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Pharmacokinetics of Isoniazid Metabolites during Pregnancy and Postpartum

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BACKGROUND

- IMPAACT P1078 evaluated the safety of isoniazid (INH) preventative therapy (IPT) initiated during pregnancy or postpartum in women with HIV (WWH) and latent tuberculosis infection.
- Hepatotoxicity occurred at higher rates (~6-7%) across both arms during the postpartum period[1] and a higher risk of adverse pregnancy outcomes was also identified with maternal IPT use during pregnancy.[2] Previous PK analyses with the parent INH form also identified lower INH exposures during pregnancy vs. postpartum.[3]
- These adverse outcomes may be due in part to toxic INH metabolites, such as hydrazine (Hz),[4] which have not been previously evaluated in pregnancy (Figure 1).

FIGURE 1. Schematic of INH Metabolism

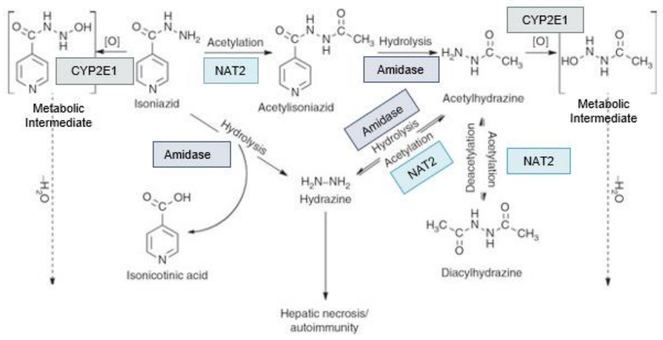


Figure adapted from Metushi IG et al.[4] *NAT2: N-acetyltransferase type 2

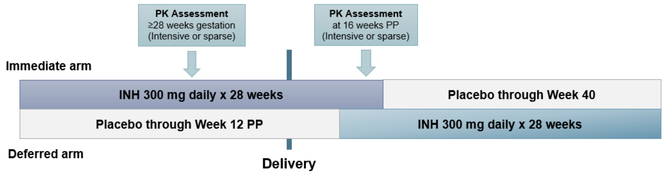
OBJECTIVE

- To describe and compare the PK of INH, isonicotinic acid (INA), acetylisoniazid (AcINH), acetylhydrazine (AcHz), and Hz in antepartum (AP) and postpartum (PP) WWH enrolled in IMPAACT P1078.

METHODS

- Participants received INH 300 mg once daily for at least 2 weeks prior to the intensive PK assessment (Figure 2).
- Samples were collected at 0, 1, 2, 4, 6, 8 and 12 h post-dose.

FIGURE 2. PK Sampling in IMPAACT P1078



- INH, INA, AcINH, AcHz, and Hz were quantified using a validated LC-MS/MS method (LLOQ 10 ng/mL for all analytes).
- Data were summarized descriptively by pregnancy status and NAT2 acetylation status (fast, intermediate, slow).
- Linear mixed models were used to compare percent differences (95% confidence intervals [CI]) between AP vs. PP for each analyte.

NAT2 and pregnancy status were both associated with INH metabolite exposures. Further research is necessary to examine potential relationships with hepatotoxicity.

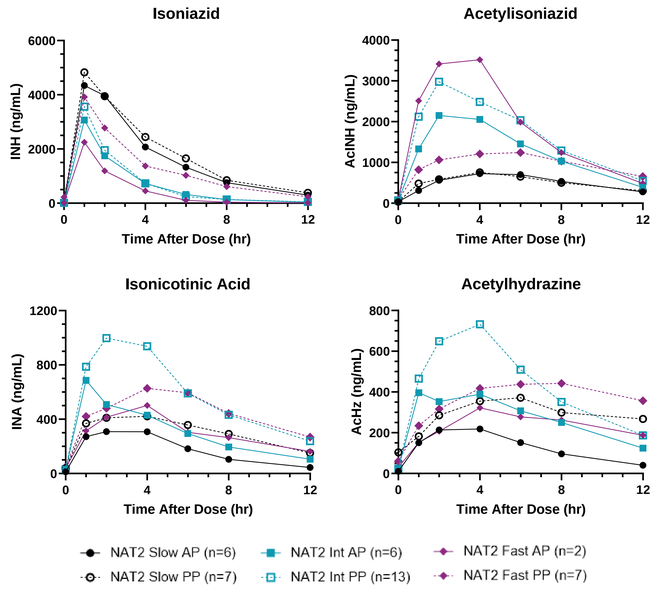
RESULTS

TABLE 1. Demographics & Clinical Characteristics

Characteristics	Pregnant (N=14)	Postpartum (N=27)
Gestational Age or Time Post-Delivery (weeks)	30 (28, 34)	16 (15, 21)
Age (years)	29 (18, 39)	29 (19, 41)
Weight (kg)	70 (54, 91)	65 (40, 91)
Race		
Black	12 (86%)	22 (81%)
Asian	2 (14%)	5 (19%)
Country		
Botswana	2 (14%)	3 (11%)
Thailand	2 (14%)	5 (19%)
Uganda	10 (72%)	19 (70%)
HIV VL <200 copies/mL[a]	13 (93%)	24 (89%)
CD4 count (cells/mm^3)	380 (247, 836)	426 (112, 1539)
SCr (mg/dL)	0.5 (0.3, 0.6)	0.5 (0.3, 0.9)
Hepatic Function		
ALT (U/L)	14 (9, 24)	32 (14, 82)
AST (U/L)[b]	22 (15, 30)	40 (27, 51)
Total bilirubin (mg/dL)[b]	0.2 (0.1, 0.3)	0.2 (0.1, 1.0)

Data available in 31 unique participants; results presented as n(%) for categorical or median (range) for continuous and reflect closest measurement to PK visit. [a]HIV viral load (VL) at entry.
[b]Data only available in 3/14 pregnant and 7/27 postpartum participants.

FIGURE 3. Median Concentration vs. Time Profiles for INH and Metabolites by NAT2 and Pregnancy Status



RESULTS

FIGURE 4. Percentage of Participants with Quantifiable Hydrazine in Plasma by Pregnancy and NAT2 status.

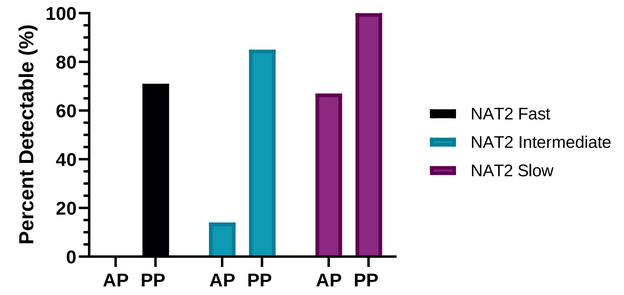


FIGURE 5. Median Concentration of Hz vs. Time Profiles by NAT2 and Pregnancy Status

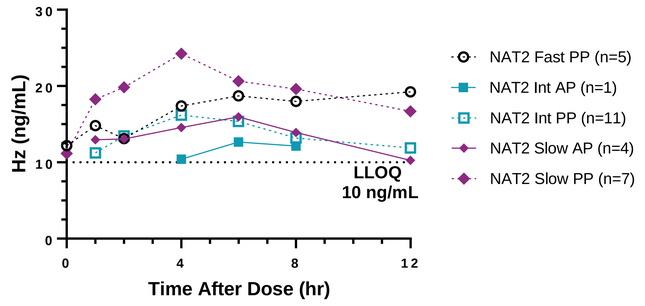


TABLE 2. Influence of Pregnancy and NAT2 Status on INH and Metabolite AUCs

Analyte	AP AUC (uM*hr)			PP AUC (uM*hr)			AP vs. PP[a]
	NAT2 Fast (n=2)[b]	NAT2 Intermediate (n=6)	NAT2 Slow (n=6)	NAT2 Fast (n=7)	NAT2 Intermediate (n=13)	NAT2 Slow (n=7)	Percent Difference (95% CI)
INH	31.9	57.7 (29.0)	142 (20.8)	82.3 (145)	60.5 (25.8)[c]	155 (18.9)	-9.2% (-21.6%, 5.0%)
AcINH	127	83.1 (45.8)	31.3 (34.5)	87.6 (60.9)	100 (53.3)[c]	33.9 (33.3)	-11.3% (-27.1%, 7.9%)
INA	16.8	34.3 (83.1)	26.3 (39.3)	29.6 (40.2)	47.4 (59.6)	43.3 (27.6)	-36.4% (-52.3%, -15.2%)
AcHz	20.2	46.4 (55.7)	39.4 (25.4)	41.0 (47.5)	61.1 (48.3)	66.3 (31.0)	-37.0% (-50.6%, -19.8%)
Hz[d]	BLQ	2.75[b]	2.47 (75.1)	6.05 (36.6)	3.90 (28.1)	7.71 (34.4)	--

Data presented as geometric mean (geometric %CV). AcINH: acetylisoniazid; AcHz: acetylhydrazine; AP: antepartum; AUC: area under the curve; BLQ: below the limit of quantitation; INA: isonicotinic acid; INH: isoniazid; Hz: hydrazine; PP: postpartum.
[a]AP vs. PP after controlling for NAT2 status [b]CV not reported [c]n=12 [d]AP: n=1 intermediate, 4 slow; PP: 5 fast, 11 intermediate, 7 slow.

CONCLUSIONS

- These data demonstrate relationships between NAT2 status and the formation of INH metabolites in pregnant and postpartum WWH.
- INA and AcHz drug exposures were higher during the PP period and Hz was quantifiable in more women during PP which may explain the higher risk of hepatotoxicity observed in these individuals.
- Analyses to examine the influence of pregnancy and other factors affecting INH metabolite PK in the overall study population and potential associations with hepatotoxicity in P1078 are ongoing.

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