 – 180)	160 (149 – 180)
Fat-free mass (kg)*	45.2 (30.3 – 59.4)	46.1 (32.4 – 60.0)

*Height was missing for 29/49 (%) participants for Day 3 and 22/40 (%) for Day 28. Missing heights were imputed with a multiple regression model based on weight and sex from a similar study[4].

RIF PK was best described by:

- Absorption delay with transit compartments
- 2-compartment disposition with liver compartment
- Liver compartment with hepatic extraction and saturable elimination described by Michaelis-Menten equation
- Autoinduction of CL (higher CL on day 28)

Acknowledgements

We would like to acknowledge the study participants, the whole study team, and UCT PK Laboratory.

Results *cont.*

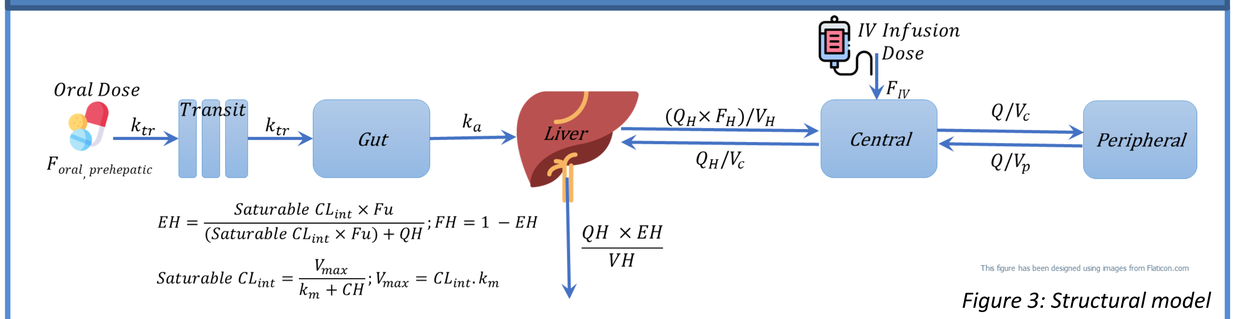

Figure 3: Structural model

Table 2: Parameter Estimates

Parameter	Estimate (95% CI) [a]	Variability estimate % (95% CI) [a,b]
Clearance intrinsic (CL_{int}) on day 3 (L/h) [c]	105 (70.5 - 130)	BSV 24.0 (17.8 – 25.9)
CL_{int} on day 28 for high-dose RIF (L/h) [c]	381 (295 - 522)	
CL_{int} on day 28 for standard-dose RIF (L/h) [c]	241 (186 - 343)	
Michaelis-Menten constant, km (mg/L) [d]	2.65 (2.02 – 4.70)	-
Volume (central), V_c (L) [c]	27.3 (24.2 – 32.3)	BSV 17.4 (14.2 – 23.8)
Volume (peripheral), V_p (L) [c]	33.5 (27.7 – 37.8)	-
Intercompartmental CL, Q (L/h) [c]	11.4 (8.21 – 13.3)	-
Absorption rate constant, k_a (1/h)	0.604 (0.500 – 0.679)	BOV 53.3 (39.1 – 58.7)
Mean transit time (h)	0.607 (0.426 – 0.591)	BOV 116 (63.9 - 124)
No. of transit compartments (.) [e]	19 fixed	-
IV bioavailability, F_{IV} (.)	1 fixed	-
Oral (prehepatic) bioavailability, $F_{oral,\ prehepatic}$ (.)[f,g]	0.944 (0.895 – 0.988)	BOV 23.0 (20.4 – 28.3)
Infusion time (h)[g]	1	BSV 18.0 (12.2 – 24.3)
Proportional error (%)	23.5 (18.1 – 24.1)	-
Additive error (mg/L) [h]	0.0634 (0.0633 – 0.0641)	-

[a] Values in parentheses are the 95% confidence interval, computed with sampling importance resampling (SIR).
[b] BSV: between-subject variability; BOV: between-occasion variability
[c] Disposition parameters were allometrically scaled by FFM. The typical values reported refer to a subject with median FFM of 46 kg.
[d] A prior of 3.35 mg/L with 30% uncertainty was used from Chirehwa et al.[3] to estimate km.
[e] The number of transit compartments was fixed to the value from Chirehwa et al.[3]
[f] Refers to the oral bioavailability before hepatic extraction
[g] Hepatic volume of distribution, V_H, hepatic blood flow, Q_H , and fraction RIF unbound were fixed to 1 L, 90 L/h, and 0.2, respectively. The V_H and Q_H values are reference values for a 70-kg adult and were scaled allometrically with FFM.
[g] The duration of IV infusion was recorded in PK visit forms.
[h] The lower boundary of the additive component of the error was fixed to 20% of LLOQ.

CL_{int} was found to be lower on the 3rd day of treatment vs on the 28th day. The degree of autoinduction was higher for the high-dose RIF (35 mg/kg) group vs the standard-dose RIF (10 mg/kg).

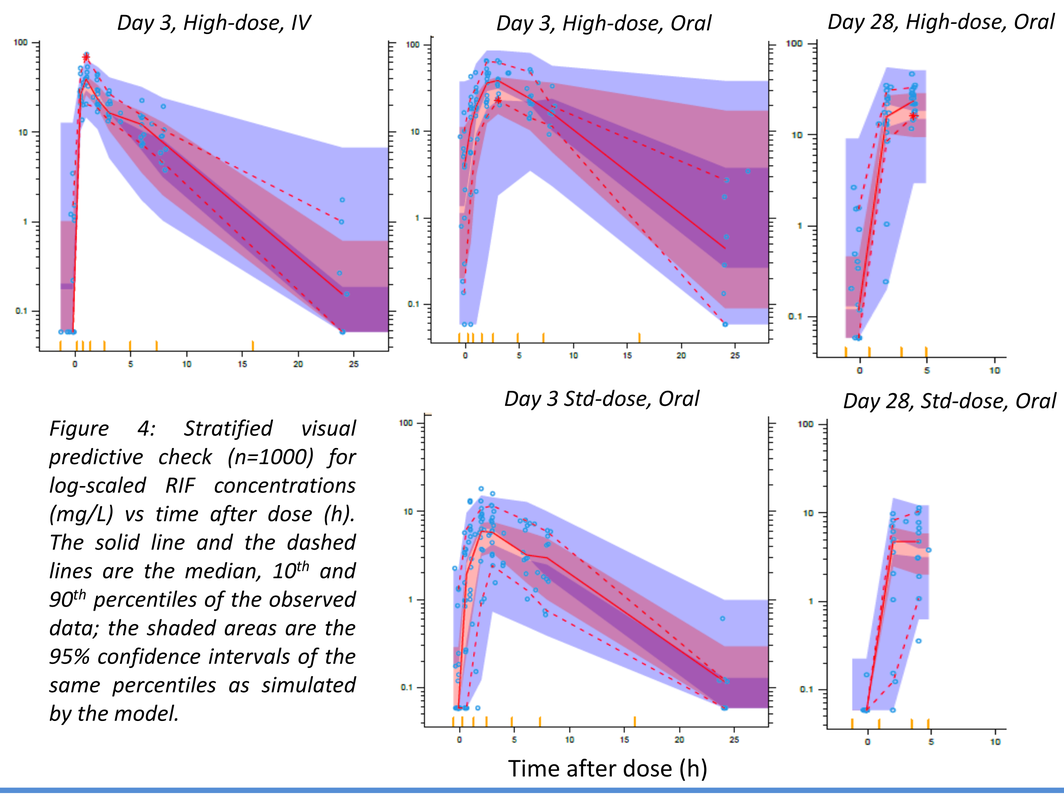

Figure 4: Stratified visual predictive check (n=1000) for log-scaled RIF concentrations (mg/L) vs time after dose (h). The solid line and the dashed lines are the median, 10th and 90th percentiles of the observed data; the shaded areas are the 95% confidence intervals of the same percentiles as simulated by the model.

Conclusion

The model by Chirehwa et al.[3] was successfully adapted to describe standard- and high-dose and oral and IV RIF.
Thanks to both IV and oral data, we could characterize 2-compartment disposition (previously reported in children[5]). Our estimate of oral bioavailability is similar to previous report[6].
CL on day 28 is higher than on day 3 due to autoinduction. CL autoinduction is higher for high-dose RIF.

References

1. Thwaites GE et al. The influence of HIV infection on clinical presentation, response to treatment, and outcome in adults with Tuberculous meningitis. *J Infect Dis.*; 2005
2. Acocella G. Pharmacokinetics and Metabolism of Rifampin in Humans. *Clin Infect Dis.*; 1983
3. Chirehwa et al. Model-Based Evaluation of Higher Doses of Riampin Using a Semi-Mechanistic Model Incorporating Autoinduction and Saturation of Hepatic Extraction. *Antimicrob Agents Chemther.*; 2016
4. Abdelwahab MT et al. Linezolid Population Pharmacokinetics in South African Adults with Drug-Resistant Tuberculosis. *Antimicrob Agents Chemother;* 2021
5. Svensson et al. Model-Based Meta-analysis of Rifampicin Exposure and Mortality in Indonesian Tuberculous Meningitis Trials. *Clin Infect Dis.*; 2020
6. Loos et al. Pharmacokinetics of oral and intravenous rifampicin during chronic administration. *Klin Wochenschr.* ;1985