Population pharmacokinetics of high-dose isoniazid in children receiving 3-month weekly isoniazid and rifapentine (3HP) for TB preventive treatment

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Background and objectives

Children are at an increased risk of developing severe forms of TB disease upon TB infection, if left untreated[1].
WHO recommends **3HP** (once weekly isoniazid and rifapentine for 3 months) regimen for the treatment of TB infection in adults (more recently in children)[2].
Isoniazid pharmacokinetics is not well characterized in children under the age of 2 years.
Children under 2 years of age are still **maturing** and developmental pharmacology impacts the pharmacokinetics of a drug.
Isoniazid clearance is impacted by the polymorphic **NAT2 enzyme**, and this effect is not well characterized in infants below 2 years of age.
Previous studies have reported **lower bioavailability** of isoniazid, especially in younger children[3].
We determined the pharmacokinetics of **high-dose isoniazid (15-25mg/kg)** given once weekly with rifapentine for 3 months for prevention of TB disease in children.

Methods

This was part of the **Tuberculosis Trials Consortium Study 35**, and it involved **children** in **South Africa aged 0 – 12 years**, with or without HIV and with exposure to drug-susceptible TB or *M.tb* infection but with no active TB disease.

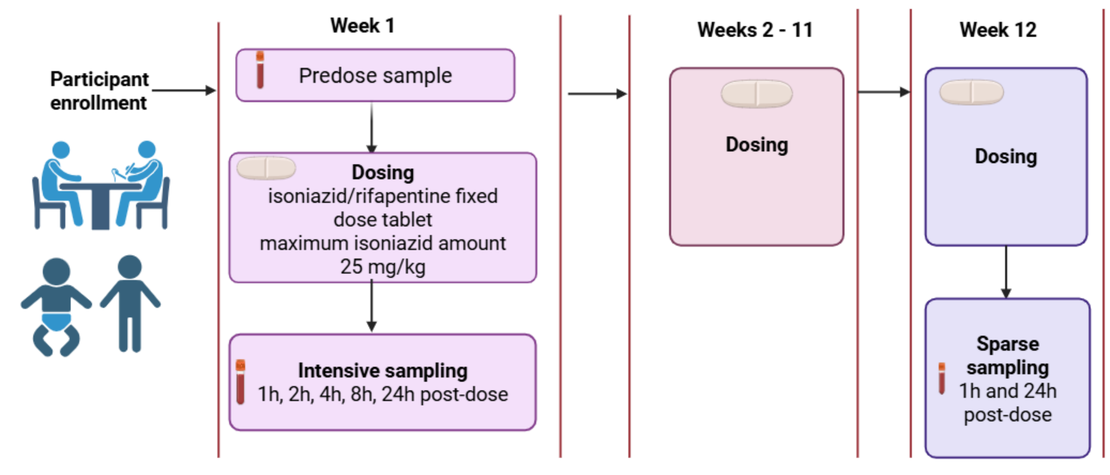


Figure 1. Study protocol

Isoniazid plasma concentrations were assayed using **LC-MS** with a **LLOQ of 0.105mg/L**.
We started analysis from a literature model that was developed for **South African** children on first line TB treatment **(10 mg/kg)**[3]. The model was updated in **NONMEM** version 7.5 using **FOCE-I**.
Below Limit of Quantification (**BLQ**) values were handled using **M7+** method[4].
Allometric scaling was tested on disposition parameters.
A **mixture model**[5] was implemented to **impute the NAT2 acetylator** status in the population.
The area under the curve (AUC) was calculated using the final model.

Results

Table 1. Participants characteristics

	Age cohorts				
Variable	**Cohort 1** ≥ 4 to ≤ 12y N = 9	**Cohort 2** ≥ 2 to < 4y N = 6	**Cohort 3** ≥ 1 to < 2y N = 19	**Cohort 4** 0 to < 1y N =19	**Overall** N = 53
Age [years]	11.2 (7.3, 12.9)	2.8 (2.6,3.1)	1.5 (1.1, 2.0)	5.76 (0.84, 11.28) months	1.3 (0.1, 12.9)
Weight [kg]	27 (18, 39)	15 (12, 15)	9 (8, 17)	7 (4, 10)	9 (4, 39)
Height [cm]	127 (112, 152)	91 (88, 96)	78 (73, 85)	66 (53, 75)	77 (53, 152)
Living with HIV	7 (78%)	0 (0%)	0 (0%)	0 (0%)	7 (13%)
Sex					
Female	4 (44%)	2 (33%)	7 (37%)	9 (47%)	22 (42%)
Male	5 (56%)	4 (67%)	12 (63%)	10 (53%)	31 (58%)
Race					
Black	2 (22%)	4 (67%)	12 (63%)	11 (58%)	29 (55%)
Mixed	7 (78%)	2 (33%)	7 (37%)	8 (42%)	24 (45%)
Median (min, max) or Frequency (%)					

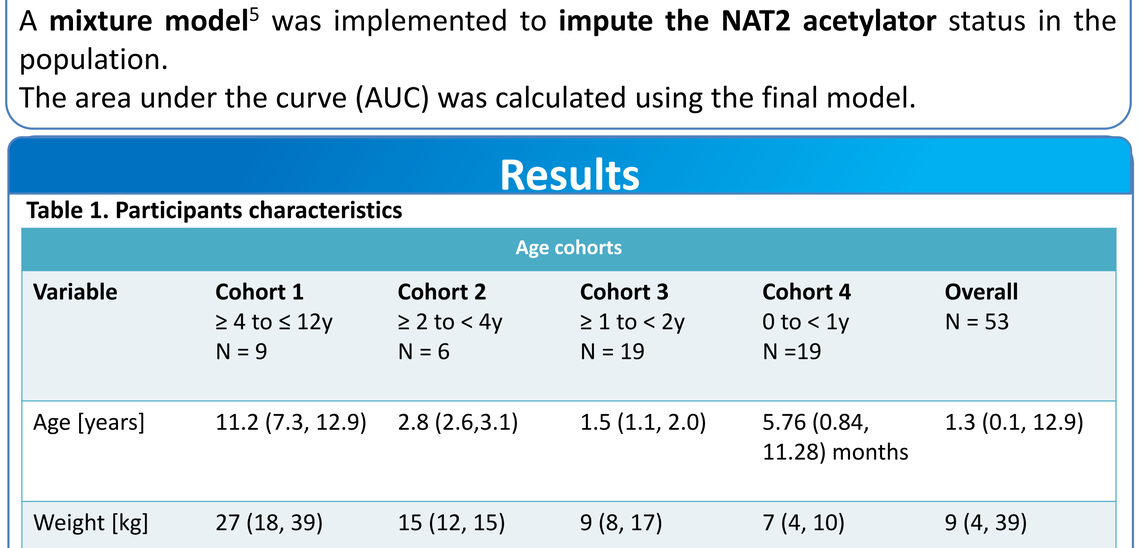


Figure 2. Final pharmacokinetic model. ktr: transit time; **NN**: number of transit compartments; **ka:** absorption rate constant**; Q:** intercompartmental clearance; **CL:** clearance; **V:** central compartment volume of distribution**; V3:** peripheral volume of distribution. **WT** represents allometric scaling with total body weight on **CL**(0.75), **Q**(0.75), **V**(1), and **V3**(1). **AGE** represents the maturation on clearance. The **mixture model** describes the differences of NAT2 acetylation within the population.

Results

Isoniazid pharmacokinetics were best described by a 2 compartment disposition model (Figure 2).
Of the total available observations, approximately **36% were BLQ** (mostly at pre-dose).
Disposition parameters (CL, Q, V and V3) were **allometrically scaled** using **total body weight**.
Mixture model was fixed to **2 subpopulations** (fast and intermediate and slow populations) for model stability (Figure 2).
Maturation function indicated that **50% maturation** is attained at approximately **1 month** and **≥98% maturation** at approximately **18 months**.
There were **no grade 3 or higher** adverse events – **good safety outcomes**.

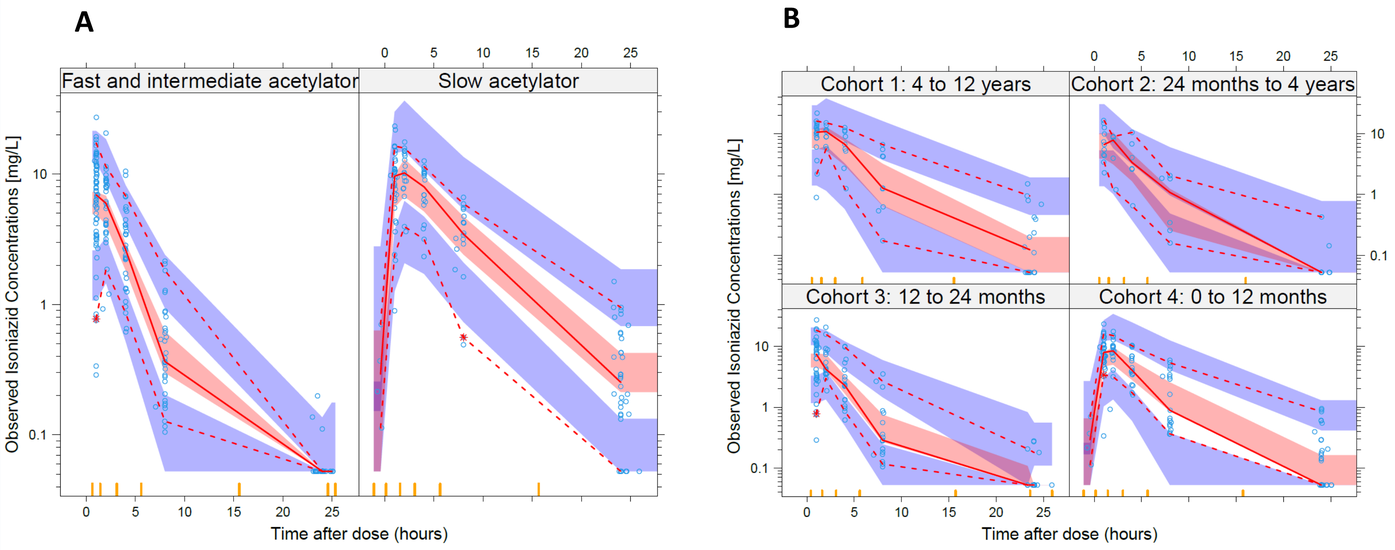


Figure 3. Visual predictive checks (VPC) of the model showing the 95% confidence interval of the model predicted and observed data. The y-axis shows the observed isoniazid concentrations in mg/L and the x-axis shows the time after last dose in hours. **A** – VPC is stratified by model imputed acetylator status. **B** – VPC is stratified by the age cohorts.

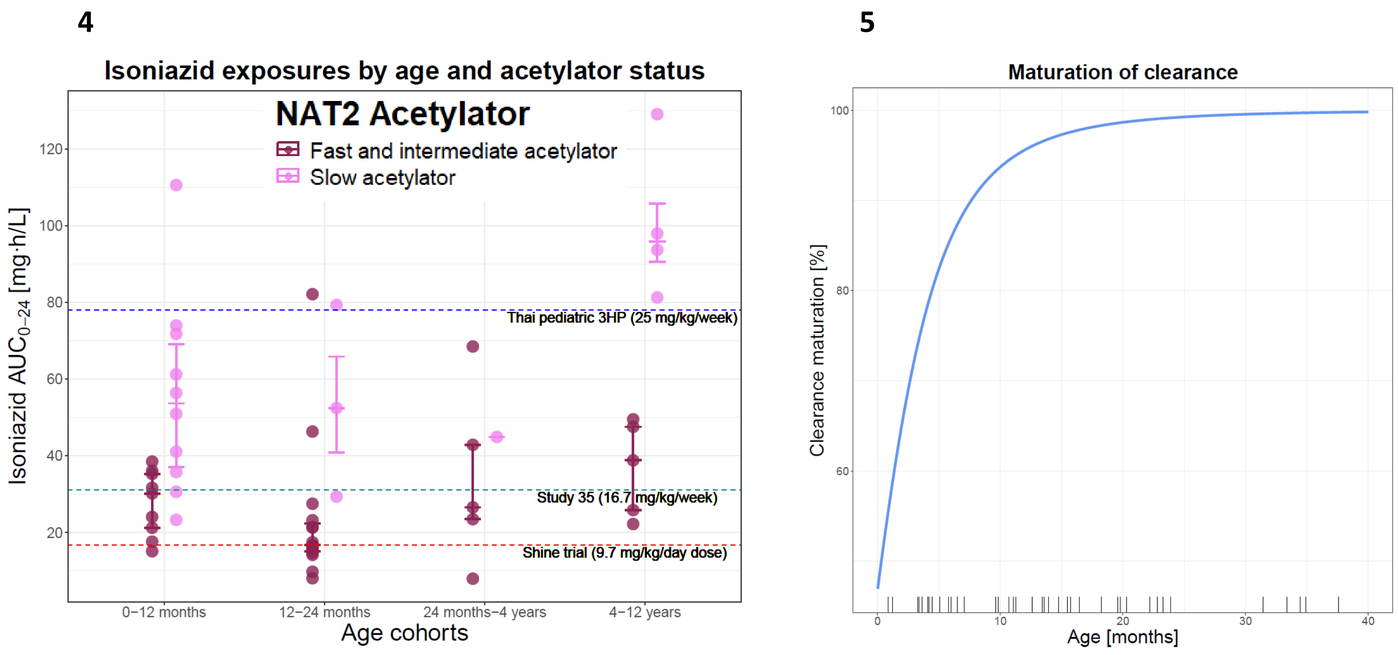


Figure 4. Jitter plot for isoniazid AUCs, y-axis shows isoniazid AUC_{0-24} in mg·h/L and the x –axis shows the 4 age cohorts in the study. The bars represent the median and the 25th and 75th percentiles. The **dark purple bars** represent the **fast and intermediate acetylator** group, and the **light purple bars** represent **the slow acetylator group**. The green dashed line shows this study's **(study 35) median** of **31 mg·h/L**. The red dashed line shows the **Shine trial**[6] median of **9.7 mg·h/L**. The blue dashed line shows the median AUC of **78 mg·h/L** from a 3HP trial[7] conducted in Thailand.

Figure 5. Maturation of clearance. The y-axis shows the maturation in percentage. The x-axis is the post-natal age in months, and the vertical lines at the bottom represent the ages in our dataset.

Conclusions

The **model (high-dose isoniazid 15-25 mg/kg)** was in line with **literature findings (first line TB treatment – 10mg/kg).**

Identified an **age effect on clearance** – maturation function in line with literature values.
Identified **NAT2 bimodal effect** on clearance.
Contrary to previous findings, age did not contribute to a change in bioavailability, which may be due to the use of the same formulation in our study.

Observed a **linear dose-exposure** relationship (Figure 4), which is in line with literature findings.
High exposures did not lead to adverse events, safety outcomes were good.
Findings from this model informed recent WHO guidelines.

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