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.

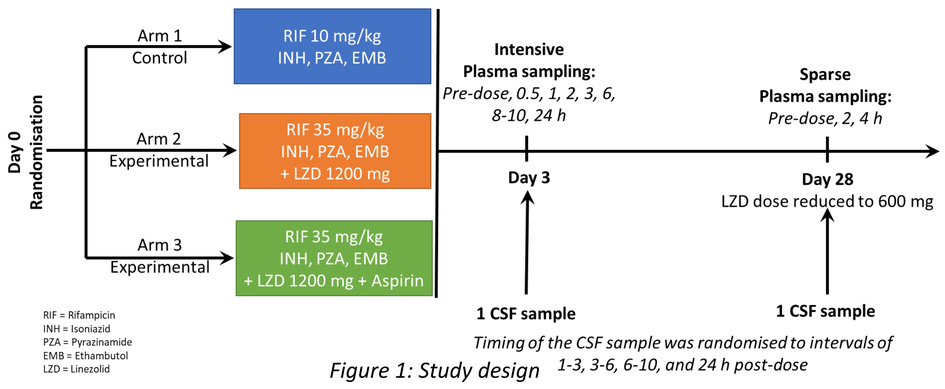

Figure 1: Study design *Timing of the CSF sample was randomised to intervals of 1-3, 3-6, 6-10, and 24 h post-dose*

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

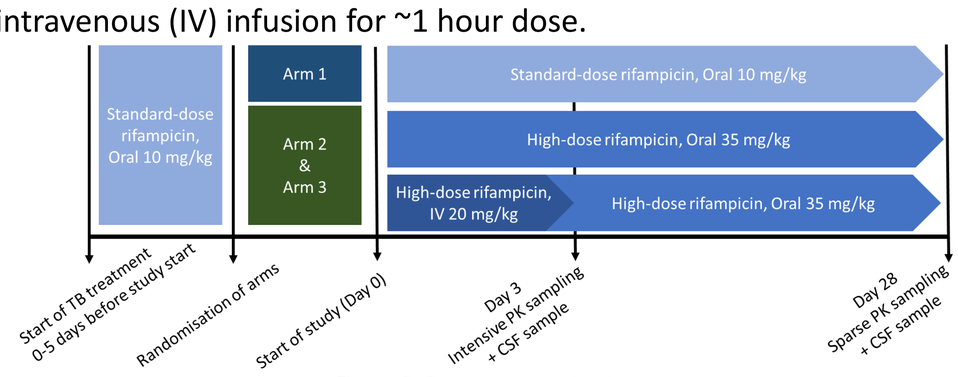

Figure 2: Second randomization

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 plasma and 44 CSF total RIF 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 (30 – 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.*

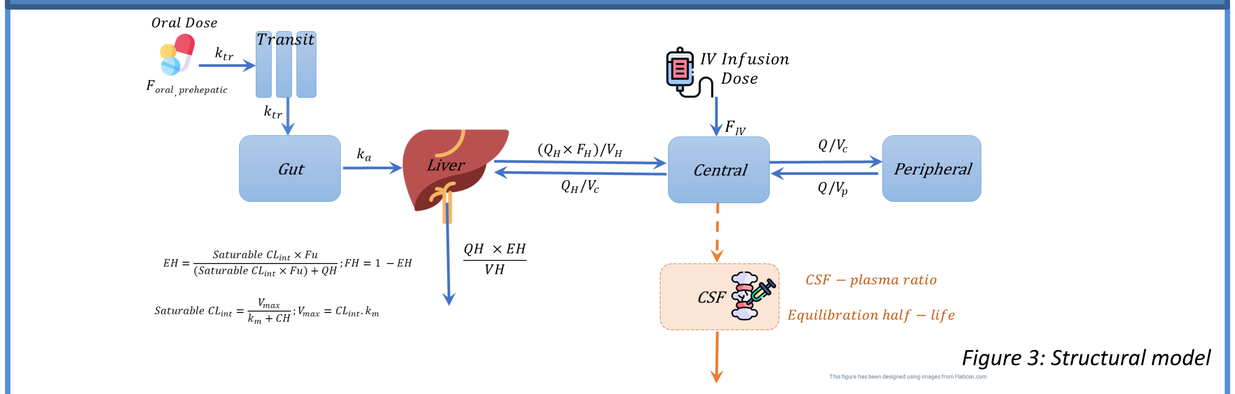

Figure 3: Structural model

Table 2: Parameter Estimates

Parameter	Estimate	Variability estimate [a] %
Clearance intrinsic (CL_{int}) of high-dose on day 3 (L/h) [b]	234	BSV = 27.6
CL_{int} of standard-dose on day 3 (L/h) [b]	169	
CL_{int} of high-dose on day 3 (L/h) [b]	359	
CL_{int} of standard-dose on day 28 (L/h) [b]	233	
Michaelis-Menten constant, km (mg/L) [c]	2.75	-
Volume (central), V_c (L) [b]	24.9	BSV = 15.7
Volume (peripheral), V_p (L) [b]	36.7	-
Intercompartmental CL, Q (L/h) [b]	12.6	-
Absorption rate constant, k_a (1/h)	0.555	BOV = 45.7
Mean transit time (h)	0.618	BOV = 116
No. of transit compartments (.) [d]	19 fixed	-
IV bioavailability, F_{IV} (.)	1 fixed	-
Oral (prehepatic) bioavailability, $F_{oral,\ prehepatic}$ (.)[e,f]	0.965	BOV = 40.0
Infusion time (h)[g]	1	BSV = 9.90
Proportional error, plasma (%)	26.5	-
Additive error, plasma (mg/L) [h]	0.0393	-
CSF-plasma ratio (.)	6.87	-
Equilibration half-life (h)	3.42	-
Proportional error, CSF (%)	66.4	-
Additive error, CSF (mg/L) [h]	0.001	-

[a] BSV: between-subject variability; BOV: between-occasion variability
[b] Disposition parameters were allometrically scaled by FFM. The typical values reported refer to a subject with median FFM of 45 kg.
[c] A prior of 3.35 mg/L with 30% uncertainty was used from Chirehwa et al.[3] to estimate km.
[d] The number of transit compartments was fixed to the value from Chirehwa et al.[3]
[e] Refers to the oral bioavailability before hepatic extraction
[f] 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).

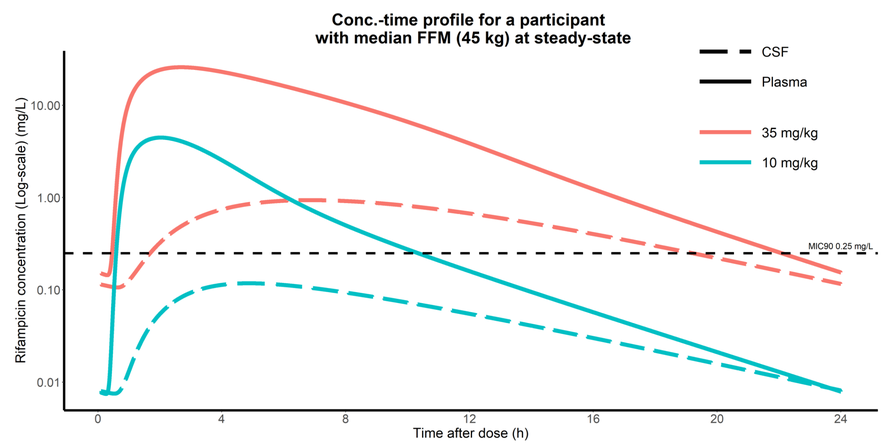

Figure 4: Typical rifampicin concentration-time profile for both standard-dose (10 mg/kg) and high-dose (35 mg/kg) rifampicin in both plasma and CSF for the typical participant in this cohort with median fat-free mass of 45 kg

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.
CSF-plasma ratio and equilibration half-life were in line with previous reports in children[5,7]

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