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Transaminitis prevalence among HIV-infected adults eligible for tuberculosis preventive therapy

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Abstract

Objective: To assess the prevalence of severe transaminitis precluding tuberculosis (TB) preventive therapy (TPT) initiation for people living with HIV (PLWH) in a high TB/HIV burden setting.

Design/Methods: We conducted a secondary analysis of data from a prospective cohort study of PLWH with pre-ART CD4+ counts ≤350 cells/uL undergoing systematic TB screening from two HIV clinics in Uganda. For this analysis, we excluded patients with culture-confirmed TB and patients without aspartate transaminase (AST) or alanine transaminase (ALT) levels measured within three months of enrollment. We compared the proportion of patients with any transaminitis (aspartate transaminase [AST] or alanine transaminase [ALT] >1 times the upper limit of normal [ULN]) and severe transaminitis (AST or ALT >3 times ULN) for patients screening negative for TB by symptoms and for those screening negative by C-reactive protein (CRP). We also assessed the proportion of patients with transaminitis by self-reported alcohol consumption.

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Author roles: CY designed the study. FCS, EA, AOA, and MK oversaw the local collection of data. JK, SM, LA, and MN were responsible for obtaining clinical measurements and data collection. LHC and CY analyzed and interpreted the data. LHC and CY drafted the manuscript. All authors reviewed and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Results: Among 313 participants (158 [50%] female, median age 34 years [IQR 27–40]), 75 (24%) had any transaminitis and six (2%) had severe transaminitis. Of 32/313 (10%) who screened negative for TB by symptoms, none had severe transaminitis. In contrast, six-times more PLWH screened negative for TB by CRP (194/313, 62%), of whom only four (2.1%) had severe transaminitis. Differences in the proportion with any and severe transaminitis according to alcohol consumption were not statistically significant.

Conclusions: Prevalence of severe transaminitis was low among PLWH without culture-confirmed TB in this setting and is therefore unlikely to be a major barrier to scaling-up TPT.

Keywords

tuberculosis; transaminitis; tuberculosis preventive therapy; liver function testing

BACKGROUND

Tuberculosis (TB) preventive therapy (TPT) reduces TB risk and death among people living with HIV (PLWH) and is recommended by the World Health Organization (WHO), but remains underutilized[1]. A significant barrier to TPT implementation has been the lack of accurate low-cost screening tests, which makes ruling-out active TB difficult. Although novel TB screening strategies such as C-reactive protein (CRP) may improve selection of PLWH for TPT[2], risk of drug-induced hepatotoxicity (which occurs in approximately 1–6% of those receiving TPT[3]) presents another potential barrier to TPT, particularly in settings where liver enzyme testing is not routinely available. However, the need for pre-TPT liver enzyme testing is greater for PLWH, who have higher rates of transaminitis than those without HIV[4–6] and are therefore at increased risk for TPT-related hepatotoxicity. WHO recommends that pre-TPT liver function testing (LFT) be performed where feasible for those at risk of liver toxicity—including PLWH—but state that routine LFT is not necessary for all patients initiating TPT.[7]

While several studies have reported transaminitis prevalence among PLWH[8,9,4,10–12], the proportion of PLWH ineligible for TPT due to elevated liver enzymes is unclear. Characterizing the burden of transaminitis among PLWH without TB (i.e., the proportion at risk for TPT-induced hepatotoxicity) is important for HIV programmes committed to implementing TPT. We aimed to determine transaminitis prevalence among PLWH undergoing TB screening in a high burden setting.

METHODS

Study population

We performed an analysis of participants enrolled in a cohort study evaluating novel TB screening algorithms in Kampala, Uganda[13–17]. We included ART-naïve adults (≥18 years) presenting to two HIV clinics for routine ART initiation with a pre-ART CD4+ T-cell count ≤350 cells/uL within three months of enrollment (07/2013–12/2016). We excluded patients taking medication with anti-mycobacterial activity within three days of enrollment, with culture-confirmed TB at baseline, and without aspartate transaminase (AST) or alanine transaminase (ALT) levels measured within three months of enrollment.

Study procedures

We collected demographic and clinical data at enrollment via chart review and a questionnaire, including information on alcohol consumption. Study staff screened participants for active TB using the WHO symptom screen and CRP levels. We considered patients to be symptom screen-positive if they reported current cough, fever, night sweats, or weight loss in the past 30 days. We measured baseline CRP levels from whole blood obtained by finger prick using a standard point-of-care (POC) assay (iCHROMA POC-CRP Reader, BodiTech Med Inc., South Korea). Here, we considered patients with POC-CRP ≥5 mg/L to have elevated CRP levels, based on current WHO recommendations[2]. We collected two spot sputum samples from all participants for comprehensive TB testing (smear microscopy, Xpert MTB/RIF, and mycobacterial culture) to ascertain prevalent TB status.

AST and ALT levels were extracted from clinic records. The laboratory range for AST was 0–40 U/L and the range for ALT was 0–41 U/L. We defined any transaminitis as AST or ALT >1 times the laboratory's upper limit of normal (ULN) and severe transaminitis as AST or ALT >3 times the ULN, the threshold used by multiple groups to identify patients ineligible for TPT[3,18,19].

Analysis

We assessed baseline characteristics, median AST and ALT levels, the proportion with AST or ALT >1 and >3 times ULN, and the proportion who screened positive for TB based on POC-CRP (≥5 mg/L) and the WHO symptom screen. We used Wilcoxon rank-sum, Kruskal-Wallis, and Chi-square or Fisher's exact tests to compare median AST and ALT levels and the proportion of patients with AST or ALT >1 and >3 times ULN for: 1) patients screening positive and negative by the WHO symptom screen and POC-CRP and 2) by self-reported alcohol consumption.

The Institutional Review Boards of the University of California, San Francisco, Makerere University School of Medicine, and the Uganda National Council for Science and Technology approved this study. All participants provided written informed consent.

RESULTS

Of 1,836 participants enrolled, we excluded 3 receiving anti-TB medications at enrollment, 184 with unknown baseline TB status, and 243 with culture-confirmed TB. Of 1,406 without active TB (i.e., potentially eligible for TPT), we excluded 1,086 without AST or ALT measurements within 3 months. There was no difference in sex (p=0.37), median age (p=0.48), median CD4 count (0.28), alcohol use (p=0.14), or the proportion who screened positive by symptoms (p=0.31) or CRP (p=0.15) between those with and without liver enzyme levels. Of 313 patients included, 158 (50%) were male, median age was 34 years (IQR 27–40), median CD4 count was 162 cells/μL (IQR 76–269), and 4 (1%) reported a history of hepatitis of any etiology (Table 1). Median AST levels were 27.8 U/L (IQR 22.1–39.4) and median ALT levels were 19.9 U/L (IQR 13.9–28.6). Seventy-five (24%) had any transaminitis (AST or ALT >1 times ULN), of whom 73 (97%) had elevated AST and 36

(48%) had elevated ALT. Six (2%) had severe transaminitis (AST or ALT >3 times ULN), of whom 6 (100%) had elevated AST and 1 (17%) had elevated ALT (Table 2). One (17%) patient with severe transaminitis reported a history of hepatitis.

Screening status

Thirty-two (10%) participants screened negative by the WHO symptom screen and would have required liver enzyme testing prior to initiating TPT. None of the 32 who screened negative by symptoms would have been ineligible for TPT by liver enzyme testing (AST or ALT >3 times ULN). Among those who screened positive by symptoms, 6/281 (2%) had AST and 1/281 (0.4%) had ALT levels >3 times ULN. Median AST and ALT levels were slightly higher for those who screened positive than those who screened negative (AST 28.4 vs. 22.5 U/L, p=0.003; ALT 20.3 vs. 15.7 U/L, p=0.02; Table 2a).

Most participants without active TB 194/313 (62%) screened negative by POC-CRP. Of the 194 screen-negative participants who would have required liver enzyme testing prior to initiating TPT, 4 (2.1%) would have been ineligible for TPT based on liver enzyme testing. Among those who screened positive by POC-CRP, 2/119 (1.7%) had AST and none had ALT >3 times ULN. Differences in median AST and ALT levels and the proportion with AST or ALT >3 times ULN were not statistically significant between those who screened positive or negative by POC-CRP (Table 2a).

Alcohol consumption

189 (60%) participants reported drinking alcohol monthly or less, 49 (16%) 2–4 times per month, 32 (10%) 2–3 times per week, and 43 (14%) ≥4 times per week. Median AST and ALT levels were higher among participants who reported consuming alcohol ≥4 times per week compared with those who reported drinking alcohol less frequently ($p<0.001$, Table 2b). Differences in the proportion of patients with any transaminitis and severe transaminitis according to alcohol consumption were not statistically significant. Half of all patients with severe transaminitis (3/6, 50%) reported no history of alcohol consumption, including one patient with ALT >3 times ULN.

DISCUSSION

In this analysis of ART-naïve PLWH undergoing systematic TB screening in Kampala, Uganda, we found that while any transaminitis was common among those without active TB (24%), prevalence of severe transaminitis was low (2%). None of the 32 participants who screened negative by symptoms and only 4/194 (2%) of those who screened negative by POC-CRP had AST or ALT >3 times ULN. Therefore, severe transaminitis is not expected to be a major barrier to scaling-up TPT in this setting, regardless of TB screening strategy; however, pre-TPT assessments for liver toxicity risk factors remain important.

Despite global efforts to improve TPT uptake, scale-up has been poor due to barriers including challenges ruling-out active TB with suboptimal screening tools. With its higher specificity and reliability over symptom-based TB screening, CRP-based screening —which was recently supported by WHO[2]—may increase the proportion of PLWH under consideration for TPT. However, drug-induced adverse events such as hepatotoxicity remain

a concern. To ensure safe scale-up of TPT, careful selection of patients for TPT and close monitoring for signs and symptoms of hepatotoxicity during TPT remains essential. Our results are consistent with prior studies reporting severe transaminitis to be rare among a general population of PLWH regardless of ART status[8,9,4,10–12]. However, direct comparison with other studies is difficult since definitions of elevated transaminases varied. Because we report transaminitis prevalence using cut-offs intended to inform TPT eligibility, these results will be important for HIV programmes considering requiring pre-TPT liver enzyme testing.

Current recommendations for pre-TPT liver enzyme testing differ across TB programmes and professional societies, however most guidelines recommend measuring ALT rather than AST[20,21], as it is a more specific marker of liver function. Here, we found only 1 participant with elevated ALT. Prevalence of elevated AST levels was also low, with only 6 participants with AST levels >3 times ULN, two of whom would have been ineligible for TPT due to screening positive for active TB. Of four screen-negative participants with AST or ALT >3 times ULN, only one would have been ineligible for TPT by history (self-reported heavy alcohol use). To streamline TPT eligibility assessments, clinicians should carefully assess all screen-negative PLWH for other TPT contraindications prior to ordering pre-TPT liver enzyme testing.

The primary limitation of this analysis is that transaminase levels were unavailable for most study participants and our study population was limited to ART-naïve individuals with advanced HIV, potentially impacting generalizability. However, there were no differences in baseline characteristics between those with and without transaminase levels. Furthermore, because liver enzymes were more likely to be ordered for patients for whom liver disease was suspected, it is possible that the true prevalence of transaminitis is lower than we report. Nevertheless, additional analyses of transaminitis prevalence in larger cohorts of PLWH being considered for TPT will be important to validate these findings. In addition, we did not capture hepatitis symptoms or clinical liver disease history, potentially understimating the proportion ineligible for TPT. Furthermore, hepatitis C testing was not performed. While isoniazid preventive therapy is generally well-tolerated among individuals with chronic hepatitis B or hepatitis C infections, WHO recommends that TPT be deferred for individuals with acute viral hepatitis;[7] more thorough assessment of hepatitis B and C prevalence would be informative to further understand transaminitis and liver toxicity risk in this population. Lastly, classification of alcohol consumption was based on self-report and therefore reporting bias is possible.

In conclusion, scaling up TPT remains essential for reducing the global burden of TB among PLWH. While novel TB screening strategies such as CRP may increase the proportion of PLWH considered for TPT, drug-related hepatotoxicity remains a concern and PLWH being considered for TPT should be assessed for liver toxicity risk factors. Our data provide valuable insights into underlying risks for TPT-related liver damage among PLWH eligible for TPT in high burden settings, demonstrating that prevalence of severe transaminitis is low and unlikely to be a major barrier to TPT implementation. Future studies should evaluate whether pre-TPT liver enzyme testing can be further limited to HIV subgroups with additional risk factors for drug-induced hepatotoxicity.

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Conflicts of Interest and Source of Funding:

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Table 1.

Patient characteristics and demographics

Characteristic	Total (N=313)
Female sex	158 (50%)
Median age, years (IQR)	34 (27–40)
Median CD4+ count (IQR)	162 (76–269)
Self-reported hepatitis[a]	4 (1%)
Alcohol consumption	
Monthly or less	189 (60%)
2–4 times per month	49 (16%)
2–3 times per week	32 (10%)
≥4 times per week	43 (14%)
HBsAg[b]	12 (4%)
POC CRP <5 mg/L	194 (62%)
WHO symptom screen negative	32 (10%)
Median AST (IQR)	27.8 (22.1–39.4)
Median ALT (IQR)	19.9 (13.9–28.6)
AST or ALT >1 times ULN[c]	75 (24%)
AST or ALT >3 times ULN[d, e]	6 (2%)

Abbreviations: IQR, interquartile range; HBsAg, Hepatitis B virus surface antigen; POC CRP, point-of-care C-reactive protein; WHO, World Health Organization; AST, aspartate transaminase; ALT, alanine transaminase; ULN, upper limit of normal

[a] 40 (13%) missing

[b] 175 (56%) missing

[c] 34 had both AST and ALT >1 times ULN; 39 had only AST >1 times ULN; 2 had only ALT >1 times ULN

[d] Laboratory ranges: ALT 0–41 U/L; AST 0–40 U/L

[e] 1 had AST and ALT >1 times ULN; 5 had only AST >3 times ULN

Table 2.

Liver enzyme levels by a) tuberculosis screening status and b) alcohol consumption.

a. TB screening status						
	WHO symptom screen negative (n=32)	**WHO symptom screen positive (n=281)**	**p-value**	**POC CRP <5 mg/L (n=194)**	**POC CRP ≥5 mg/L (n=119)**	**p-value**
Median AST (IQR)	22.5 (20.8–26.6)	28.4 (22.4–40.0)	0.003	26.8 (22.1–37.2)	29.3 (21.8–43.6)	0.20
AST >1 times ULN	3 (9.4%)	70 (24.9%)	0.049	36 (18.6%)	37 (31.1%)	0.01
AST >3 times ULN	0 (0%)	6 (2.1%)	0.99	4 (2.1%)	2 (1.7%)	0.99
Median ALT (IQR)	15.7 (11.9–21.1)	20.3 (14.0–29.7)	0.02	20.3 (14.6–27.2)	18.8 (12.2–30.4)	0.49
ALT >1 times ULN	1 (3.1%)	35 (12.5%)	0.15	20 (10.3%)	16 (13.5%)	0.40
ALT >3 times ULN	0 (0%)	1 (0.4%)	0.99	1 (0.5%)	0 (0%)	0.99
b. Alcohol consumption						
		None (n=189)	**2–4x per month (n=49)**	**2–3x per week (n=32)**	**≥4x per week (n=43)**	**p-value**
Median AST (IQR)		27.0 (21.1–36.6)	26.3 (20.9–36.4)	30.7 (22.9–38.9)	34.8 (25.0–50.0)	0.03
AST >1 times ULN		39 (20.6%)	11 (22.5%)	6 (18.8%)	17 (39.5%)	0.07
AST >3 times ULN		3 (1.6%)	1 (2.0%)	0 (0%)	2 (4.7%)	0.40
Median ALT (IQR)		19.3 (14.3–27.3)	17.2 (12.2–25.1)	20.9 (12.6–30.7)	25.7 (17.2–39.3)	0.02
ALT >1 times ULN		20 (10.6%)	3 (6.1%)	3 (9.4%)	10 (23.3%)	0.08
ALT >3 times ULN		1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0.99

Laboratory ranges: ALT 0–41 U/L; AST 0–40 U/L

Abbreviations: CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; ULN, upper limit of normal; IQR, interquartile range