Model based evaluation of higher doses of rifampicin using a semi-mechanistic model incorporating auto-induction and saturation of hepatic extraction

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Background and Objectives

- Rifampicin is the mainstay of 1st line tuberculosis (TB) treatment
- Rifampicin, which is hepatically cleared, induces its own metabolism (auto-induction) and undergoes extensive first-pass metabolism [1]
- The onset and extent of auto-induction have not been adequately described
- Saturation of hepatic extraction of rifampicin at higher doses has been reported [2] and characterising the process becomes important if the dose of rifampicin is to be increased

Objectives

1. To describe rifampicin PK among TB patients accounting for auto-induction of clearance and saturation of hepatic extraction using a population model
2. Explore changes in exposure when dose is increased beyond currently recommended level

Methods

Data:

- 61 (33 females) HIV/TB co-infected and treatment naïve patients from South Africa commenced weight-adjusted doses (10 mg/kg on week days; 10 patients received treatment every day) of rifampicin as part of TB treatment.
- Blood samples were collected pre-dose, and at 1, 2, 4, 6, 8 and 12 hours post dose on each PK sampling day i.e. day 0, 7, 14 & 28
- Demographic data of 870 TB patients from South Africa & West Africa were used to simulate higher doses of rifampicin

Model building:

- NONMEM 7.3 (FOCE-I),
- Pirana,
- PSN,
- Xpose

Table 1. Characteristics of 61 patients with HIV/TB

covariate	median	range
Age (yrs)	32	18 – 47
Weight (kg)	55.2	34.4 – 98.7
Height (m)	1.59	1.41 – 1.81
Fat free mass (kg)	42.2	28.0-57.6

Results

Model structure is in Figure 1 and final parameter estimates in Table 2

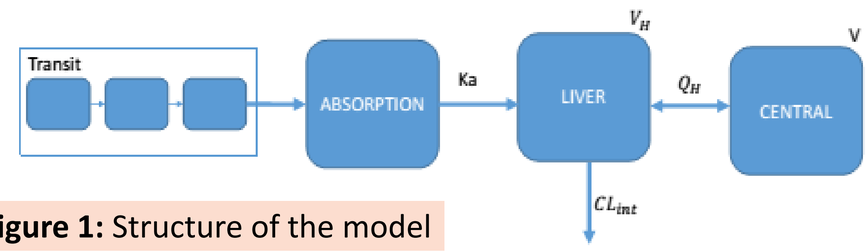

Figure 1: Structure of the model

A **well-stirred liver model** [3] was used to describe both **hepatic clearance and first-pass metabolism** due to hepatic extraction (E_H).

$$E_H = \frac{CL_{int} \cdot f_u}{CL_{int} \cdot f_u + Q_H} \; ; \; CL_{int} = \frac{CL_{int,max} \cdot K_m}{C_H + K_m}$$

For a typical individual, volume of liver (V_H) was fixed to 1 L , hepatic plasma flow (Q_H) 50 L/h and free fraction of rifampicin (f_u) at 20%

C_H is the **concentration of rifampicin in the liver** that drives intrinsic clearance (CL_{int})

Allometric scaling was applied to all clearance and volumes parameters, including liver compartment to account for body size using **fat free mass (FFM)** [4]

Auto-induction of rifampicin was characterised using an exponential maturation on $CL_{int,max}$ from day 0 to steady-state with an induction half-life $\left(t_{1/2}^{ind}\right)$

$$CL_{int,max} = CL_{int,max}^{0} + \left(CL_{int,max}^{0} - CL_{int,max}^{ss}\right)\left(1 - e^{-\ln(2)\cdot t \div t_{1/2}^{ind}}\right)$$

Table 2: Final parameter estimates (5th and 95th percentile)*

Parameter	Typical Value	BSV or BOV+ [%]
$CL_{int,max}^{0}$ [L/h]	93.2 (82.4-106)	22.5 (19.5-28.7); 21.9 (18.4-26.2)+
V [L]	50.1 (48.3-52.9)	14.2 (11.7-16.6)
F (pre-hepatic)	1 FIX	11.0 (9.9-15.3)+
KA [1/h]	1.96 (1.70-2.11)	81.2 (75.6-88.5)+
MTT [h]	0.71 (0.67-0.81)	62.7 (57.4-76.6)+
NN	19.3 (18.5-21.9)	-
$CL_{int,max}^{0}$ [L/h]	176 (156-202)	22.5 (19.5-28.7); 21.9 (18.4-26.2)+
$t_{1/2}^{ind}$ [days]	4.5 (4.0-4.8)	-
Km [mg/L]	3.35 (3.0-3.56)	-
Add err [mg/L]	0.06 (0.06-0.07)	-
Prop err [%]	10.8 (10.3-12.2)	-

All CL and V parameters reported for FFM of 42kg
*Percentiles from nonparametric bootstrap (n=50) of the final model

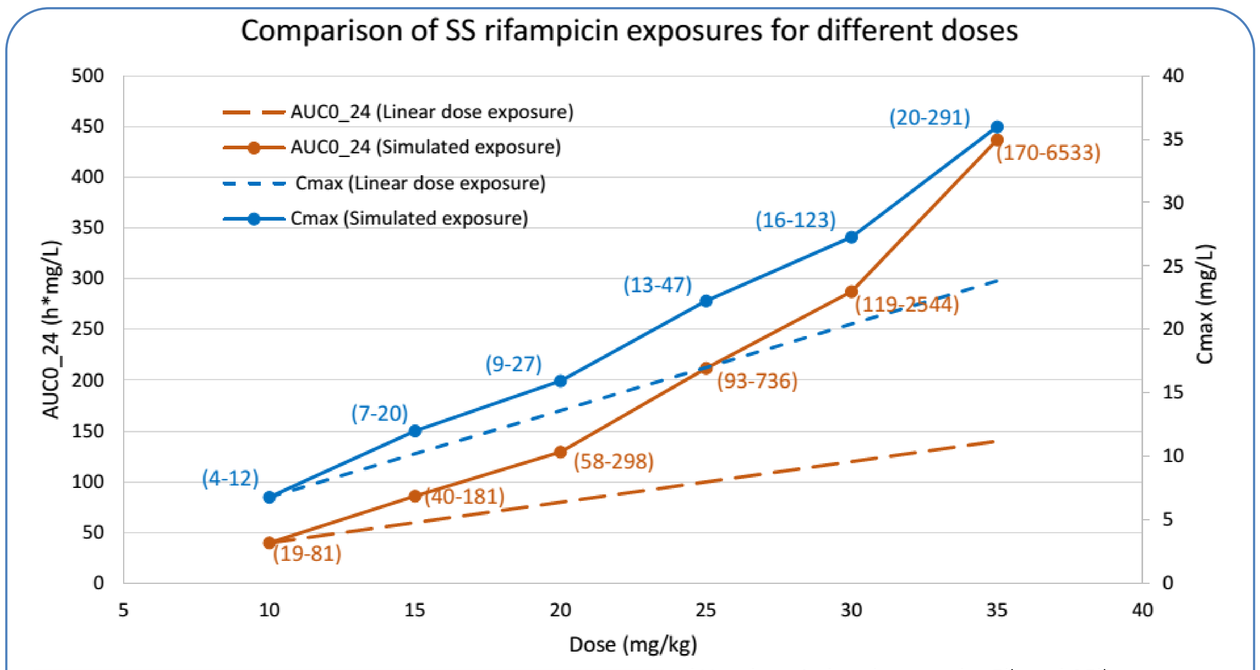

Figure 2: Rifampicin exposures at different dose*

*Numbers in bracket are the 5th and 95th percentiles of the distribution of simulated AUCs

Maximum intrinsic clearance of rifampicin **almost doubled** from first dose to steady state (Table 2) with an induction half-life of 4.5 days

Intrinsic clearance was saturable and followed **Michaelis-Menten kinetics**

Incorporating saturation of hepatic extraction explained the higher bioavailability among patients receiving 5 tablets and the **correlation between absorption and bioavailability**: fast absorption was correlated with high bioavailability

Simulations show that higher 24 post-dose concentrations will be detected if dose is increased to 30 or 35 mg/kg compared to current dose

Non-linear increase in exposure measured by AUC or Cmax was observed when dose was increased beyond the currently recommended (Figure 2)

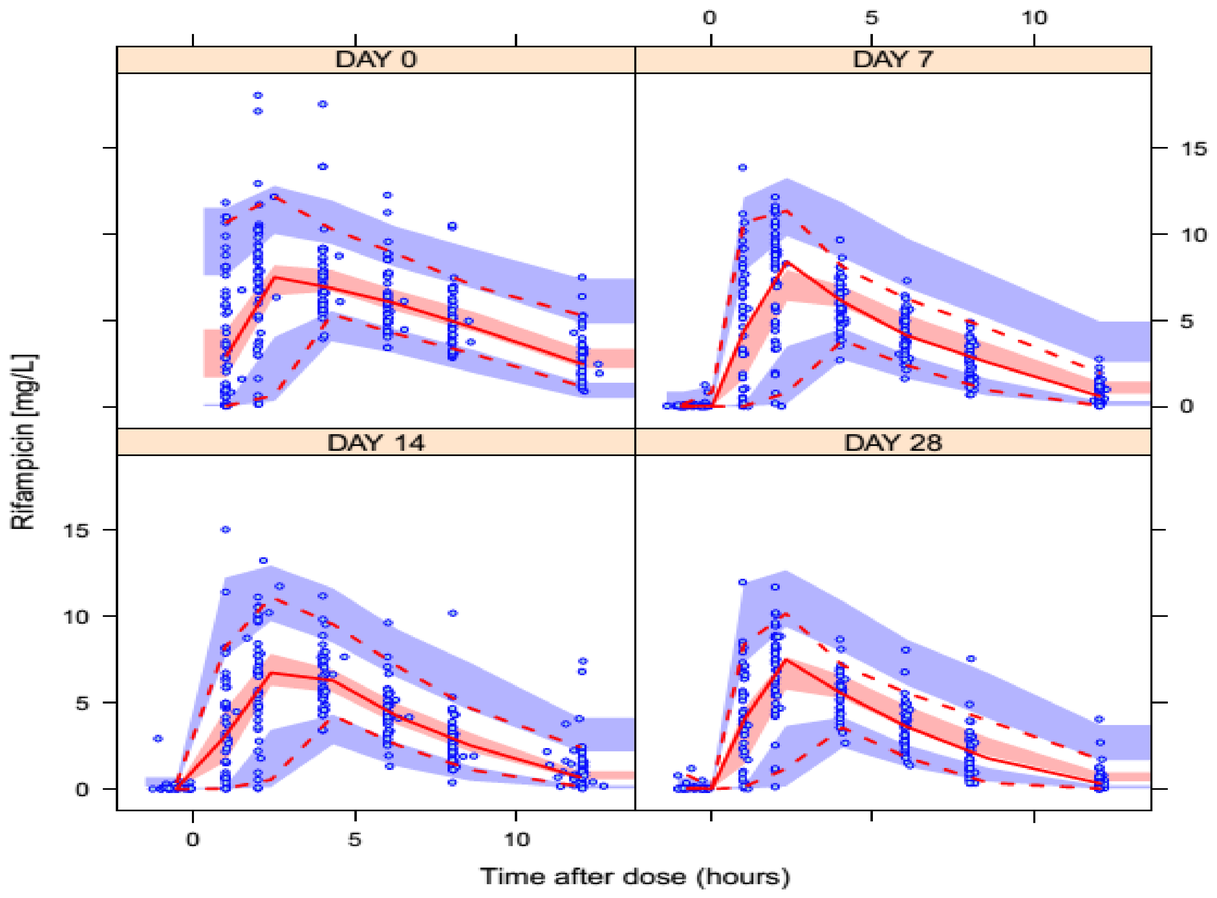

Figure 3: Visual predictive check*

* The figure shows a comparison of the 5th, 50th and 95th percentiles of the distribution of the observations (red lines) and confidence bands around the percentiles for simulated predictions.

Conclusions

Model predicts **that increasing the dose of rifampicin** result in a **more than proportional increase in exposure,** similar to recent report on high dose rifampin [5]

Auto-induction of rifampicin clearance is almost complete **after 3 weeks of treatment initiation**

With the currently recommended dose of rifampicin, the model predicts **saturation of hepatic extraction** and larger exposures in patients with higher weight (and proportionally lower FFM), as previously observed [6]

The **potential for increased toxicity** with the **nonlinear increase in rifampicin exposures** warrants thorough investigation

More work is needed to investigate whether **higher rifampicin doses** may lead to **more pronounced induction**

References

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