Title

Higher Levels of Alcohol Use Are Associated With Latent Tuberculosis Infection in Adults Living With Human Immunodeficiency Virus

Journal

Clinical Infectious Diseases, 72(5)

ISSN

1058-4838

Authors

Puryear, Sarah B
Fatch, Robin
Beesiga, Brian
et al.

Publication Date

2021-03-01

DOI

10.1093/cid/ciaa527

Peer reviewed

Clinical Infectious Diseases

BRIEF REPORT

Higher Levels of Alcohol Use Are Associated With Latent Tuberculosis Infection in Adults Living With Human Immunodeficiency Virus

Sarah B. Puryear,[1,2] Robin Fatch,[3] Brian Beesiga,[4] Allen Kekibiina,[5] Sara Lodi,[6] Kara Marson,[1] Nneka I. Emenyonu,[3] Winnie R. Muyindike,[5] Dalsone Kwarisiima,[4] Judith A. Hahn,[1] and Gabriel Chamie[1]

[1]Division of HIV, Infectious Diseases and Global Medicine, University of California San Francisco, San Francisco, California, USA, [2]Center for AIDS Prevention Studies, University of California San Francisco, San Francisco, California, USA, [3]Department of Medicine, University of California San Francisco, San Francisco, California, USA, [4]Infectious Diseases Research Collaboration, Kampala, Uganda, [5]Mbarara University of Science and Technology, Mbarara, Uganda, and [6]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA

We assessed associations between hazardous alcohol use and latent tuberculosis infection (LTBI) among adults living with human immunodeficiency virus (HIV) in Uganda. We compared tuberculin skin test positivity across medium, high, and very-high alcohol use levels, classified by AUDIT-C scores. In multivariable analysis, very high use was associated with LTBI (adjusted odds ratio 1.61, 95% confidence interval: 1.03–2.50).

Keywords. alcohol; HIV; tuberculosis (TB); latent TB infection; Africa.

The risk of tuberculosis (TB) disease is significantly higher among persons living with human immunodeficiency virus (PLHIV) versus HIV-negative individuals [1]. For the 25% of PLHIV who report heavy alcohol use, the risk of TB disease increases 3-fold compared to nondrinkers [2]. The association between alcohol use and TB disease has been attributed to alcohol-induced immunosuppression and increased transmission due to social marginalization and drift [3]. This higher risk includes both primary TB disease (from recent TB infection) and reactivation TB disease (from latent tuberculosis infection (LTBI)). Despite this, the relative contribution of alcohol use to the risk of TB infection acquisition among PLHIV is not well understood.

Although recent tuberculin skin test (TST) surveys in high HIV prevalence populations in sub-Saharan Africa have not found an association between alcohol use and LTBI [4–6], the risk likely varies by amount of alcohol use. To date, no studies have investigated whether higher levels of alcohol use result in higher LTBI rates. In this study, we sought to understand the relationship between hazardous levels of alcohol use and LTBI among PLHIV.

METHODS

We conducted a cross-sectional study to evaluate the associations between alcohol use levels and LTBI among PLHIV with hazardous alcohol use in Southwestern Uganda from April 2018 to July 2019. Participants included adults who underwent TST placement during screening for the Drinkers' Intervention to Prevent Tuberculosis (DIPT) study, an ongoing randomized controlled trial of economic incentives to reduce drinking and improve isoniazid preventive therapy (IPT) completion in persons engaged in hazardous alcohol use with HIV/TB coinfection (NCT03492216). We recruited participants from 2 urban (Mbarara Municipal Clinic [MMC] and Immune Suppression Syndrome [ISS] clinic) and 2 rural (Ruhuko and Rugazi Health Centers) clinic sites.

Given the increased risk of IPT toxicity with alcohol use, the parent study restricted eligibility for TST placement to PLHIV who were ≥18 years old, on non-nevirapine-based antiretroviral therapy for ≥6 months, and reported no history of TB disease or IPT. Eligible participants had positive point-of-care urine dipstick ethyl glucuronide (EtG) (alcohol biomarker) tests (cutoff ≥ 300 ng/mL) [7] and endorsed hazardous drinking within the prior 3 months, defined as an Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score ≥3 if female and ≥4 if male [8]. They were excluded if liver transaminases were >2 times the upper limit of normal or if pregnant. If participants met eligibility criteria and had hazardous drinking and a positive EtG, we placed a TST.

The primary exposure of interest was hazardous alcohol use level, measured by AUDIT-C score and classified as medium (AUDIT-C 4–5 men/3–5 women), high (6–7), and very high (8–12) [9]. The outcome of interest, LTBI, was defined as a positive TST, which was an induration of ≥5 mm without symptoms of TB disease. We excluded participants with TST results obtained outside of the 48–72 hour period after placement.

Statistical Analysis

Bivariate analyses (χ^2 test for categorical variables, Wilcoxon rank sum for continuous variables) determined associations between participant characteristics and TST positivity. A multivariable logistic regression model was fit to estimate the association between drinking level and TST-positivity, adjusting for age, sex, and study site. We computed 95% confidence intervals (95% CI)

Received 16 December 2019; editorial decision 15 April 2020; accepted 30 April 2020; published online May 6, 2020.

Correspondence: S. B. Puryear, Division of HIV, Infectious Diseases (ID), and Global Medicine, 995 Potrero Ave, Ward 84, San Francisco, CA 94110 (sarah.puryear@ucsf.edu).

Clinical Infectious Diseases® 2021;72(5):865–8

DOI: 10.1093/cid/ciaa527

using robust standard errors to account for clustering by study site. We performed analyses using STATA version 14.2.

Ethical Approval

All participants provided written consent for parent study screening. The study was approved by the University of California, San Francisco Institutional Review Board, and the Research Ethics Committees of Mbarara University of Science and Technology, Makerere University School of Medicine, and the Ugandan National Council for Science and Technology.

RESULTS

A total of 866 of 1733 (50%) adult PLHIV screened with AUDIT-C and urine EtG had hazardous alcohol use and were EtG positive. Among these 866, 119 (14%) were excluded: 113 (13%) for elevated transaminases and 6 (1%) for pregnancy. Of the 747 eligible for TST placement, 18 (2%) declined and 729 (98%) consented to TST placement. Among the 729 consenting to TST, this analysis excluded 112 (15%) for not returning for TST reading within 48–72 hours and included 617 (85%) who completed TST screening. The majority of participants (452/617 [73%]) were male with a median age of 40 years (interquartile range [IQR], 32–48) (Table 1). TB symptom screening was negative in 99.5% (614/617) of individuals; the 3 individuals endorsing symptom(s) were ruled out for TB disease.

The median AUDIT-C score was 6 (IQR 5–8). Drinking levels were medium (AUDIT-C 4–5 men/3–5 women) in 41% (256/617), high (AUDIT-C 6–7) in 31% (191/617), and very high (AUDIT-C 8–12) in 28% (170/617) of participants. Drinking levels differed between clinic sites, with medium level use most common at Rugazi (52%), Ruhoko (51%), and ISS (40%) and very high level use most common at MMC (48%). Participants most commonly reported a drinking frequency of 2–3 times per week (258/617, 42%), 5–6 drinks per session (245/617, 40%), and binge drinking (≥6 drinks on one occasion) at least monthly (238/617, 39%).

The prevalence of LTBI, measured by TST positivity, was 35% (217/617), with heterogeneity by clinic site, ranging from 22% (44/199) at Ruhoko to 44% (90/206) at MMC (Table 1). LTBI prevalence was highest with very high level use (77/170, 45%) relative to high-level (62/191, 33%) and medium-level use (78/256, 31%).

In the multivariate model adjusting for sex, age, and clinic, very high level alcohol use was associated with TST-positivity compared to medium level use (adjusted odds ratio (aOR) 1.61, 95% CI: 1.03–2.50, $P = .04$). High-level drinking had a nonsignificant association with TST positivity compared to medium-level use (aOR 1.05, 95% CI: .69–1.59, $P = .83$). Clinic site was also associated with TST positivity (Table 1).

DISCUSSION

In this cross-sectional study of PLHIV engaged in hazardous alcohol use, we found that very high level alcohol use was associated with LTBI compared to medium-level use. Studies have demonstrated that persons engaging in heavy drinking have an increased risk of TB disease compared to nondrinkers [2, 10]. Our results suggest that this risk may be partly attributable to higher rates of LTBI with hazardous alcohol use, especially very high level use.

The increased risk of TB disease with hazardous alcohol use is well established. A systematic review found that low-to-moderate alcohol intake had no association with TB disease risk, but heavy use (≥40 g/day) increased the odds of TB disease 2.9-fold [2]. In a more recent meta-analysis, alcohol intake ≤60 g/day had no effect on TB disease risk, but consumption >60 g/day was associated with a 68% higher risk compared to no use and showed a dose-response relationship with increasing levels >60 g/day [10]. However, prior research on differing alcohol use levels and LTBI risk in PLHIV is limited. Studies in South Africa, Zambia, and Uganda—where HIV, TB, and alcohol use rates are high—found no association between any alcohol use and LTBI [4–6]. We found that, compared to medium level use, very high level use was associated with a significantly higher prevalence of LTBI. These findings suggest that higher rates of LTBI with very high level use may contribute to the increased risk of TB disease among persons engaged in hazardous alcohol use. This may be compounded by alcohol-mediated immunosuppression [10] increasing primary TB disease incidence and rates of reactivation [11].

The mechanisms underlying the association between higher levels of alcohol use and LTBI observed could not be ascertained in this study. Potential mechanisms include biologic, structural, and social-behavioral pathways and are likely multifactorial. Chronic alcohol use disrupts the innate and adaptive immune systems [3], which may increase susceptibility to TB infection [10]. Alcohol inhibits interferon-gamma production [2], suppresses alveolar macrophage function [3, 10], and disrupts antigen-specific T-cell activation and proliferation [2, 3, 10]. From a structural standpoint, persons engaged in alcohol use may spend more time in congregate locations with increased TB transmission, such as bars, prisons, or homeless shelters. From a social-behavioral standpoint, they may be more likely to socially mix with other persons engaged in alcohol use [2], who have higher rates of TB disease and are more likely to have smear-positive pulmonary TB [12], increasing infection risk.

Our study has several limitations. First, we did not capture CD4 counts and could not account for this in the multivariable model. Individuals with lower CD4 counts are more likely to be TST anergic, resulting in false-negative tests. However, persons with higher-level alcohol use are more likely to have poorly controlled HIV, resulting in misclassification as TST-negative and biasing results toward the null. Second, our study population did not include low-level or nondrinkers as comparison groups. However, the goal of this analysis was not to establish drinking as a risk factor for LTBI but to understand how LTBI risk varies over drinking levels. Third, alcohol use levels were

Table 1. Characteristics of Persons Living with HIV Who Engage in Hazardous Alcohol Use, by TST Result, April 2018 through July 2019 (n = 617)

	TST-negative (n = 400, 64.8%)	TST-positive (n = 217, 35.2%)	Bivariate	aOR	Multivariate
	N (%) or median (IQR)	N (%) or median (IQR)	*P* value[a]	(95% CI)	*P* value
Age (years)	39 (32–49)	40 (32–47)	.78	.99 (.84, 1.16)[b]	.91
Sex			.70		.86
Male	291 (72.8)	161 (74.2)		1.00	
Female	109 (27.3)	56 (25.8)		.97 (.65, 1.43)	
TB symptoms			.69	…	
No symptoms	398 (99.5)	216 (99.5)		…	
Cough only	1 (0.25)	1 (0.5)		…	
Cough, night sweats, and weight loss	1 (0.25)	0 (0.0)		…	
AUDIT-C score	6 (5–6)	7 (5–8)	**<.01**	**…**	
AUDIT-C level[c]			**<.01**	…	
Medium (4–5 ♂; 3–5 ♀)	178 (44.5)	78 (35.9)		1.00	
High (6–7)	129 (32.3)	62 (28.6)		1.05 (.69, 1.59)	.83
Very high (8–12)	93 (23.3)	77 (35.5)		1.61 (1.03, 2.50)	**.04**
Drinking frequency			.53	…	
Monthly or less	4 (1.0)	3 (1.4)		…	
2–4 times a month	120 (30.0)	54 (24.9)		…	
2–3 times a week	166 (41.5)	92 (42.4)		…	
4+ times a week	110 (27.5)	68 (31.3)		…	
Drinking intensity			.07	…	
0 drinks	2 (0.5)	0 (0.0)		…	
1–2 drinks	7 (1.8)	1 (0.5)		…	
3–4 drinks	157 (39.3)	65 (30.0)		…	
5–6 drinks	154 (38.5)	91 (41.9)		…	
7–9 drinks	37 (9.3)	29 (13.4)		…	
10+ drinks	43 (10.8)	31 (14.3)		…	
Binge drinking[d]			.10	…	
Never	93 (23.3)	40 (18.4)		…	
Less than monthly	137 (34.3)	68 (31.3)		…	
Monthly	104 (26.0)	54 (24.9)		…	
Weekly	45 (11.3)	35 (16.1)		…	
Daily or almost daily	21 (5.3)	20 (9.2)		…	
TST size (mm)	0 (0-0)	19 (14–22)		…	
Clinic			**<.01**	…	
MMC (urban)	116 (29.0)	90 (41.5)		1.00	
ISS (urban)	40 (10.0)	22 (10.1)		.79 (.43, 1.44)	.44
Rugazi (rural)	89 (22.3)	61 (28.1)		1.03 (.65, 1.63)	.89
Ruhoko (rural)	155 (38.8)	44 (20.3)		.42 (.27, .67)	**<.01**

P-values in bold denote statistical significance at the p<0.05 level.

Abbreviations: aOR, adjusted odds ratio; AUDIT-C, Alcohol Use Disorders Identification Test-C; CI, confidence interval; IQR, interquartile range; ISS, immune suppression syndrome; MMC, Mbarara Municipal Clinic; TB, tuberculosis; TST, tuberculin skin test.

[a]χ^2 test for categorical variables and Wilcoxon rank sum for continuous variables.

[b]Age per 10 years increase used for aOR estimation.

[c]AUDIT-C levels defined as medium (AUDIT-C 4–5 if male, 3–5 if female), high (6–7), and very high (8–12).

[d]Binge drinking defined as ≥6 drinks on 1 occasion.

based on self-report, which is subject to error and social desirability bias. This was minimized by the concomitant use of AUDIT-C, a validated tool, and confirmatory alcohol biomarker (EtG) testing. Finally, we did not capture data on socioeconomic status or comorbidities (eg, malnutrition, tobacco use) that may influence LTBI risk and differ by alcohol use level. This may have caused overestimation of the LTBI attributable to alcohol; however, potential confounding was reduced by using medium level use as the comparison group. Nonetheless, our study has several strengths, including the use of an EtG to confirm hazardous alcohol use. Second, we captured levels of alcohol use, allowing for more granular examination of the effect of hazardous drinking on LTBI than previously reported. Third, we included rural and urban sites with varying rates of LTBI and alcohol use. This augments the diversity of the study population, adding to the generalizability of results.

Alcohol use is a measurable and modifiable risk factor for latent TB infection and TB disease. Our finding of increasing

prevalence of LTBI at the highest levels of hazardous alcohol use among PLHIV suggests that their increased risk of TB disease may be attributable, in part, to higher rates of LTBI.

Notes

Author contributions. S. B. P., J. A. H., and G. C. contributed to the study design, data analysis and interpretation, literature search, and writing of the manuscript. R. F. and S. L. contributed to study design, data analysis and interpretation, and writing of the manuscript. B. B., A. K., K. M., N. I. E., W. R. M., and D. K. contributed to study design, data interpretation, and writing of the manuscript. Authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments. The authors gratefully acknowledge the Ministry of Health of Uganda, our research and administrative teams in San Francisco and Uganda, collaborators and advisory boards, and especially all participants involved.

Financial support. This work was supported by grants from the National Institutes of Health through the National Institute on Alcohol Abuse and Alcoholism [U01AA026223 to J. A. H., U01AA026221 to G. C., and K24AA022586 to J. A. H.]; and the National Institutes of Mental Health [T32MH19105 supporting S. B. P.].

Potential conflicts of interest. R. F., K. M., J. A. H., and G. C. report grant support from the National Institutes of Health during the conduct of the study. Additionally, G. C. reports grants from the Gates Foundation, outside of the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. WHO. Global Tuberculosis report 2019. Geneva, Switzerland: World Health Organization, **2019**.
2. Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis: a systematic review. BMC Public Health **2008**; 8:289.
3. Rehm J, Samokhvalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB): a systematic review. BMC Public Health **2009**; 9:450.
4. Muyindike WR, Fatch R, Cheng DM, et al. Abstract 933: tuberculin skin test response among HIV-infected alcohol users on antiretrovirals in Uganda. In: 41st Annual Scientific Meeting of the Research Society on Alcoholism. San Diego, California, USA, **2018**.
5. Shanaube K, Hargreaves J, Fielding K, et al. Risk factors associated with positive QuantiFERON-TB gold in-tube and tuberculin skin tests results in Zambia and South Africa. PLoS One **2011**; 6:e18206.
6. Ncayiyana JR, Bassett J, West N, et al. Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. BMC Infect Dis **2016**; 16:661.
7. Leickly E, Skalisky J, McPherson S, Orr MF, McDonell MG. High agreement between benchtop and point-of-care dipcard tests for ethyl glucuronide. Ther Drug Monit **2017**; 39:461–2.
8. Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res **2007**; 31:1208–17.
9. Williams EC, McGinnis KA, Edelman EJ, et al. Level of alcohol use associated with HIV care continuum targets in a national US sample of persons living with HIV receiving healthcare. AIDS Behav **2019**; 23:140–51.
10. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lonnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J **2017**; 50: 1700216.
11. Amoakwa K, Martinson NA, Moulton LH, Barnes GL, Msandiwa R, Chaisson RE. Risk factors for developing active tuberculosis after the treatment of latent tuberculosis in adults infected with human immunodeficiency virus. Open Forum Infect Dis **2015**; 2:ofu120.
12. Fiske CT, Hamilton CD, Stout JE. Alcohol use and clinical manifestations of tuberculosis. J Infect **2009**; 58:395–401.