N-acetyltransferase 2 polymorphism and risk of antituberculosis induced Hepatotoxicity in Thai People with HIV

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BACKGROUND

- The NAT2 slow acetylator phenotype is associated with a higher risk of isoniazid-induced hepatitis.
- There is a high prevalence of slow acetylators in the Thai population. This study aimed to explore the link between NAT2 genotypes and hepatitis risk in Thai people living with HIV (PLWH) after initiating isoniazid containing regimens for TB preventive therapy (TPT) or TB treatment.

METHODS

- A prospective cohort of 500 Thai PLWH receiving isoniazid with rifapentine (1HP/3HP) for TPT or HRZE for active TB were genotyped for six NAT2 single nucleotide polymorphisms (SNPs).
- Hepatotoxicity (Grade 2 or higher), characterized by aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding 2.5 times the upper limit of normal (ULN), was assessed across NAT2 phenotypes (rapid, intermediate, slow acetylator) and genotypes.
- Multiple logistic regression adjusting for age, sex, BMI, baseline CD4, antiretroviral therapy (ART) regimen and duration, viral hepatitis co-infection and antituberculosis regimen were used to assess associations between NAT2 genotypes/phenotypes and hepatotoxicity.

RESULTS

- Among the 500 participants, 440 (88%) received TPT, while 60 (12%) underwent treatment for active TB. Of the total, 151 (30%) were slow, 163 (32.8%) intermediate, and 186 (37.2%) rapid acetylators. Age, BMI, CD4, HBV or HCV co-infection, liver enzyme levels were comparable between the groups. Hepatotoxicity (grade 2-4) occurred in 53 participants (10.6%) overall: 25 (47)% slow, 18 (34%) intermediate, and 10 (19%) rapid acetylators ($p < 0.001$).
- As a percentage of each acetylator group, hepatotoxicity was observed in 16.6% of slow, 11% of intermediate, and 5.4% of rapid acetylators ($p < 0.001$).
- The NAT2 *6A/*6A genotype was associated with a significantly increased risk of hepatotoxicity (adjusted OR 2.6 (95%CI 1.3-5.2), p = 0.008), whereas NAT2 *4/*4, the wild-type fast acetylator and most common genotype (24%), provided protection against hepatotoxicity (adjusted OR 0.2 (95%CI 0.06-0.66), p = 0.008).
- Slow and intermediate acetylators had significantly higher hepatotoxicity risk compared to rapid acetylators, with adjusted ORs of 3.7 (95% CI 1.6–8.7, p = 0.003) and 2.5 (95% CI 1.1–6.2, p = 0.04), respectively.

Slow/intermediate acetylator phenotypes and the NAT2 **6A/*6A* genotype increase hepatotoxicity risk in Thai PLWH on anti-TB treatment, while wild-type Rapid acetylators **(NAT2 **4/*4)*** were protective. **NAT2 genotyping enables precision medicine by identifying high-risk individuals, guiding isoniazid dosing, and minimizing hepatotoxicity in PLWH.**

Table1: Baseline characteristics at the time of anti-TB initiation

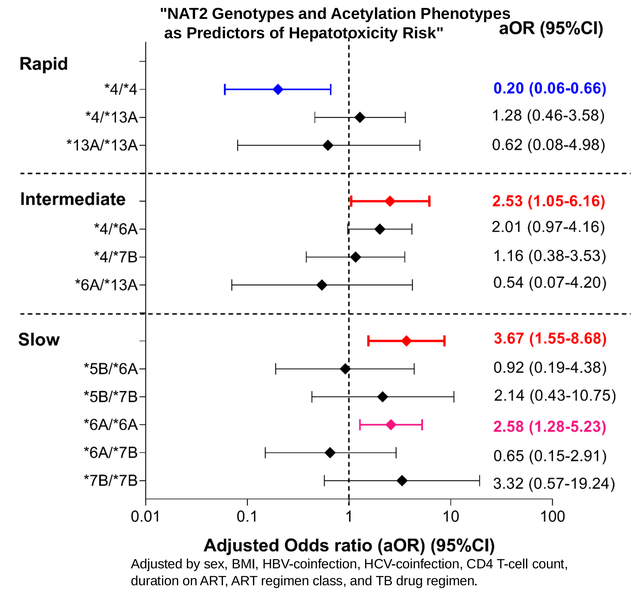
	Total (N=500)	No Hepatoxicity Grade 0-1 (N=447)	Hepatotoxicity Grade 2-4 (N=53)	P-value
Age (years), median (IQR)	30.1 (25.3-38.1)	30.6 (25.2-38.6)	28.4 (26.3-34)	0.28
Gender Male, n (%)	449 (89.8)	398 (89)	51 (96.2)	0.15
BMI (kg/m^2), median (IQR)	21.9 (19.7-24.7)	21.9 (19.8-24.7)	21.8 (19.5-24.6)	0.65
HCV, n (%)	23 (4.6)	20 (4.5)	3 (5.7)	0.73
HBV, n (%)	49 (9.8)	44 (9.8)	5 (9.4)	0.92
AST (U/L), median (IQR)	26 (22-35)	26 (22-33.5)	36 (23-66)	0.001
ALT (U/L), median (IQR)	35 (24-50)	35 (24-50)	40 (28-104)	<0.001
CD4 cell count (cells/mm^3), median (IQR)	335 (222-477)	334 (222-480)	338 (241-456)	0.80
Viral load<50 copies/mL, n (%)	162 (65.9)	149 (66.5)	13 (59.1)	0.48
ART regimen, n (%)				0.14
NNRTI-based	338 (67.9)	300 (67.4)	38 (71.7)	
INSTI-based	158 (31.7)	144 (32.9)	14 (26.4)	
Pis-based	2 (0.4)	1 (0.2)	1 (1.9)	
Anti TB regimen, n (%)				0.04
1HP	225 (45)	194 (43.4)	31 (58.5)	
3HP	217 (43.4)	199 (44.5)	18 (34)	
2HRZE/4HR	29 (5.8)	25 (5.6)	4 (7.6)	

CONCLUSIONS

NAT2 *6A/*6A genotype, slow and intermediate acetylator phenotypes significantly increased the risk of antituberculosis drug-induced hepatotoxicity. Incorporating NAT2 genotyping and therapeutic drug monitoring into clinical practice could help optimize isoniazid dosing and reduce the risk of hepatotoxicity, especially in PLWH with elevated baseline transaminase.

Table2: Prevalence of hepatoxicity by genotypes and acetylator phenotype

	N	N (%) Grade 2-4 hepatotoxicity
Rapid acetylator genotype		
NAT2 *4/*4	120	4 (3.3)
NAT2 *4/*12A	3	0 (0)
NAT2 *4/*13A	46	5 (10.9)
NAT2 *13A/*13A	17	1 (5.9)
Intermediate acetylator genotype		
NAT2 *4/*5B	18	0 (0)
NAT2 *4/*6A	77	12 (15.6)
NAT2 *4/*6B	8	0 (0)
NAT2 *4/*7A	1	0 (0)
NAT2 *4/*7B	33	4 (12.1)
NAT2 *5B/13A	4	0 (0)
NAT2 *6A/*13A	19	1 (5.3)
NAT2 *7B/*13A	3	1 (33.3)
Slow acetylator genotype		
NAT2 *5B/*5B	4	0 (0)
NAT2 *5B/*6A	15	2 (13.3)
NAT2 *5B/*7B	10	2 (20)
NAT2 *6A/*6A	88	17 (19.3)
NAT2 *6A/*7B	28	2 (7.1)
NAT2 *7B/*7B	6	2 (33.3)
Acetylator phenotype		
– Rapid	186	10 (5.4)
– Intermediate	163	18 (11)
– Slow	151	25 (16.6)



Adjusted by sex, BMI, HBV-coinfection, HCV-coinfection, CD4 T-cell count, duration on ART, ART regimen class, and TB drug regimen.

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