

Pharmacogenetics-guided isoniazid dosing in individuals with tuberculosis and HIV

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Background and objectives

Isoniazid (INH) is a first-line agent for TB treatment and its PK are influenced by genetic variability.

Single nucleotide polymorphisms (SNPs) in the NAT2 gene categorise individuals into slow, intermediate, or fast acetylators, impacting INH metabolism and exposure.¹ Subtherapeutic INH levels are frequently observed in people with HIV, potentially reducing treatment efficacy.²

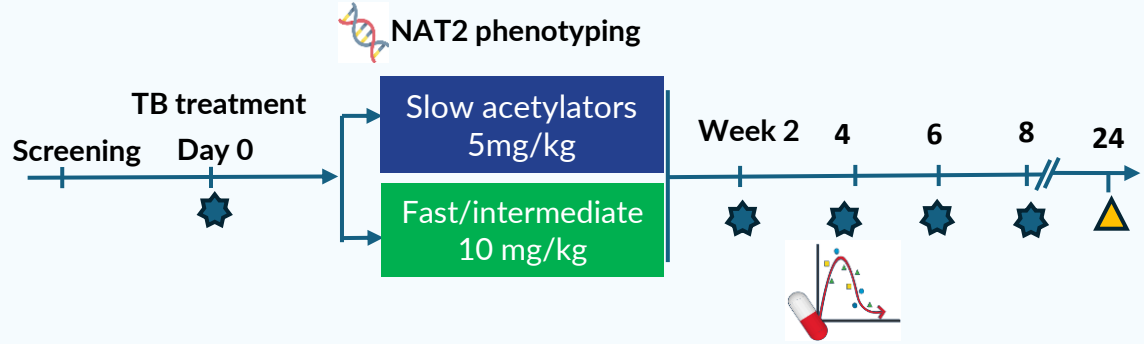
Standard INH dosing (5 mg/kg) targets peak concentrations (C_{max}) of 3–6 mg/L, associated with optimal mycobactericidal activity.³

Objective: To evaluate whether genotype-guided INH dosing (5 mg/kg in slow acetylators; 10 mg/kg in intermediate/fast acetylators) optimizes drug exposure across NAT2 acetylator phenotypes

Methods

PHINX was a phase IIb trial among adult patients with HIV-associated TB in Kampala, Uganda.

Figure 1. PHINX study schematic



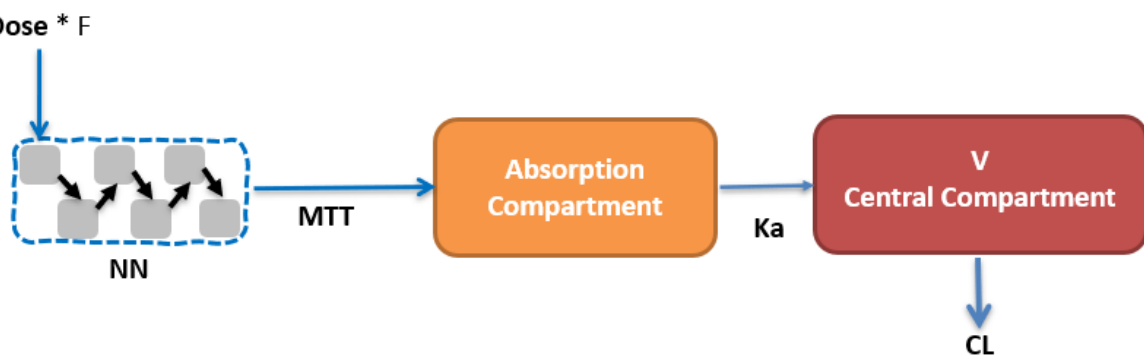
Data was analysed in NONMEM using previously published model.⁴

Results

Table 1. Participant characteristics

Characteristic	
n	31
Age, yr.	36 (18-60)
Male, n (%)	16 (52)
NAT2 acetylator, n (%)	
Slow	21 (68)
Intermediate	10 (32)

Figure 2. Isoniazid pharmacokinetics model

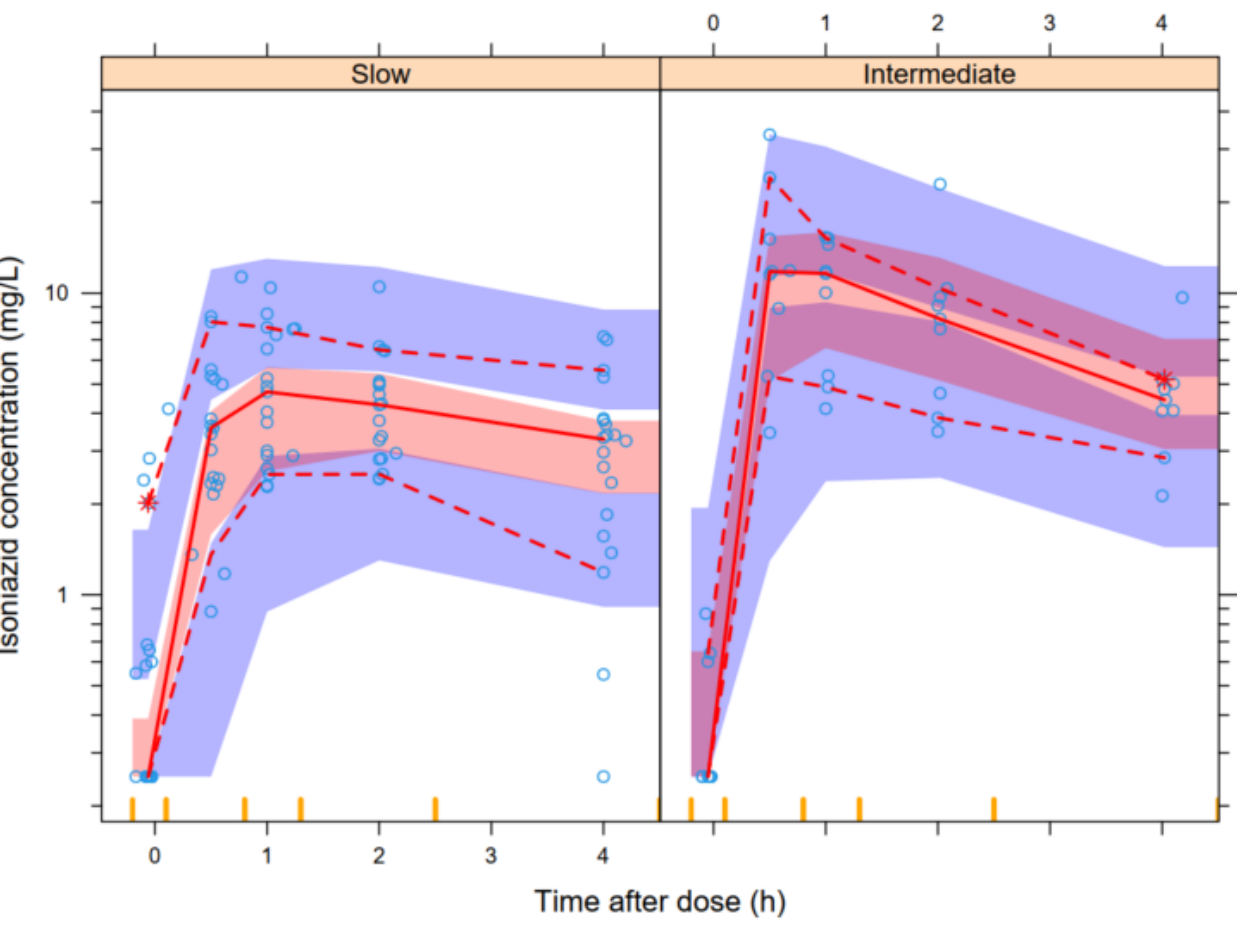


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Results

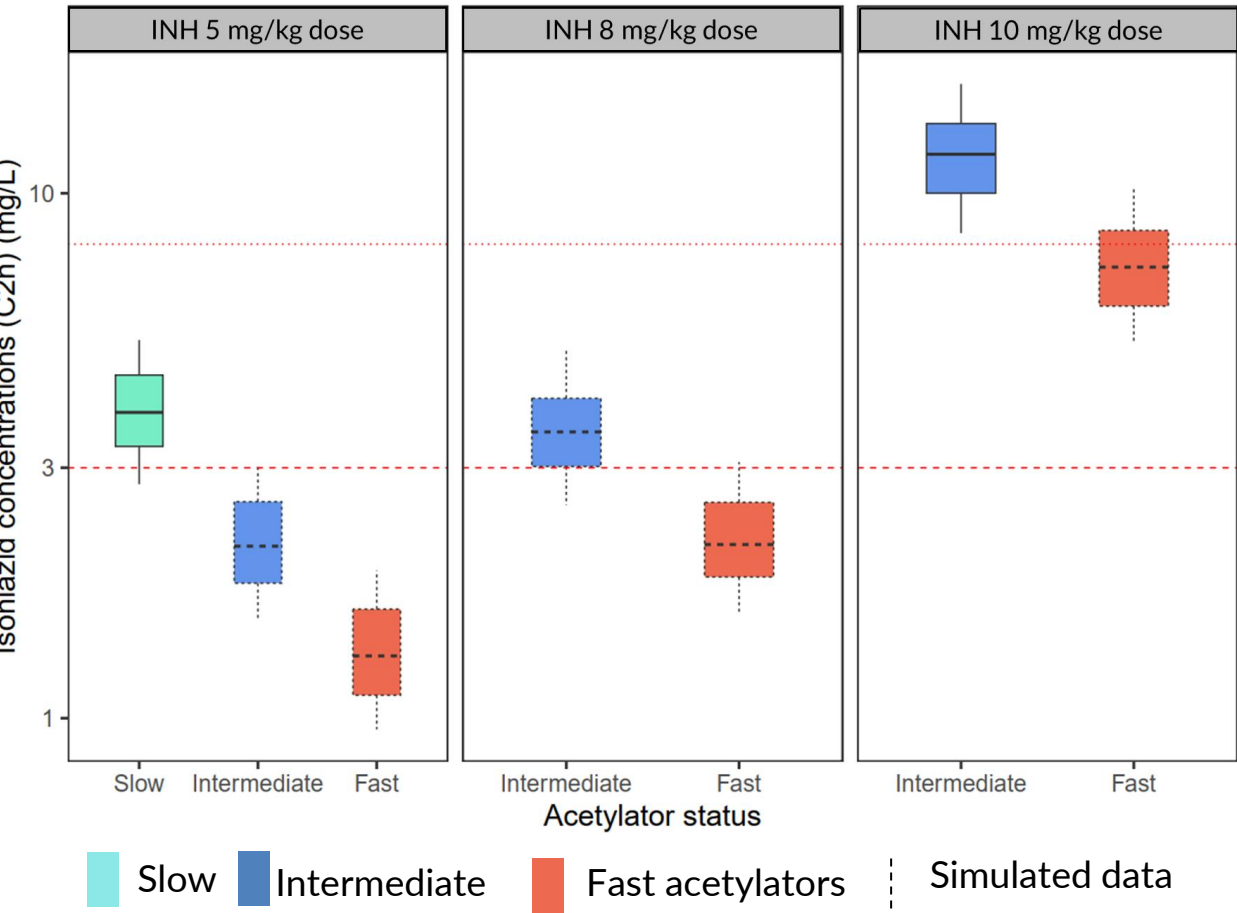
Figure 3. VPC stratified by rifampicin regimen



The typical CL for the slow acetylators was 9.27 L/h while that for the intermediate acetylators was 18.9 L/h.

The bioavailability of INH was 29% higher in the intermediate acetylators who received another formulation to top-up their dose

Figure 4. Simulated peak isoniazid concentrations



CONCLUSION

- There were no fast acetylators in our study population.
- The standard 5 mg/kg dose was appropriate for slow acetylators.
- The higher 10 mg/kg dose was predicted to be suitable for fast acetylators but may be excessive for intermediate acetylators.
- An 8 mg/kg dose appears optimal for intermediate acetylators based on simulations.

Funded by:

