



Population pharmacokinetic analysis of isoniazid in plasma and cerebrospinal fluid from adults with HIV-associated tuberculosis meningitis

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Background and objectives

Tuberculosis Meningitis (TBM) represents the most severe manifestation of infection by *Mycobacterium tuberculosis*, especially among individuals with **HIV**, where mortality rates can exceed **50%**.¹

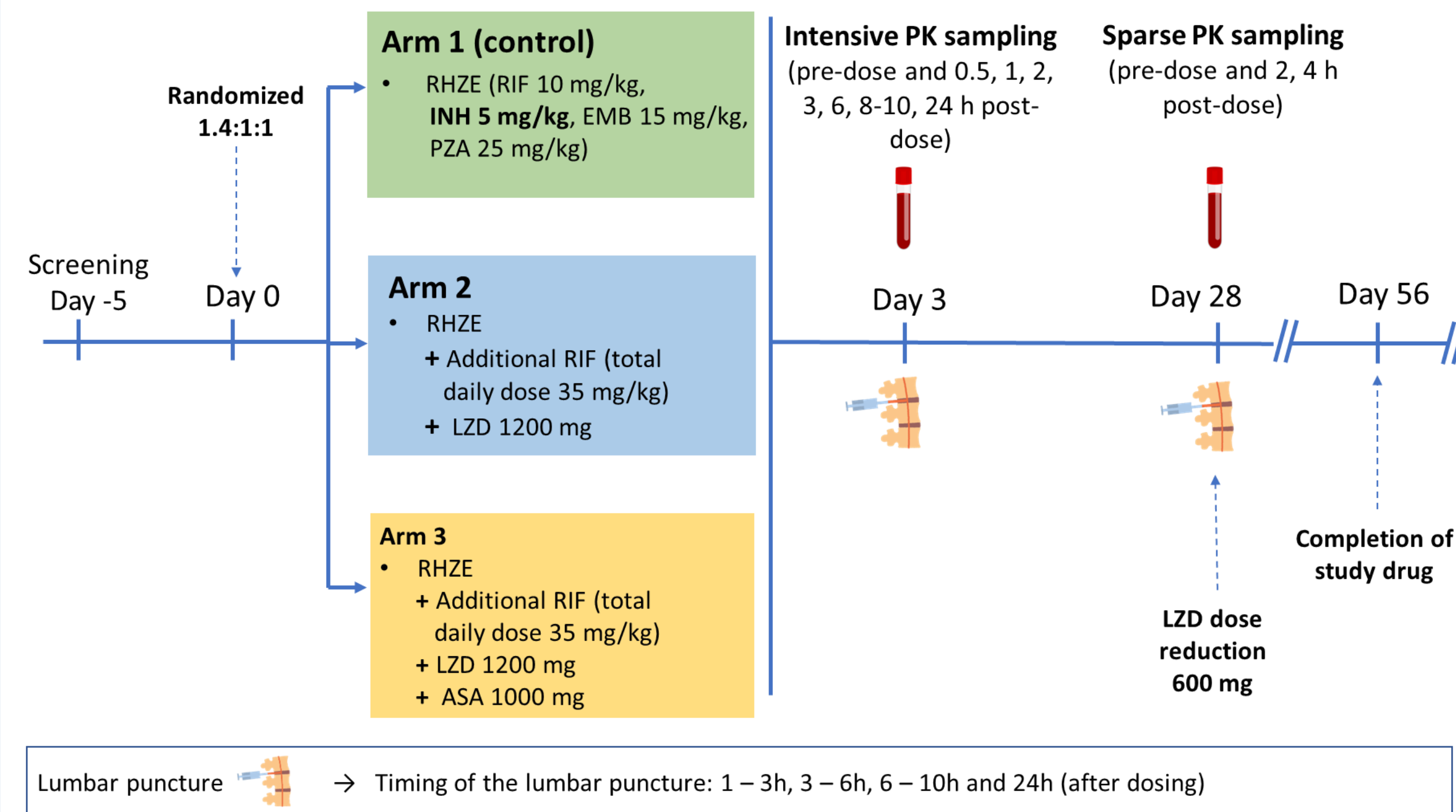
The current **WHO guidelines** for **TBM treatment** recommend the same regimen as **pulmonary tuberculosis (TB)**, albeit for an extended duration, regardless of the **anti-TB drugs' ability to penetrate the central nervous system**.¹

Isoniazid (INH) is a key **first-line drug** in **TB treatment**.² Although well studied in pulmonary TB, the **plasma pharmacokinetics (PK)** of **INH** and its penetration into **cerebrospinal fluid (CSF)** require further research in **TBM**, especially in the context of **South African TBM patients**, where there is a high burden of **TB/HIV coinfection**.

We characterized the **PK of INH** in **plasma and CSF** from **South African adults with HIV-associated TBM**.

Methods

This PK study was nested in LASER-TBM, a phase 2a, randomized and multicentre clinical trial carried out among adults living with HIV and newly diagnosed TBM in South Africa.¹



INH plasma and CSF concentrations were measured using **liquid chromatography tandem mass spectrometry** with a limit of quantification (**LOQ**) of **0.105 mg/L for plasma** and **0.0586 mg/L for CSF**. Samples below the **LOQ** were imputed as **LOQ/2**, and the **additive error** was fixed to at least **20% of the corresponding LOQ** as an adaptation of the M6 method suggested by Beal *et al.*³

The N-acetyltransferase 2 (**NAT2**) genotype was determined in consenting participants. A **mixture model** was used to differentiate between different **NAT2 phenotypes** in participants lacking genotypic data.

The **PK analysis** was performed using **FOCE-I** in **NONMEM**.

Results

Table 1. Participants characteristics

	First visit (day 3) (n = 49)	Second visit (day 28) (n = 34)
Males	27 (55)	20 (59)
Female	22 (45)	14 (41)
Weight (kg)	59.5 (30.0-107)	61.7 (37.4-105)
Height (cm) ^b	160 (148-180)	160 (149-180)
Fat-free mass (kg) ^a	45.2 (30.3-59.4)	45.5 (32.4-60.0)
Age (years)	39 (25-78)	39(25-57)
NAT2 acetylator phenotype		
Slow	6 (12.2)	3 (8.8)
Intermediate	17 (34.7)	13 (38.2)
Rapid	8 (16.3)	6 (17.6)
Missing information	18 (36.8)	12 (35.4)
Antiretroviral therapy (ART)		
On ART	15 (30.6)	10 (29.5)
ART Naïve	20 (40.8)	14 (41.1)
Previous ART	14 (28.6)	10 (29.4)

Data is presented as median (range) or n (%).

^a Fat-free mass was calculated by applying the formula from Janmahasatian *et al.*⁴

^b Height data was missing for 29 participants on day 3 and for 19 participants on day 28.

- A total of 27.5% (114/414) of plasma concentrations and 2.2% (1/44) of CSF concentrations were BLQ.

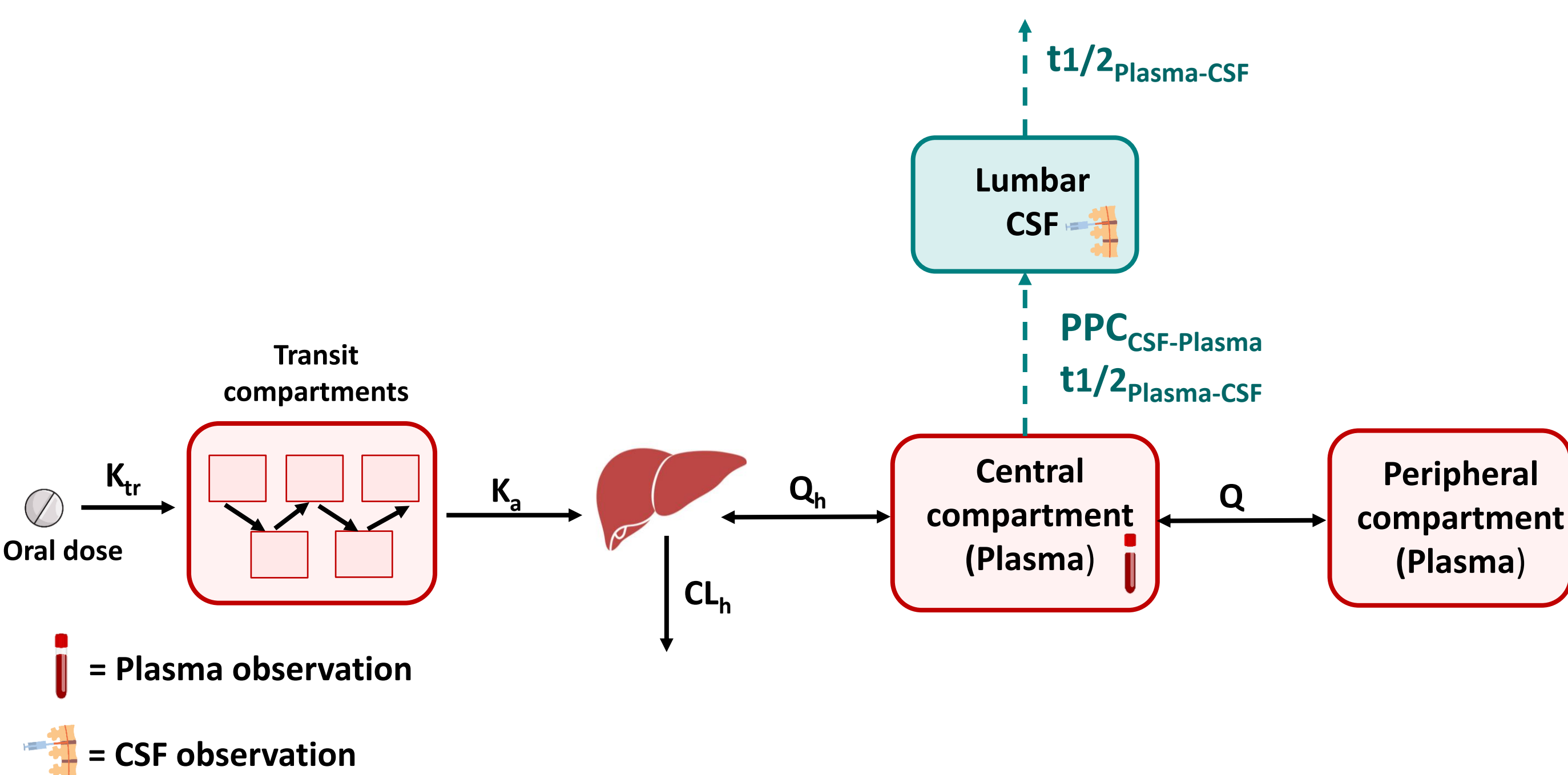


Figure 2. Final pharmacokinetic model. Ktr: transit rate constant; Ka: absorption rate constant; Q_h: hepatic blood flow; Q: intercompartmental clearance; CL_h: hepatic clearance; t_{1/2}_{Plasma-CSF}: equilibration half-life between plasma and cerebrospinal fluid, which describe how soon the change in plasma concentrations is reflected in the CSF; PPC_{CSF-Plasma}: pseudo-partition coefficient which represents the relative drug exposure in CSF compared to plasma at steady state.

Results

- INH effectively penetrated the CSF, reaching a steady-state CSF exposure similar to that in plasma (PPC_{CSF-Plasma} = 1.04).
- INH plasma and CSF concentrations equilibrated with a half-life of 3.87 hours.
- High-dose rifampicin did not affect INH PK.
- Fat-free mass was a better predictor of the body size effect on disposition parameters than body weight.

Table 2. Final parameter estimates

Parameter	Typical value (95% CI) ^a	Variability (95% CI) ^a
Clearance (L/h) ^b		
Slow acetylator	14.63 (12.1 – 17.1)	Between subject: 22.5 (17.0 – 30.5)
Intermediate acetylator	32.2 (28.6 – 37.0)	
Rapid acetylator	64.7 (54.1 – 77.7)	
Central volume of distribution (L) ^b	43.6 (39.7 – 48.7)	
Intercompartmental clearance (L/h) ^b	5.02 (3.41 – 6.56)	
Peripheral volume of distribution (L) ^b	22.3 (15.5 – 30.3)	
Bioavailability	1 Fixed	Between occasion: 32.1 (24.9 – 39.5)
Mean absorption transit time (h)	0.24 (0.16 – 0.32)	Between occasion: 139 (114 - 178)
Number of absorption transit compartments (.) ^c	5 Fixed	
First-order absorption rate constant (h ⁻¹)	2.21 (1.59 – 3.08)	Between occasion: 87.0 (64.6 - 121)
Hepatic blood flow (L/h) ^d	81.0 Fixed	
CSF-to-plasma pseudo-partition coefficient, PPC _{CSF-Plasma} (.)	1.04 (0.76 – 1.38)	
Plasma-to-CSF equilibrium half-life, t _{1/2} _{Plasma-CSF} (h)	3.87 (2.47 -7.59)	
Proportional error for plasma (%)	16.4 (14.5 – 19.2)	
Additive error for plasma (mg/L) ^e	0.02 Fixed	
Proportional error for CSF (%)	58.8 (46.9 – 82.7)	
Additive error for CSF (mg/L) ^e	0.01 Fixed	

^a 95% confidence intervals (CI) were obtained using sampling-importance resampling.

^b Parameters allometrically scaled by fat-free mass. The reported typical values refer to the typical individual in the cohort with fat-free mass of 45 kg.

^c Number of transit compartments was fixed to 5 (based on the model's estimation) to enhance stability. A sensitivity analysis showed the value of number of transit compartments was not critical.

^d The hepatic blood flow value for the typical individual in the cohort (with a body weight of 60 kg) is equivalent to 90 L/h in a 70 kg individual.

^e The estimate of the additive component of the residual unexplained variability did not significantly differ from its lower boundary of 20% of LOQ and it was fixed to this value.

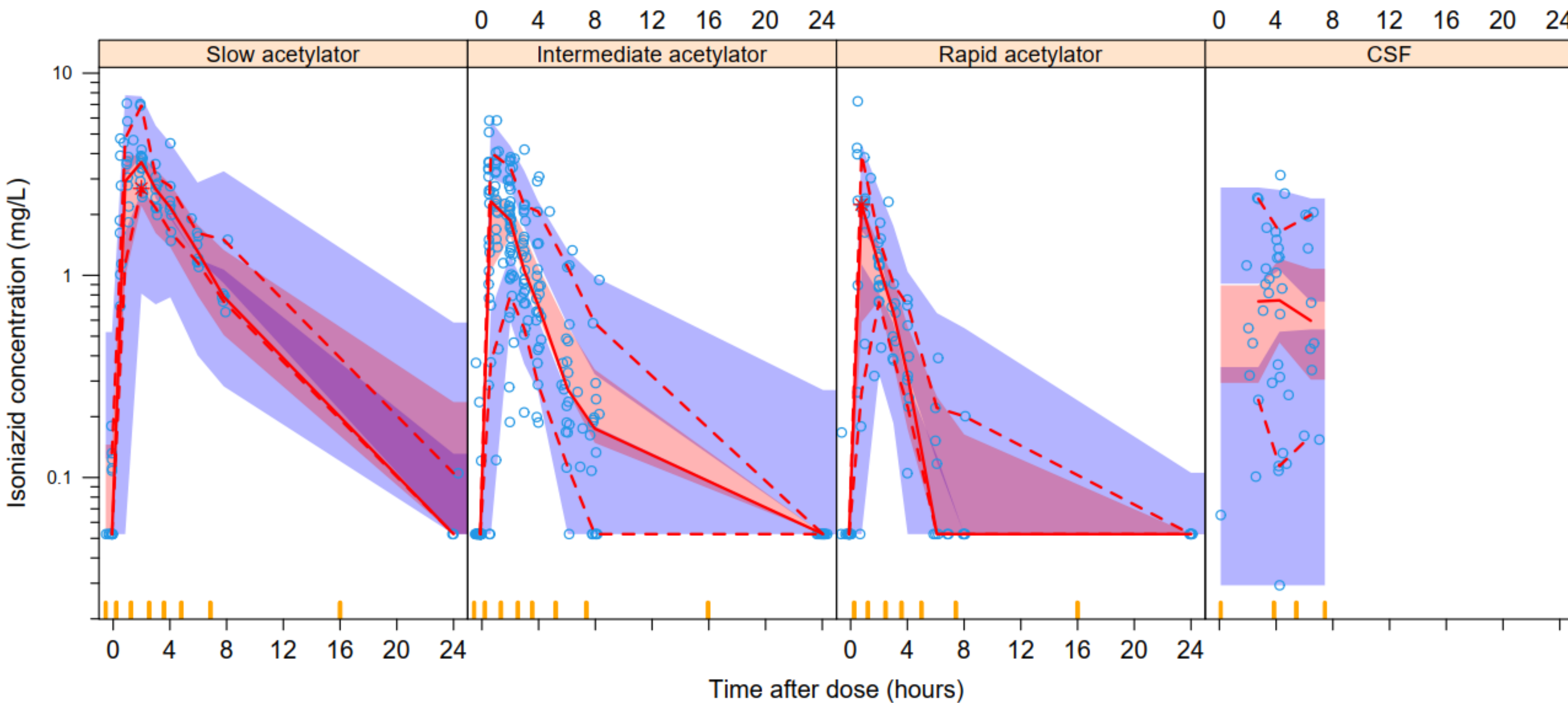


Figure 3. Visual predictive check for isoniazid plasma (stratified by NAT2 acetylator phenotype) and cerebrospinal fluid concentrations versus time after dose. The blue circles represent the original data, the red dashed and solid lines are the 10th, 50th, and 90th percentiles of the observed data, while the shaded areas represent the corresponding model-predicted 95% confidence intervals.

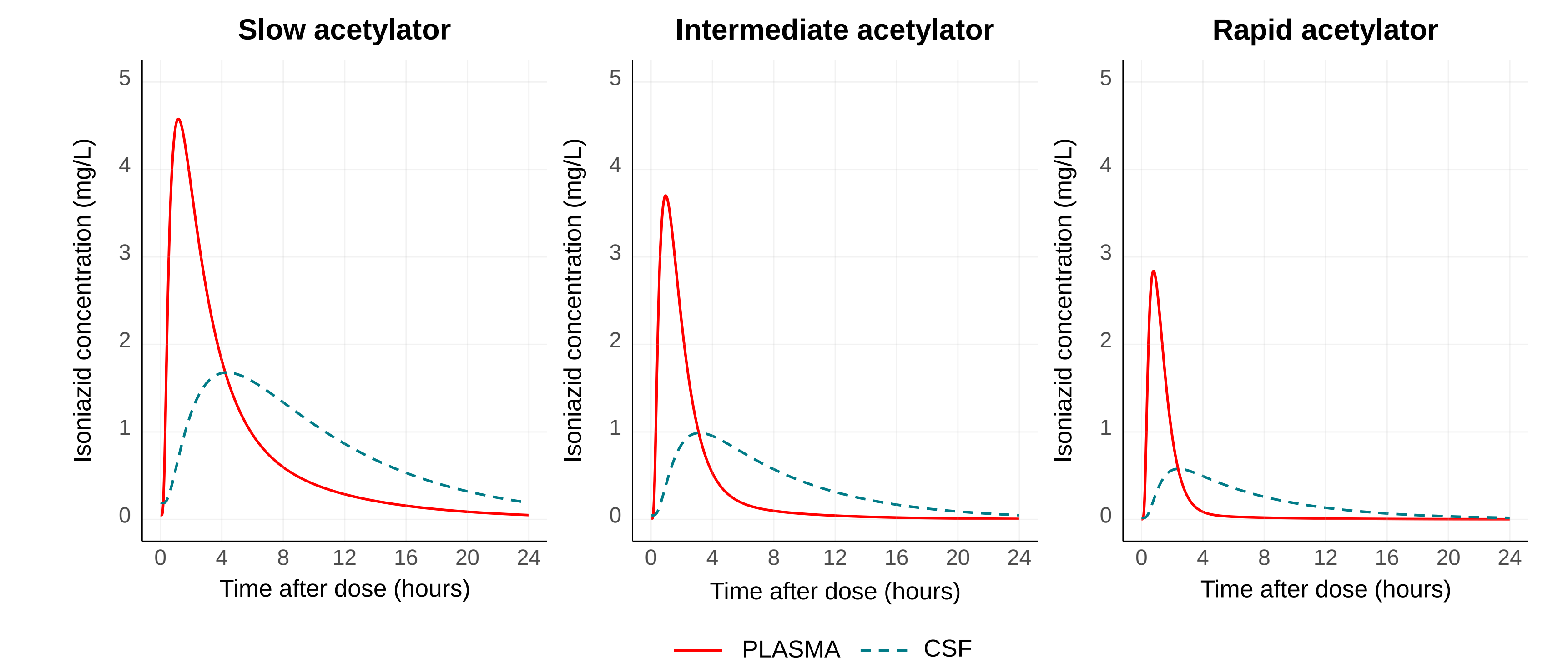


Figure 4. Isoniazid simulated concentration-time profiles at steady state for the typical individual of each NAT2 acetylator phenotype.

Conclusions

- Our model shows that INH achieves exposure in CSF that mirrors its exposure in plasma, supporting further efficacy evaluations in TBM.
- Our parameter estimates are consistent with published PK models using data from pulmonary TB patients,^{2,5} suggesting that INH plasma PK in TBM patients is similar to pulmonary TB, even when co-administered with a high dose of RIF, providing evidence for combined use.
- Our model provide a tool to explore alternative isoniazid dosing strategies once the efficacy targets in TBM are established.

Acknowledgements

We acknowledge the patients and the whole study team. Computations were performed using facilities provided by the University of Cape Town's ICTS High Performance Computing team: <https://ucthpc.uct.ac.za/>.

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