

# Isoniazid Toxicity among PWH with Latent TB who Consume Alcohol: A Single Arm Trial

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## BACKGROUND

- Isoniazid (INH) preventive therapy (IPT) reduces new TB disease among persons living with HIV (PWH), yet IPT deferral is suggested for persons with harmful alcohol use due to concerns about liver toxicity.
- The primary aim was to quantify the risk of severe toxicity on IPT among PWH with latent TB infection (LTBI) and with and without recent alcohol consumption, in southwestern Uganda.

## METHODS

- Single arm trial (300 mg INH + 25 mg pyridoxine oral, daily for 6 months)
- Eligibility**
  - Adults (age ≥ 18 years), on ART for ≥6 months (not on NVP), Tuberculin skin test positive (≥5mm), normal (≤2x ULN) ALT and AST, no history of prior TB or TB medications, no anticonvulsant use, not pregnant
  - Self-report prior 3 months alcohol use or alcohol abstinence for 1 year, 2:1 ratio
- Study procedures**
  - Study visits at 2 weeks, 1 month, and monthly thereafter, until 1 month after IPT completion: INH refills, ALT/AST monitoring, symptom monitoring
  - Research visits: Structured interview at baseline, 3, and 6 months
  - Lab testing: Viral load at baseline, phosphatidylethanol (PEth) alcohol biomarker at baseline, 3 months, 6 months
- Definitions**
  - Primary outcome:** Grade 3 or higher toxicity defined as ALT or AST ≥5x ULN or severe INH-related symptoms
  - Secondary outcome:** Grade 2 toxicity defined as ALT or AST >2-5x ULN or moderate INH-related symptoms
  - Primary predictor:** biomarker-confirmed alcohol use level at baseline
    - None: AUDITC=0 and PEth<8ng/mL
    - Low: AUDITC: 1-2 (women), 1-3 (men), PEth ≥8 to <50 ng/mL
    - Medium: AUDITC: 3-5 (women), 4-5 (men), PEth ≥50 to <200 ng/mL
    - High/very high: AUDITC ≥ 6 or PEth ≥200 ng/mL
- Analyses**
  - Generalized estimating equation (GEE) models with the logit link, robust standard errors, exchangeable working correlation structure

Few serious (Grade 3+) INH-related toxicities among PWH with LTBI, overall and by alcohol use.

## RESULTS

### Characteristics (n=301)

- Sex=female: 51.2%
- Age (median): 40 (IQR: 33-47)
- Viral suppression (<40 copies/ml): 92.1%

### Grade 3+ INH-related toxicities All resolved after INH discontinuation to Grade 1 or lower

- Overall (n=301): 8.3% (95% CI: 5.4-12.0)
- Among those with current alcohol use (n=200): 6.0% (95% CI: 3.1-10.2)
- Among those without current alcohol use (n=101): 12.9% (95% CI: 7.0-21.0)

### Grade 2 INH-related toxicities (among those without a Grade 3+ toxicity)

- Overall (n=276): 21.7% (95% CI: 17.0-27.1)
- Among those with current alcohol use (n=188): 25.0% (95% CI: 19.0-31.8)
- Among those without current alcohol use (n=88): 14.8% (95% CI: 8.1-23.9)

### Multivariable analyses

- No association found between biomarker-confirmed alcohol use and Grade 3+ toxicity
- There was an association found with Grade 2 toxicities.

Table. Adjusted odds ratios (aOR) for the associations of biomarker-confirmed alcohol use with Grade 3 and higher toxicity and Grade 2 toxicity (among those without Grade 3+ toxicity).

	Grade 3 or higher toxicity		Grade 2 toxicity	
	aOR (95% CI) Adjusted for age, sex, health status, and study visit	p-value	aOR (95% CI) Adjusted for age, sex, health status, study visit, and ART adherence	p-value
<b>Biomarker-confirmed alcohol use</b>		0.32		<0.01
None	1.00		1.00	
Low	0.43 (0.13, 1.44)		1.11 (0.44, 2.76)	
Medium	0.36 (0.10, 1.29)		0.69 (0.25, 1.91)	
High/very high	0.56 (0.16, 1.93)		3.63 (1.48, 8.93)	

## CONCLUSIONS

- Summary**
  - Grade 3 or higher INH-related toxicities among PWH with LTBI were infrequent among those with recent alcohol use and those who do not consume alcohol, and all resolved after INH discontinuation.
  - We did not detect an association between biomarker-confirmed alcohol use and Grade 3 or higher toxicities.
  - Grade 2 toxicities were more common, and high/very high-risk biomarker-confirmed alcohol use was associated with Grade 2 toxicities.
- Limitations**
  - Persons with baseline ALT/AST >2x the ULN were excluded, and monitoring was frequent (monthly). This limits generalizability.
- Discussion**
  - Alcohol use does not appear to pose an increased risk for serious IPT toxicity among those without significant liver enzyme elevations at baseline (≤2x ULN) in PWH on ART, and therefore IPT should not be deferred

## ADDITIONAL KEY INFORMATION

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