Characterization of rifampicin pharmacokinetics in Tanzanian and South African populations

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Context

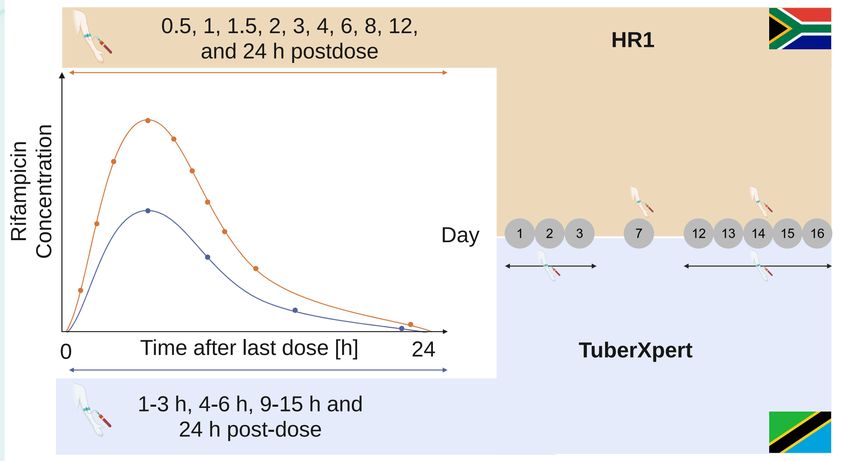
- **Rifampicin** is a cornerstone first-line anti-tuberculosis (TB) drug, but its **non-linear, highly variable and autoinductive pharmacokinetics (PK)** can result in subtherapeutic exposures.
- **Genetic polymorphisms of the organic anion-transporting polypeptide 1B1 (OATP1B1)** - which differ across ethnic groups - can substantially alter rifampicin PK.
- These complexities call for **optimized, individualized dosing strategies to ensure efficacy.**

Objectives

- **Describe and characterize autoinductive and saturable PK** of rifampicin using the population approach.
- **Identify and quantify individual and population variability** susceptible to alter rifampicin PK.

Methods

- A stepwise analysis comparing various compartmental models with linear and non-linear absorption and elimination were conducted with MonolixSuite™ (v2024R1). Inter-individual variability (IIV), and inter-occasion variability (IOV) on PK parameters were sequentially tested. Likewise, study effect was assessed as a covariate effect.
- Different residual error models were evaluated to characterize the unexplained variability.
- Visual Predictive Checks (VPC, n=1000) and bootstrap evaluations (n=2000) were performed to assess performance of the models.



- Data were collected through prospective rifampicin plasma concentrations sampled from TB patients at Kibong'oto Infectious Diseases Hospital, Tanzania, within the frame of the TuberXpert project[1] and completed with retrospective data from the South African HIGHRIF1 (HR1) study.

Results

Table 1. Characteristics of the TuberXpert (Tanzania, $n_{patients}$=42, $n_{samples}$ = 278) and HR1 (South Africa, $n_{patients}$=92, $n_{samples}$ = 1945) population

	Median (range) or n (%)									n (%)	
Population Characteristics	**TuberXpert**	**HR1**			**TuberXpert**	**HR1**				**TuberXpert**	**HR1**
Age [years]	44 (25-65)	*NA*	**Malnutrition**	Severely Underweight	14 (26)	*NA*	**Patients per Dosing Weight**	10 [mg/kg]		38 (90)	8 (9)
Female	11 (74)	*NA*		Moderately Underweight	3 (5)	*NA*		20 [mg/kg]		0 (0)	15 (16)
Weight [kg]	49 (31-65)	*NA*		Mildly Underweight	9 (17)	*NA*		25 [mg/kg]		1 (2)	15 (16)
Body Mass Index [kg/m²]	17.35 (12.10-24.70)	*NA*		No Malnutrition	16 (30)	*NA*		30 [mg/kg]		3 (7)	15 (16)
FFM [kg]	42.51 (19.94-50.44)	44.09 (28.50-57.86)		Overweight	9 (17)	*NA*		35 [mg/kg]		0 (0)	14 (15)
HIV positive patients	20 (48)	*NA*		Obese	3 (5)	*NA*		40 [mg/kg]		0 (0)	15 (16)
DM patients	6 (14)	NA						50 [mg/kg]		0 (0)	10 (11)

HIV, Human Immunodeficiency Virus; **DM,** diabetes mellitus; **FFM**, fat-free mass according to [2]; malnutrition status according to [3]

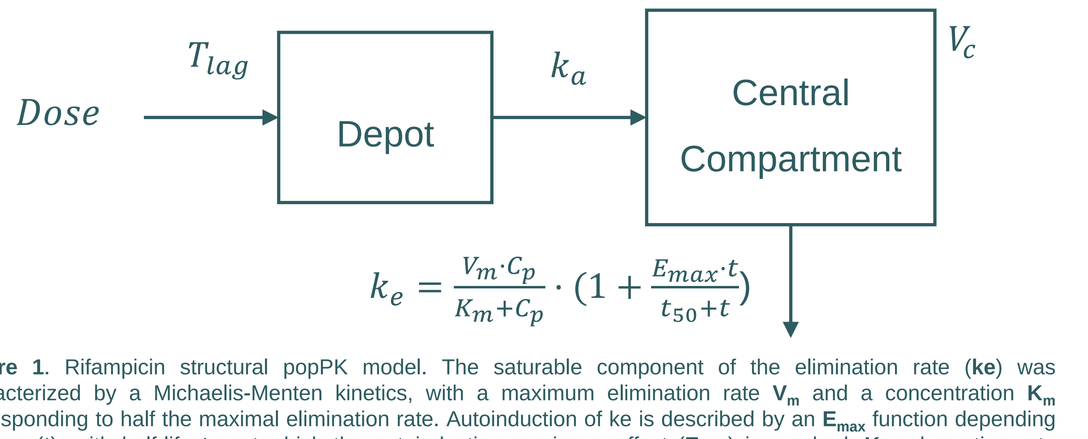


Figure 1. Rifampicin structural popPK model. The saturable component of the elimination rate (**ke**) was characterized by a Michaelis-Menten kinetics, with a maximum elimination rate V_m and a concentration K_m corresponding to half the maximal elimination rate. Autoinduction of ke is described by an E_{max} function depending on time (**t**), with half-life t_{50}, at which the autoinduction maximum effect (E_{max}) is reached. **Ka**, absorption rate constant; **V**, volume of distribution; T_{lag}, lag time.

Table 2. Final population PK parameters estimates and bootstrap results

		Final model	Bootstrap (n = 2000)
Parameter		**Estimate (RSE [%])**	**Median ($CI_{95\%}$)**
T_{lag} [h]		0.32 (12)	0.31 (0.24-0.38)
	ω_{Tlag} [CV%]	75 (22)	95 (47-161)
	γ_{Tlag} [CV%]	96 (17)	95 (45-112)
ka [h^{-1}]		2.64 (6)	2.58 (2.33-2.89)
	ω_{ka} [CV%]	38 (12)	36 (27-45)
V [L]		41 (3)	40 (38-42)
	ω_{Vc} [CV%]	18 (12)	19 (15-24)
$V_{m\text{-}HR1}$ [mg/h]		124 (13)	125 (95-161)
$V_{m\text{-}TuberXpert}$ [mg/h]		420 (10)	459 (354-601)
	ω_{Vm} [CV%]	38 (24)	33 (18-50)
K_m [mg/L]		27.5 (12)	30.1 (24.3-38.5)
	ω_{Km} [CV%]	46 (23)	46 (25-73)
$E_{max\text{-}HR1}$		3.31 (15)	3.94 (2.87-5.27)
$E_{max\text{-}TuberXpert}$		0.46 (16)	0.53 (0.23-0.88)
	ω_{Emax} [CV%]	24 (30)	21 (10-36)
t_{50} [h]		157 (20)	196 (134-287)
	ω_{t50} [CV%]	65 (23)	57 (30-92)
$Correlation_{Vm\text{-}Km}$ [%]		83 (4)	105 (67-161)
$\sigma_{prop\text{-}TuberXpert}$ [%]		25 (10)	24 (20-30)
$\sigma_{prop\text{-}HR1}$ [%]		23 (5)	24 (21-26)

ω, inter-individual variability; **γ**, inter-occasion variability; **$CI_{95\%}$**, 95% confidence interval; **σ_{prop}**, proportional error; **RSE**, Relative standard error.

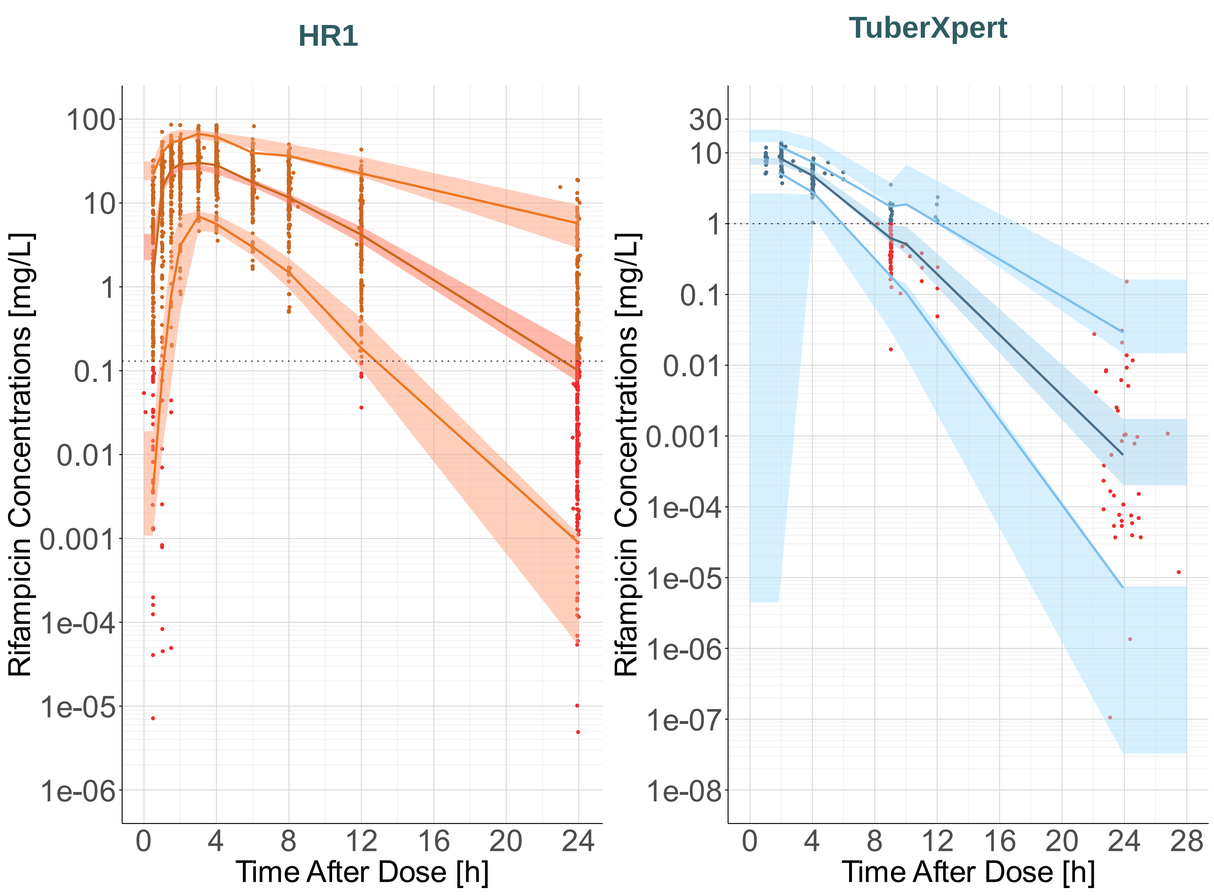


Figure 2: HR1 (Left) and TuberXpert (Right) VPC of the current model in log-transformed y axis. The points indicate the observed concentrations and the red dots their counterparts below the quantification limits (dotted lines, 0.13 mg/L and 1 mg/L for respectively TuberXpert and HR1). The solid lines represent the corresponding observed median and percentiles 5th and 95th. Shaded area depicts the prediction of the 90% confidence interval of the median and the 5th and 95th percentiles.

- **Substantial study effect was observed,** underlining marked population differences in the elimination process of rifampicin.
- **HR1** and **TuberXpert** populations increase their elimination by **3.76-fold and 1.38-fold**, respectively, once **autoinduction steady-state is reached, after roughly a month** of continuous treatment of rifampicin.

Conclusion

- We successfully characterized **rifampicin's non-linear, saturable kinetics and time-dependent autoinduction**.
- **Significant inter-study differences**—likely due to ethnic variability in OATP1B1 polymorphism—were observed, possibly because Tanzanian patients are more prone to carry genotypes linked to reduced rifampicin exposure and thus faster eliminations[4].
- **Substantial interindividual variability in rifampicin PK** was observed, emphasizing the need to individualized and monitoring solutions to improve TB patients' care**.**
- Further investigations relying on these findings will contribute to the **development of a model-informed precision dosing software tailored to the Tanzanian routine clinical care.**

1. Thoma Y, Cathignol AE, Pétermann YJ, Sariko ML, Said B, Csajka C, et al. JMIR Res Protoc. 2024 Oct 21;13:e58720. **2.** Anderson BJ, Holford NHG. Annu Rev Pharmacol Toxicol. 2008;48(1):303–32. **3.** Edition 7. MANUAL FOR MANAGEMENT OF TUBERCULOSIS AND LEPROSY IN TANZANIA. **4.** Petermann YJ, Said B, Cathignol AE, Sariko ML, Thoma Y, Mpagama SG, et al. JAC Antimicrob Resist