Pregnancy is Associated with Decreased Serum Isoniazid Levels in Women Living with HIV

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Background and Objectives

TB predominantly affects women of reproductive age and pregnant women are at elevated risk of progression from latent to active TB.

WHO guidelines recommend >6 months of isoniazid (INH) preventive therapy for people living with HIV from low and middle income countries where TB is endemic, including pregnant women.

Very scarce data is available on INH PK during pregnancy.

Methods

Prospective cohort of pregnant, HIV+ women at 14 to 34 weeks of gestation and on or starting ART.

The women were either immediately started on **INH 300-mg daily for 28 weeks then switched to placebo** (arm A) or started on placebo then switched to INH at 12 weeks postpartum (arm B).

PK sampling at ≥ 2 weeks after recruitment and during pregnancy, and then at around **12-21 weeks after delivery**.
Blood samples for intensive sampling collected pre-dose,1, 2, 4, 6, 8, 12 hours post-dose, and sparse sampling at around 2 h after dose. Genomic DNA was extracted to identify genotype of NAT2. Depending on the genotype patients were assigned to either **fast, intermediate or slow acetylation** [1]

Population PK modelling in NONMEM [2] was used to interpret the data.
2-compartment model, transit compartment absorption [3], and hepatic clearance and first-pass metabolism due to hepatic extraction E_h.
Allometric scaling [4] of clearance (CL) and volume (V) based on body weight (WT) and fat-free mass (FFM).

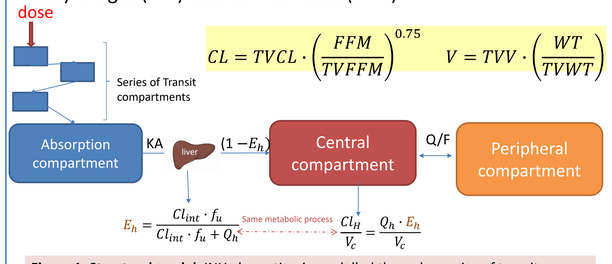

Figure 1: Structural model. INH absorption is modelled through a series of transit compartments. Elimination is from central compartment with first-order kinetics

Results - Study population

32 and 815 women were intensively and sparsely sampled, respectively. 88% of the women were concomitantly receiving efavirenz-based HAART. Summary of characteristics in Table 1.

Results – PK model

Table 1 Patient's characteristics

Characteristics	Pregnancy (n=420)	Postpartum (n=637)
Age in years, median (range)	29 (18 - 45)	29 (18 - 45)
Weight in Kg, median (range)	68 (42 - 164)	61 (38 - 118)
Fat-Free Mass in kg, median (range)	40 (25 - 65)	38 (25-59)
Gestation/postnatal age in weeks, median (range)	26 (14 - 34)	16 (7 - 23)
Concomitant ART, N(%)		
Efavirenz-based HAART	371 (88)	563 (88)
Nevirapine-based HAART	37 (9)	64 (10)
Lopinavir-based HAART	12 (3)	8 (2)
Atazanavir-based HAART	0 (0)	2 (0)
Duration on EFV regimen (days)	125 (18 - 3800)	264 (1 - 4228)
Viral load (copies/mL)	<40 (<40 - 237332)	<40 (<40 – 465894)
Phenotype Frequency for NAT2, N (%)		
Fast	52 (12%)	70 (11%)
Intermediate	140 (33%)	202 (32%)
Slow	159 (39%)	199 (31%)
Missing	69 (16%)	166 (26%)

Model assumption: The free fraction of INH (f_u) in plasma was assumed 95% [5]. For a typical individual (70kg male), liver hepatic plasma flow (Q_h) 50 L/h and scaled to each patient's size using individual weight.

Parameter estimates: Table 2, visual predictive check: Figure 2.

As expected the **effect of NAT2 genotype was significant in isoniazid clearance. E**ach phenotype had a specified estimated clearance.

After adjusting for the effect of body size (with allometry) and *NAT2* genotype, **pregnancy increased isoniazid clearance by 26%.**

Table 2 Final parameter estimates

Parameter	Typical Value	Parameter variability
Clearance[b] – CL [L/h] NAT2 Fast	68.7	BSV: 69.2%
Clearance[b] – CL [L/h] NAT2 intermediate	36.6	
Clearance[b] – CL [L/h] NAT2 slow	13.8	
Central Vol of distribution[b] – V [L]	37.6	
Peripheral Vol of distribution[b] – V [L]	13.3	
Intercompartmental clearance[b] – Q [L/h]	3.32	
Absorp. rate constant - ka [1/h]	2.69	BOV: 145%
Absorp. mean transit time – MTT [h]	0.342	BOV: 116%
Number of abs. transit cmpts – NN [ ]	48.4	
Bioavailability – F [ ]	1 FIXED	BOV: 12.3%
Proportional Error [%]	13.2%	
Additive Error [mg/L]	0.0378	
Pregnancy effect on CL [%]	+26.3%	

[a] The parameter variability was included either as between-subject (BSV) or between-occasion (BOV) assuming a lognormal distribution. It is reported here as approximate %CV.
[b] The values of CL and V were allometrically scaled, so the typical values reported here refer to the median body weight of the cohort included in the PK model, 67 kg for volume and median fat-free mass of 38 kg for CL.

Results – PK model

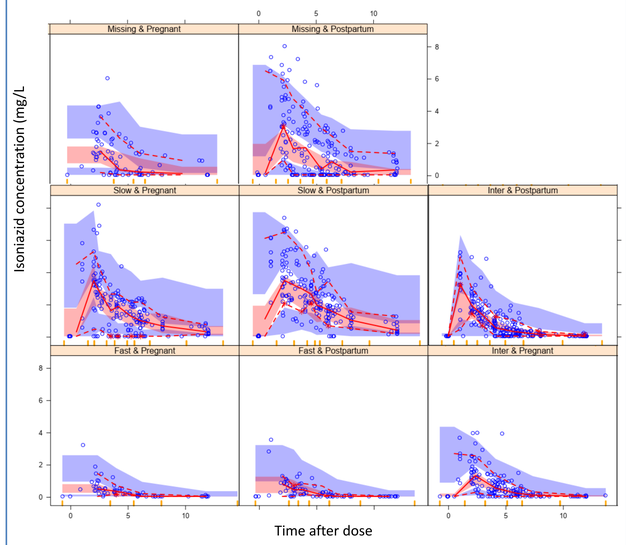

Figure 2: Visual predictive check. Visual predictive check [6] of the INH model, stratified by pregnancy status and NAT2 genotype.
The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observations, while the shaded areas represent the 95% model-predicted confidence intervals for the same percentiles.

Based on the model individual Bayesian estimates (figure 3), the median (interquartile range) isoniazid area under the concentration-time curve ($AUC_{0\text{-}24}$) during pregnancy or intra-partum was 8.05 mg·h/L (4.43-16.7), compared to 11.1 (6.26 – 23.9) post-partum. Maximum concentration during pregnancy and postpartum were 2.89 mg/L (1.97 – 4.13) vs. 3.69 (2.64 – 5.13), respectively.

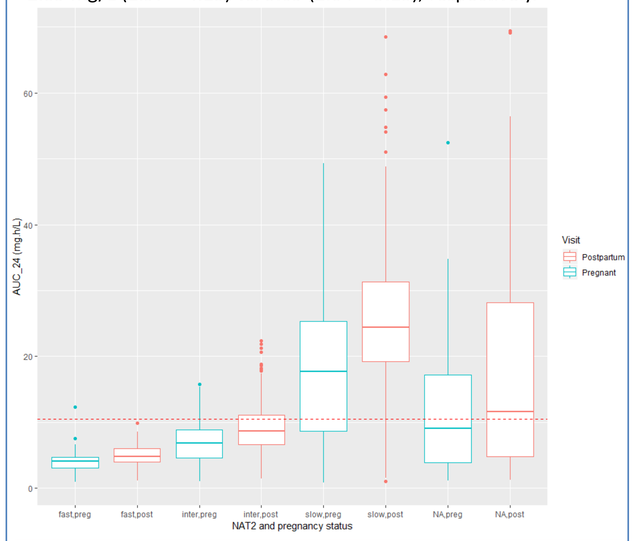

Figure 3: Boxplots of $AUC_{0\text{-}24}$ for isoniazid stratified by pregnant status and NAT2 metabolizer status. The dashed red line represents the exposure ($AUC_{0\text{-}24}$=10.52 mg.h/L) associated with 90% early bactericidal activity of isoniazid [7].

Discussion

Isoniazid exposure was decreased during pregnancy, due to increased clearance.

Overall, the clearance of isoniazid in all the three NAT2 acetylator groups was higher compared to historical nonpregnant ranges, irrespective of pregnancy.

The consequences of this reduction in exposure on the safety and effectiveness of isoniazid preventive therapy is being further investigated.

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