Pharmacokinetics of isoniazid preventive therapy among HIV-infected pregnant women in high tuberculosis incidence settings

Kamunkhwala Gausi[1], Lubbe Weisner[1], Jennifer Norman[1], Carole L. Wallis[2], Carolyne Onyango-Makumbi[3], Tsungai Chipato[4], Gerhard Theron[5], David W. Haas[6], Timothy R. Sterling[6], Renee Browning[7], Nahida Chakhtoura[8], Adriana Weinberg[9], Grace Montepiedra[10], Amita Gupta[11] , Paolo Denti[1] and the IMPAACT P1078 (TB APPRISE) Study Group Team[12]

(1) Div of Clinical Pharmacology, University of Cape Town, South Africa. (2) BARC Laboratories South Africa, Johannesburg, South Africa. - (3) Makerere University, Kampala, Uganda. (4) University of Zimbabwe, Dept of Obstetrics and Gynaecology, Harare, Zimbabwe. (5) Dept of Obstetrics and Gynaecology, Stellenbosch University, Cape Town, South Africa. (6) Vanderbilt University Medical Center, Nashville, Tennessee. (7) Div of AIDS, National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA. (8) NIH, Eunice Kennedy Shriver National Institute of Child Health and Human Development , Bethesda MD, USA. (9) University of Colorado Denver Anschutz Medical Campus, Aurora, CO, USA. (10) Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA, USA (11) Johns Hopkins University School of Medicine, Baltimore, MD, United States. (12)Research Group: IMPAACT P1078 Study Group Team.

Background and Objectives

TB predominantly affects women of reproductive age and pregnant women are at increased 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.**

Objective: Evaluate the **effect of pregnancy and co-concomitant ART on the pharmacokinetics of isoniazid.**

Methods

HIV infected pregnant women at 14 to 34 weeks of gestation and on or starting ART (88% on efavirenz) were recruited.

Immediately initiated **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).

Intensive PK sampled (**pre-dose,1, 2, 4, 6, 8 and 12 hours** after INH dosing), sparse PK sampled (**around 2** hours after dose) once at ≥ 2 weeks after recruitment and again at 12-21 weeks after delivery.

NAT2 genotype information was captured, categorizing patients into extensive, intermediate or slow acetylators [1]. When missing, **mixture model** was used to assign phenotype [2].

Intensive data used to develop the base model, sparse data was fitted on the model developed. **Outliers** in sparse data were identified (using CWRES>4) and removed from modelling.

BLQ were imputed with LLOQ/2 (0.105 ug/ml), and the lower limit of the additive error was fixed to 20% of the LLOQ. Additive error for imputed data inflated by 50% 0f LLOQ.

Modelling procedure in NONMEM 7.4.3, using PsN.

Results - Study population

Table 1 Patient 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) at baseline	<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%)

Population Pharmacokinetic analysis

- 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).

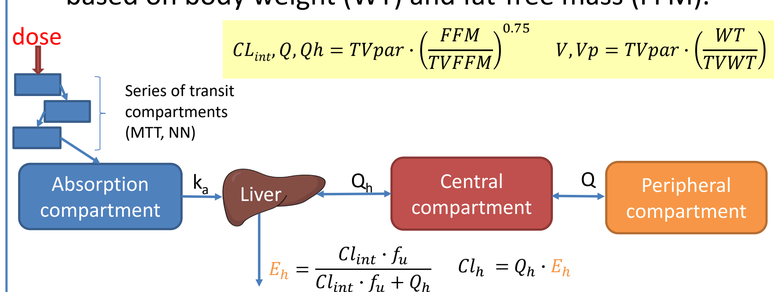

Figure 1: Structural model. Absorption is modelled through a series of transit compartments. The hepatic extraction (E_h) is responsible for both first-pass metabolism and the systemic elimination with first-order kinetics

Results

32 and 815 women were intensively and sparsely sampled, 210 women have PK data BOTH during pregnancy and postpartum respectively. Summary of characteristics in Table 1.

Model assumption: The free fraction of INH (f_u) in plasma was assumed 95% [5]. For a typical individual (67kg), liver hepatic plasma flow (Q_h) was 37.4 L/h and scaled to each patient's size using individual FFM.

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

As expected, the **effect of NAT2 genotype was significant in isoniazid clearance.** Each phenotype had a specified estimated clearance (see Table 3).

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

No significant difference observed in clearance between patients on efavirenz or nevirapine-based HAART.

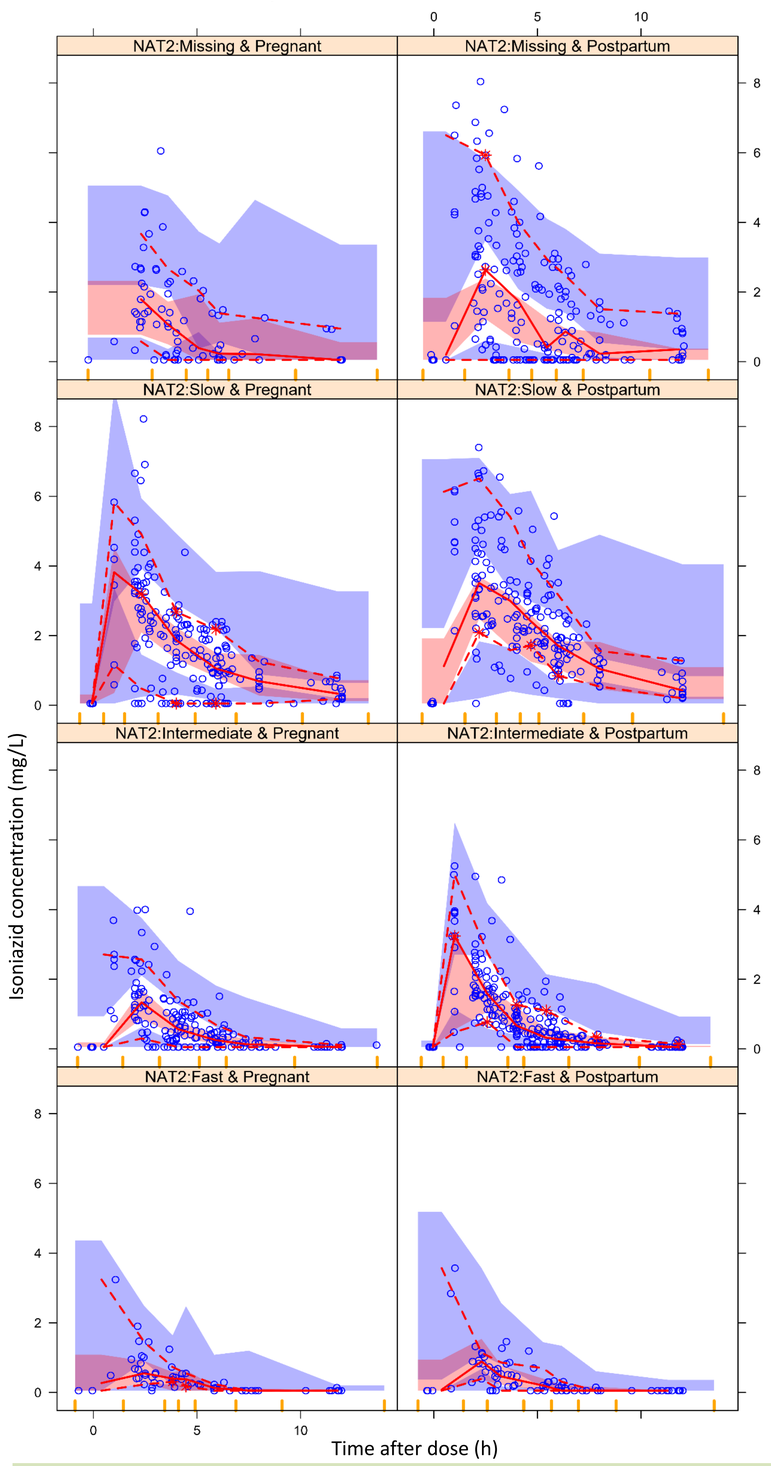

Figure 2: Visual predictive check. Visual predictive check [6] of the INH model, stratified by pregnancy status and NAT2 genotype.
The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observations, while the shaded areas represent the 95% model-predicted confidence intervals for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

Table 2 Final parameter estimates

Parameter	Typical Value (95%CI[a])	Variability[c], %CV (95% CI[a])
CLint[b] [L/h] NAT2 Fast	72.3(61.5-86.7)	BSV: 69.2(64.2-74.2)
CLint[b] [L/h] NAT2 Intermediate	38.5(34.6-43.2)	
CLint[b] [L/h] NAT2 Slow	14.5(13.1-16.0)	
Central Vol of distribution[b] – V [L]	37.6(33.9-40.7)	
Peripheral Vol of distribution[b] – V [L]	13.3(10.5-16.9)	
Intercompartmental clearance[b] – Q [L/h]	3.32(2.53-4.54)	
Absorp. rate constant - ka [1/h]	2.69(1.92-3.51)	BOV: 145(116-172)
Absorp. mean transit time – MTT [h]	0.342(0.209-0.459)	BOV: 116(98.7-150)
Number of abs. transit cmpts – NN [ ]	48.4(22.2-83.8)	
Bioavailability – F [ ]	1 FIXED	BOV: 12.3(8.20-15.7)
Proportional Error [%]	13.2(11.3-15.3)	
Additive Error [mg/L]	0.0378(0.0335-0.0449)	
Pregnancy effect on CL [%]	+26.3(19.8-33.2)	

[a] 95% confidence intervals (CIs) obtained with the SIR procedure
[b] The values of clearances and volumes of distribution were allometrically scaled, so the typical values reported here refer to the typical body size in the cohort included in the PK model (67 kg body weight for volumes of distribution and 38 kg fat-free mass for clearances).
[C] 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.

Table 3 Isoniazid clearance

NAT2 Phenotype	Intrinsic Clearance – Clint(L/h)	Hepatic Clearance – CLh (L/h)	Extraction Ratio - Eh (fraction)	Bioavailability after first pass – Fh (fraction)	Oral Clearance - CL/F (L/h)
Fast	72.3	24.22	65%	35%	68.7
Intermediate	38.5	18.49	49%	51%	36.6
Slow	14.5	10.07	27%	73%	13.8

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. Lower AUC during both pregnant and postpartum were observed compared to literature [7].

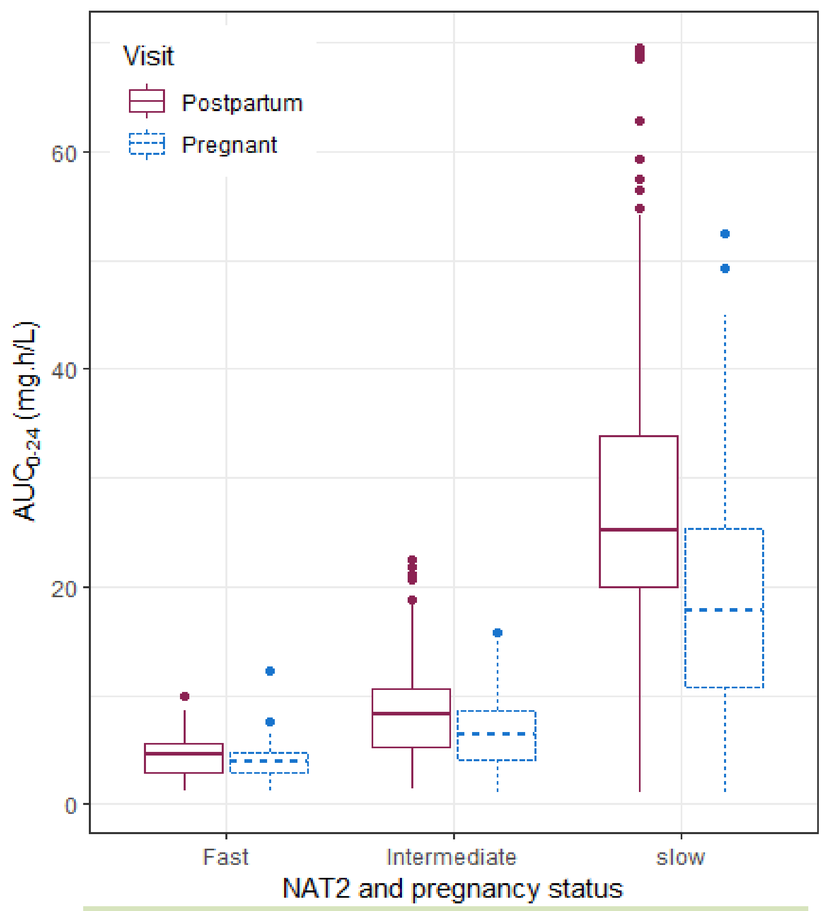

Figure 3: Boxplots of AUC_{0-24} for isoniazid stratified by pregnant status and NAT2 metabolizer status.

Conclusions

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

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

The consequences of this reduction in exposure on the safety and effectiveness of isoniazid preventive therapy needs further investigation.

References

[1] Luetkemeyer, A. F., Rosenkranz, S. L., Lu, D., Grinsztejn, B., Sanchez, J., Ssemmanda, M., ... & Haas, D. W. (2015). Combined effect of CYP2B6 and NAT2 genotype on plasma efavirenz exposure during rifampin-based antituberculosis therapy in the STRIDE study. Clinical Infectious Diseases, 60(12), 1860-1863
[2] Keizer RJ, Zandvliet AS, Beijnen JH, Schellens JHM, Huitema ADR. Performance of Methods for Handling Missing Categorical Covariate Data in Population Pharmacokinetic Analyses. AAPS J [Internet]. 2012 Sep [cited 2019 Feb 28];14(3):601–11
[3] Savic, R. M., Jonker, D. M., Kerbusch, T., & Karlsson, M. O. (2007). Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. Journal of pharmacokinetics and pharmacodynamics, 34(5), 711-726.
[4] B. J. Anderson and N. H. G. Holford, "Mechanism-based concepts of size and maturity in pharmacokinetics.," Annu. Rev. Pharmacol. Toxicol., vol. 48, pp. 303–32, Jan. 2008.
[5] Clemmesen JO, Tygstrup N, Ott P. Hepatic plasma flow estimated according to Fick's principle in patients with hepatic encephalopathy: evaluation of indocyanine green and D-sorbitol as test substances. Hepatology 1998; 27: 666–73. 29
[6] Keizer, R. J., Karlsson, M. O., & Hooker, A. (2013). Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. CPT: pharmacometrics & systems pharmacology, 2(6), 1-9.
[7] Daskapan A, Idrus LR, Postma MJ, Wilffert B, Kosterink JGW,... & Alffenaar J-WC. 2019. A Systematic Review on the Effect of HIV Infection on the Pharmacokinetics of First-Line Tuberculosis Drugs. Clin Pharmacokinet 58:747–766.

Acknowledgements and Support

The study team is very grateful to the women who participated in this study. We appreciate the contributions of the following individuals: Gary Maartens, and Marilyn Solomons from University of Cape Town.

This work was supported by The National Institute of Allergy and Infectious Diseases (NIAID), The Eunice Kennedy Shriver, National Institute of Child Health and Human Development (NICHD), Scientific Collaboration with the Tuberculosis Trials Consortium (TBTC) of the Centers for Disease Control and Prevention. My PhD funders, the Virtual consortium whose aim is to investigate the challenges of TB treatment for individuals on second-line ART whilst promoting African leadership and capacity building. NRF/STINT grant for the sponsorship to attend the Uppsala summer school.
The University of Cape Town analytical lab that performed that drug quantification assay was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health .

Contact details: gsxkam002@myuct.ac.za