Determinants of alcohol use among people living with HIV initiating isoniazid preventive therapy in Ethiopia

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ABSTRACT

Background: Hepatotoxicity, an adverse effect of isoniazid preventative therapy (IPT), is exacerbated by alcohol consumption. Although the WHO recommends IPT for people living with HIV (PLHIV), it is contraindicated in regular alcohol users. The objective of this study was to identify the prevalence and determinants of alcohol use among PLHIV initiating IPT in Ethiopia.
Methods: Baseline data (July 2013-May 2015) from 316 participants in the Enhance Initiation and Retention in IPT Care for HIV (ENRICH) study were used to assess the prevalence of alcohol use. Multinomial logistic regression was used to identify determinants of non-hazardous and hazardous alcohol use, compared to no alcohol use.
Results: Overall, 41.8% of participants reported alcohol use, of which 45.5% reported hazardous use. Compared to non-alcohol users, hazardous users were younger (adjusted odds ratio [AOR]: 1.06; 95% confidence interval [95% CI]: 1.02, 1.11), more likely to be male (AOR: 6.40; 95% CI: 3.17, 12.93), Orthodox (AOR: 3.96; 95% CI: 1.74, 9.00), have larger support networks (AOR: 3.82; 95% CI: 1.61, 9.06), and report greater amount (AOR: 14.80; 95% CI: 5.76, 38.02) and frequency (AOR: 5.91; 95% CI: 2.75, 12.67) of khat use.
Conclusions: Alcohol use was prevalent in this population, and current WHO guidelines would exclude a substantial proportion of the population from receiving IPT. PLHIV in this region would benefit from routine screening for alcohol and khat use, and from substance use education and counseling while receiving IPT until it can be determined whether alcohol users can safely receive IPT.

1. Introduction

Tuberculosis (TB) is the leading cause of mortality among people living with HIV (PLHIV), and despite antiretroviral therapy (ART) scale up, TB incidence remains 2–10 fold higher than in HIV-negative populations (Kwan and Ernst, 2011; World Health Organization, 2018b). The World Health Organization (WHO) classifies Ethiopia as one of fourteen high priority countries with overlapping epidemics of TB, TB/HIV co-infection and multidrug-resistant TB (MDR-TB) (World Health Organization, 2018b). In 2017, the incidence and mortality rates of TB among PLHIV in Ethiopia were 12 and 3.5 per 100,000 population, respectively (World Health Organization, 2018b).

Isoniazid preventive therapy (IPT) has proven efficacious in reducing the risk of TB among PLHIV exposed to *Mycobacterium tuberculosis* by up to 96%, and the risk of death by 37%, irrespective of ART use

(Badje et al., 2017; Semu et al., 2017). Given the high risk of TB among PLHIV, WHO guidelines recommend that all PLHIV who are not suspected of active TB be placed on at least 6 months of IPT as part of a comprehensive HIV care package (World Health Organization, 2018c). In 2017, only 45% of HIV-positive Ethiopians newly enrolled in HIV care received IPT (World Health Organization, 2018b).

Hepatotoxicity is a frequent side effect of IPT, and may be a life-threatening adverse event that is further exacerbated by alcohol use (Saukkonen et al., 2006). The WHO guidelines state that regular and heavy alcohol use is a contraindication to IPT (World Health Organization, 2018c). This guidance has been adopted by many high TB and HIV burden sub-Saharan African countries, including Ethiopia, where the prevalence of heavy episodic alcohol use is as high as 45% (World Health Organization, 2018a). Moreover, hazardous alcohol use, HIV and TB are closely interrelated, and hazardous alcohol use not only

increases the likelihood of isoniazid-induced hepatotoxicity, but also the risks of HIV and TB. Based on current WHO guidance, as many as 30% of PLHIV in sub-Saharan African countries may be excluded from receiving this potentially life-saving preventive medication due to hazardous alcohol use (World Health Organization, 2018a).

There is some evidence to suggest that use of khat, a plant-based amphetamine-like substance with psychoactive and hallucinogenic properties, may also be associated with hepatotoxicity (Chapman et al., 2010; Stuyt et al., 2011). Khat is a deep-rooted social and cultural tradition in Ethiopia and is more commonly used by men (Al-hebshi et al., 2006). It is usually chewed at special social gatherings, but is also used frequently by laborers, craftsmen, farmers and students for its stimulant-like effects and to reduce physical fatigue. In Ethiopia, khat use prevalence estimates range from 30 to 50%, and are higher in the Muslim population. Though understudied, khat use may be an additional cause for concern when initiating IPT among PLHIV in Ethiopia, and more evidence is needed on khat use patterns and the adverse effects of khat use among those initiated on IPT.

This study aims to identify the prevalence and determinants of alcohol and khat use among PLHIV enrolled in care and initiating IPT in Ethiopia.

2. Methods

2.1. Study participants

Data were drawn from the Enhance Initiation and Retention in IPT Care for HIV (ENRICH) study, described elsewhere (Howard et al., 2017). The sample included 316 PLHIV enrolled in care from 10 HIV study clinics in Dire Dawa and Harari, Ethiopia. Potential participants were referred to the ENRICH study by the clinic nurse at each site, who also assessed IPT eligibility according to Ministry of Health guidelines. Ethiopian Ministry of Health guidelines state that patients are eligible to initiate IPT if they do not have symptoms suggestive of TB, active hepatitis, regular and heavy alcohol use or peripheral neuropathy. Participants were eligible for the ENRICH study if they initiated IPT during the study period, were 18 years or older, spoke one of four local languages and provided informed consent. Participants were enrolled between July 2013 and May 2015 during routine clinic visits occurring within three days of IPT initiation. Written informed consent was obtained prior to all study-related activities. The study was approved by ethical review boards at Columbia University Medical Center and the Ethiopia National Research Ethics Review Committee and is registered with ClinicalTrials.gov (protocol #NCT01926379).

2.2. Study measures

Participants completed a standardized interviewer-administered questionnaire at baseline that included sociodemographic and psychosocial characteristics, alcohol and khat use, barriers to medical care, and attitudes toward IPT. HIV-related clinical data, including CD4 count and ART use were abstracted from medical records.

2.3. Primary outcome

The Alcohol Use Disorder Identification Test (AUDIT) was developed by the WHO and assesses alcohol use behaviors in the year prior to administration (Saunders et al., 1993). It consists of 10-items that are rated on a five-point Likert scale, and has a maximum summary score of 40. Participants who indicated that they had not consumed alcohol in the past year were characterized as having no alcohol use. Using established scoring criteria, participants who scored less than eight were characterized as having non-hazardous alcohol use; those who scored greater than or equal to eight were characterized as having hazardous alcohol use (Saunders et al., 1993). The AUDIT has previously been used to measure alcohol use in Ethiopia, (Babor et al., 2001) and was

found to be a reliable measure of hazardous alcohol use in this sample (Cronbach α: 0.835).

2.4. Correlates of alcohol use

Sociodemographic characteristics examined included age, gender, educational attainment, marital status, wealth, employment and religion. Economic status was based on 11 questions on ownership of items and characteristics of living spaces. A wealth score was generated using principal components analysis, which was then grouped into quintiles following the method used by the Ethiopian Demographic and Health Surveys (Rutstein et al., 2004; Vyas and Kumaranayake, 2006). Clinical characteristics of HIV included CD4 count and ART status.

Psychosocial characteristics included whether participants had disclosed their HIV status, depressive symptoms, and size of support network. The 9-item Patient Health Questionnaire (PHQ-9) was used to assesses frequency of depressive symptoms in the two weeks prior to the interview, with responses ranging from not at all (0) to nearly every day (3). Summary scores of 1–5, 6–10, 11–15, and 16–20 represented mild, moderate, moderately severe and severe depressive symptoms, respectively. The PHQ-9 is a valid and reliable measure of depression symptomology, (Kroenke et al., 2001) which has been previously used in Ethiopia, (Gelaye et al., 2013) and was a reliable measure in this sample (Cronbach α: 0.844). Social support network size was measured using the question "How many people provided help or encouragement to you in the past month?" Responses were categorized as 0, 1–2, or 3 or more.

Because khat use is common in Ethiopia, we included five multiple-choice questions that assessed khat use in the past month, frequency of khat use (per week and per day), amount of typical khat consumption, and frequency of alcohol use after khat use. The response categories for questions about frequency of khat use and khat use after alcohol use in the past month included never, weekly or less, 2–3 times a week, 4–5 times a week, or 6–7 times a week. Overall frequency of khat use in the past month was collapsed into never, weekly or less, or more than weekly. Frequency of khat use after alcohol consumption in the past month was collapsed into never and ever. To assess the amount of khat used on a typical occasion of khat use, participants were asked if they consumed 125 g, 250 g, 500 g, 1000 g or more than 1000 g. Responses were then collapsed into 125 g, or 250 g or greater.

Barriers to medical care and attitudes toward IPT were assessed by asking participants whether "[they were] too drunk or high" to obtain medical care in the past 30 days, and whether "[they] would stop taking [their] IPT medicines if [they] couldn't drink alcohol." Responses were dichotomized as yes or no.

2.5. Data analysis

Descriptive statistics were used to describe the study sample according to alcohol consumption patterns (no alcohol use, non-hazardous alcohol use or hazardous alcohol use). Bivariate associations of the correlates described above, and alcohol use patterns were examined using Pearson's chi-squared or Fisher's exact test for categorical variables, and ANOVA for continuous variables. Predictors that had moderately significant differences by alcohol consumption pattern (p < 0.10) were then individually entered into a multinomial logistic regression model to estimate independent factors of non-hazardous and hazardous use of alcohol compared to no alcohol use. Odds ratios for each predictor variable were adjusted only by health facility, to account for any site-level differences due to clustering. All statistical analyses were completed using IBM SPSS version 24.

3. Results

Of 316 participants enrolled, approximately two-thirds were female (63.3%), employed (67.4%), or Ethiopian Orthodox (64.6%). Less than

Table 1

Characteristics of PLHIV Initiated on IPT in Ethiopia by Alcohol Use Patterns[*].

Characteristic	Total sample N (%)	No alcohol use N (%)	Non-hazardous alcohol use N (%)	Hazardous alcohol use N (%)	p-value
	316 (100.0)	184 (58.2)	72 (22.8)	60 (19.0)	
Median age (IQR), years	30.0 (26.0-38.8)	31.5 (27.0-40.0)	33.5 (27.0-40.8)	28.5 (23.0-35.0)	0.001
Gender, n (%)					< 0.001
Male	116 (36.7)	49 (42.2)	30 (25.9)	37 (31.9)	
Female	200 (63.3)	135 (67.5)	42 (21.0)	23 (11.5)	
Marital Status, n (%)					0.148
Previously married/Single	186 (58.9)	104 (55.9)	40 (21.5)	42 (22.6)	
Married/Co-habitation	130 (41.1)	80 (61.5)	32 (24.6)	18 (13.8)	
Educational attainment, n (%)					0.008
No school	69 (21.8)	52 (73.9)	6 (8.7)	11 (15.9)	
Primary school	159 (50.3)	87 (54.7)	39 (24.5)	33 (20.8)	
Secondary school or more	88 (27.8)	45 (51.1)	27 (30.7)	16 (18.2)	
Wealth Index[†], n (%)					0.006
Lowest	62 (19.6)	41 (66.1)	7 (11.3)	14 (22.6)	
Second	68 (21.5)	41 (60.3)	10 (14.7)	17 (25.0)	
Middle	42 (13.3)	23 (54.8)	10 (23.8)	9 (21.4)	
Fourth	104 (32.9)	64 (61.5)	28 (26.9)	12 (11.5)	
Highest	38 (12.0)	14 (36.8)	16 (42.1)	8 (21.1)	
Employed, n (%)					0.006
Yes	213 (67.4)	111 (52.1)	55 (25.8)	47 (22.1)	
No	103 (32.6)	73 (70.9)	17 (16.5)	13 (12.6)	
Religion[†], n (%)					< 0.001
Ethiopian Orthodox	204 (64.6)	94 (46.1)	64 (31.4)	46 (22.5)	
Muslim	94 (29.7)	76 (80.9)	5 (5.3)	13 (13.8)	
Other	17 (5.4)	14 (82.4)	2 (11.8)	1 (5.9)	
HIV disclosure, n (%)					0.241
Yes	236 (74.7)	131 (55.5)	57 (24.1)	48 (20.3)	
No	80 (25.3)	53 (66.3)	15 (18.8)	12 (15.0)	
Depressive symptoms, n (%)					0.634
None	217 (68.7)	132 (60.8)	47 (21.7)	38 (17.5)	
Mild	68 (21.5)	34 (50.0)	18 (26.5)	16 (23.5)	
Moderate-Severe	31 (9.8)	18 (58.1)	7 (22.6)	6 (19.4)	
Size of social support network, n (%)					0.007
0	128 (40.5)	79 (61.7)	28 (21.9)	21 (16.4)	
1-2	117 (37.0)	77 (65.8)	22 (18.8)	18 (15.4)	
3 or more	71 (22.5)	28 (39.4)	22 (31.0)	21 (29.8)	
Frequency of khat use, n (%)					< 0.001
Never	180 (57.0)	121 (67.2)	43 (23.9)	16 (8.9)	
≤ Weekly	47 (14.9)	21 (44.7)	14 (29.8)	12 (25.5)	
> Weekly	89 (28.2)	42 (47.2)	15 (16.9)	32 (36.0)	
Amount of khat use, n (%)					< 0.001
None	180 (57.0)	121 (67.2)	43 (23.9)	16 (8.9)	
125 g	91 (28.8)	49 (53.8)	23 (25.3)	19 (20.9)	
≥ 250 g	45 (14.2)	14 (31.1)	6 (13.3)	25 (55.6)	
Frequency of concurrent khat and alcohol use, n (%)					< 0.001
Never	285 (90.2)	183 (67.2)	69 (24.2)	33 (11.6)	
Ever	31 (9.8)	1 (3.2)	3 (9.7)	27 (87.1)	
Substance use as a barrier to medical care	10 (3.2)	2 (20.0)	1 (10.0)	7 (70.0)	0.001
Alcohol as a barrier to IPT	250 (79.1)	141 (56.4)	63 (25.2)	46 (18.4)	0.137
Median CD4 cell count/μL (IQR)	291.0 (167.5-486.0)	280.5 (168.8-476.0)	285.5 (170.8-546.5)	320.0 (164.5-492.0)	0.851
On ART, n (%)					0.602
Yes	245 (77.8)	146 (59.6)	54 (22.0)	45 (18.4)	
No	70 (22.2)	37 (52.9)	18 (25.7)	15 (21.4)	

[*] Alcohol use categorized by AUDIT scores; AUDIT = 0: no alcohol use; AUDIT < 8: non-hazardous alcohol use; AUDIT ≥ 8: hazardous alcohol use.

[†] Economic status and religion may not add up to row total due to missing data.

half (41.1%) were married, and the majority had disclosed their HIV status (74.7%) and were on currently on ART (77.8%). When examining alcohol use patterns, 184 (58.2%) reported no alcohol use, 72 (22.8%) reported non-hazardous alcohol use, and 60 (19.0%) reported hazardous alcohol use in the past year (Table 1).

Determinants of non-hazardous and hazardous alcohol use by multivariable analysis are presented in Table 2. Compared to no alcohol use, hazardous alcohol use was associated with younger age (adjusted odds ratio [AOR]: 1.06; 95% confidence interval [CI]: 1.02, 1.11), male gender (AOR: 6.40; 95% CI: 3.17, 12.93), and Ethiopian Orthodox (compared to Muslim) religion (AOR: 3.96; 95: CI: 1.74, 9.00). Additionally, those reporting social support networks consisting of three or more people had greater odds (AOR: 3.82; 95% CI: 1.61, 9.06) of hazardous alcohol use, compared to those reporting no social support

network. Furthermore, any frequency and amount of khat use was associated with greater odds of hazardous alcohol use. Specifically, those with more than weekly khat use and amounts greater than 250 g compared to no khat use were associated with 5.91 (95% CI: 2.75, 12.67) and 14.80 (95% CI: 5.76, 38.02) greater odds of hazardous alcohol use, respectively.

Similar to hazardous alcohol use patterns, male gender (AOR: 2.39; 95% CI: 1.27, 4.49) and Ethiopian Orthodox religion (AOR: 12.35; 95% CI: 4.38, 34.85) were also associated with non-hazardous alcohol use. No associations were found between age or khat use and non-hazardous alcohol use. When comparing non-hazardous alcohol use to no alcohol use, higher socioeconomic status was associated with non-hazardous alcohol use. Specifically, when compared to those who completed no school, had lowest wealth and were not employed, participants who

Table 2

Determinants of Non-Hazardous and Hazardous Alcohol Use compared to No Alcohol Use among PLHIV Initiating IPT.

Characteristic	Hazardous Alcohol Use		Non-Hazardous Alcohol Use	
	AOR[*,†]	95% CI[†]	AOR[*,†]	95% CI[†]
Age (years)	0.99	0.96, 1.02	**1.06**	**1.02, 1.11**
Gender				
Female	ref		ref	
Male	**2.39**	**1.27, 4.49**	**6.40**	**3.17, 12.93**
Marital Status				
Previously married/ Single	ref		ref	
Married/Co-habitation	1.06	0.59, 1.91	0.54	0.28, 1.05
Educational attainment				
No school	ref		ref	
Primary school	**4.45**	**1.68, 11.82**	2.17	0.94, 5.04
Secondary school or more	**6.08**	**2.17, 17.10**	2.25	0.87, 5.84
Wealth Index				
Lowest	ref		ref	
Second	1.54	0.51, 4.62	1.44	0.57, 3.61
Middle	2.43	0.79, 7.60	0.91	0.31, 2.65
Fourth	1.91	0.73, 5.01	0.45	0.17, 1.17
Highest	**3.90**	**1.24, 12.30**	0.83	0.26, 2.67
Employed				
Yes	**2.21**	**1.13, 4.33**	2.09	0.97, 4.38
No	ref		ref	
Religion				
Muslim	ref		ref	
Ethiopian Orthodox	**12.35**	**4.38, 34.85**	**3.96**	**1.74, 9.00**
Other	2.14	0.33, 13.98	0.480	0.05, 4.48
Size of social support network				
0	ref		ref	
1-2	1.19	0.56, 2.51	1.10	0.48, 2.55
3+	**2.48**	**1.12, 5.50**	**3.82**	**1.61, 9.06**
Frequency of khat use				
Never	ref		ref	
≤ Weekly	1.49	0.65, 3.42	**3.91**	**1.52, 10.07**
> Weekly	1.01	0.48, 2.10	**5.91**	**2.75, 12.67**
Amount of khat use (grams)				
None	ref		ref	
125 g	1.22	0.63, 2.38	**2.69**	**1.20, 6.01**
≥ 250 g	1.13	0.19, 6.77	**14.80**	**5.76, 38.02**

Note: Statistically significant findings in bold.
[†] Adjusted odds ratio (AOR); confidence interval (CI).
[*] Odds ratios adjusted by health facility.

had completed primary (AOR: 4.45; 95% CI: 1.68, 11.82) or secondary school and higher (AOR: 6.08; 95% CI: 2.17, 17.10), had highest wealth (AOR: 2.34; 95% CI: 1.02, 5.39), and were employed (AOR: 3.90; 95% CI: 1.24, 12.30) had higher odds of non-hazardous alcohol use.

Alcohol use was highly correlated with khat use, and the prevalence of khat use in the past month increased with increasing severity of alcohol use. Among hazardous alcohol users, almost half (45%) had also used khat in the past month (data not shown). Additionally, we found that hazardous alcohol users had a 12.4 (95% CI: 2.50, 61.64) greater odds of reporting being too drunk or too high as a barrier to obtaining medical care when compared to those who did not use alcohol (data not shown). Furthermore, 250 (79.1%) participants agreed with the statement "I would stop taking my IPT medicines if I couldn't drink alcohol," with no significant difference observed between hazardous and non-hazardous users (Table 1).

4. Discussion

This study aimed to identify the prevalence and determinants of alcohol use among PLHIV initiating IPT in Ethiopia, a high burden TB and TB/HIV country. Overall, 41.8% of participants reported alcohol use within the past year, of which 54.5% reported non-hazardous alcohol use and 45.5% reported hazardous alcohol use. Hazardous alcohol use rates were largely consistent with previous studies of alcohol use among PLHIV in Ethiopia, suggesting that drug-induced hepatotoxicity may be of particular concern among PLHIV receiving IPT in Ethiopia (Bultum et al., 2018; Soboka et al., 2014).

People with hazardous alcohol use are at an increased risk for latent TB infection (LTBI) and for progression of LTBI to active TB, and thus the WHO guidelines stating that regular and heavy alcohol use is a contraindication to IPT may result in a substantial proportion of the population at increased risk for TB being excluded from receiving preventive treatment. A modeling study found that the benefits of 6 months of IPT among PLHIV on ART who are heavy drinkers outweigh the risks in high TB prevalence settings, but not in low prevalence settings (Freiman et al., 2018). WHO guidelines that recommend deferring TB preventive treatment in heavy and regular alcohol users do not consider the heterogeneity of TB incidence and HIV prevalence across countries. Currently, true equipoise exists as to whether IPT should be provided for heavy alcohol users, and current studies are underway to better understand the safety, tolerability and completion rates of IPT among regular alcohol users in sub-Saharan Africa (Clinicaltrials.gov protocol #NCT03302299).

Until we have clinical trial data regarding whether PLHIV who are regular and heavy alcohol users can safely be placed on IPT, increased monitoring for symptoms of hepatotoxicity, clinically significant adverse events and/or or liver enzymes could be implemented (World Health Organization, 2018c); however, such monitoring may not be feasible in resource-constrained settings. Additionally, all patients should receive alcohol and substance use screening, education and counseling about the dangers of continued alcohol and substance use over the course of IPT, which could have beneficial effects on ART and IPT adherence in addition to reducing hepatotoxic effects. Brief alcohol screening tools such as short versions of the AUDIT and the Fast Alcohol Screening Test (FAST) have been validated for use in HIV clinics in resource-constrained settings (Morojele et al., 2016).

We found higher odds of alcohol consumption among males, those with higher socioeconomic status, and those with larger social support networks. Males tend to have higher and more frequent alcohol consumption due to biological differences (such as metabolism rates, tolerance and body size), gender roles, and social and cultural influences related to norms, values and constraints (Wilsnack et al., 2009). Gendered alcohol consumption differences presented in this study are consistent with findings from other lower- and middle-income countries (Obot and Room, 2005), and suggest that men could benefit from gender-transformative alcohol intervention strategies that focus on motivational interviewing, behavioral management and goal-setting (Giusto and Puffer, 2018).

The evidence regarding the association between alcohol consumption and socioeconomic status in sub-Saharan Africa is mixed (Allen et al., 2018). In this study, we observed greater non-hazardous alcohol use among those with greater socioeconomic resources as measured by educational attainment, wealth index and employment. This pattern was not consistent with hazardous alcohol use, however. Furthermore, we found greater non-hazardous and hazardous alcohol use among those with larger social support networks. Prior studies have also found alcohol consumption patterns to positively correlate with larger social networks (Bullers et al., 2001; Rosenquist et al., 2010). Although alcohol may act as a coping mechanism for some PLHIV, it may also be a social activity for those who have the social resources to participate (Lyimo et al., 2014). Similar to previous findings in Ethiopia, Muslim religion was associated with lower odds of hazardous alcohol use, likely due to religious practices (Soboka et al., 2014).

Consistent with prior studies in Ethiopia, our findings indicate that khat use is associated with a higher odds of alcohol use among PLHIV

(Abebe et al., 2005; Soboka et al., 2014). Habitual khat users generally use khat for the stimulant effects, and then subsequently use alcohol as a depressant to counteract the effects of khat (Cox and Rampes, 2003). In this study, we found that nearly 10% of participants used alcohol subsequent to khat use at least once in the past month. Habitual khat use affects all physiological systems, and the negative health effects of khat contribute to psychiatric complications including depression and psychoses, respiratory problems including tuberculosis, and hepatobiliary problems, including cirrhosis (Cox and Rampes, 2003). Though the mechanisms for khat-induced hepatotoxicity are largely unknown, chronic liver disease among khat users has been reported and it can be theorized that frequent khat use may also exacerbate the hepatotoxic effects of alcohol and IPT among PLHIV (Chapman et al., 2010; Stuyt et al., 2011).

Alcohol increases HIV risk behaviors, and the risk of acquiring both HIV and TB (Alemu et al., 2016; Hahn et al., 2011; Lönnroth et al., 2008). Among PLHIV, alcohol substantially impacts disease progression due to poor ART uptake, medication adherence and retention in care, making viral suppression more difficult to achieve (Azar et al., 2010; Hendershot et al., 2009; Shuper et al., 2010). In this study, hazardous and non-hazardous alcohol users reported their drinking or substance use habits as a barrier to obtaining medical care, and most reported that not being able to drink alcohol would deter IPT use. Studies from Ethiopia have found that khat also increases HIV risk behaviors, increases the risk of acquiring HIV and TB, and reduces medication adherence for both ART and anti-TB medications (Alemu et al., 2016). Therefore, alcohol and khat are drivers of both HIV and TB, significantly impact disease progression by affecting medication adherence and treatment retention and have been found to have adverse hepatotoxic effects independent of IPT use. For these reasons, it is important to address alcohol and substance use among PLHIV prior to IPT initiation, and for the duration of treatment.

Strengths of this study include use of a well-validated measure of alcohol use in a subgroup of patients at higher risk for TB and hepatotoxicity. Though some studies necessitate the need for different cut-off scores, (Meneses-Gaya et al., 2009) the AUDIT demonstrated high reliability in this sample. This study is not without limitations. The relatively small number of participants that were categorized as non-hazardous and hazardous alcohol users limited the sample size and resulted in wide confidence intervals around the point estimates in this analysis. Because ENRICH was an implementation science study, we relied on the clinic nurses to assess for IPT eligibility, and their assessment of alcohol use may not have been standardized. In Ethiopia, Ministry of Health guidelines state that PLHIV are ineligible for IPT if they have symptoms suggestive of TB, active hepatitis, regular and heavy alcohol use or peripheral neuropathy. Whether and how thoroughly nurses screened for alcohol use prior to IPT initiation is not known. If nurses had excluded heavy drinkers from receiving IPT based on Ministry of Health guidelines, the true prevalence of alcohol use among PLHIV enrolled in HIV care would be higher than that found among ENRICH study participants. Self-reported alcohol and other substance use is also likely to be underestimated (Davis et al., 2010), and the 19% that report hazardous alcohol use in this study is likely to be a lower-bound estimate. Furthermore, because we only examined baseline cross-sectional data, we cannot assess changes in alcohol use patterns after IPT initiation. Without counseling and education, alcohol use is unlikely to change. Finally, generalizability of these findings to PLHIV in other settings outside of Ethiopia or sub-Saharan Africa may be limited due to differences in social norms surrounding alcohol and khat use.

5. Conclusion

Given the high proportion of alcohol users in sub-Saharan African countries, current WHO guidelines would systematically exclude a large proportion of the population at greatest need for IPT. Findings from this study highlight the need to integrate alcohol and substance use screening in HIV clinics prior to IPT initiation. WHO guidelines recommend that all PLHIV who are unlikely to have active TB be placed on TB preventive treatment, yet exclude heavy and regular alcohol users. Strong evidence from clinical trials is lacking among PLHIV with hazardous alcohol use making it a research priority. Until it can be determined whether PLHIV who are regular and heavy alcohol users can safely be placed on IPT, increased monitoring for symptoms of hepatotoxicity, clinically significant adverse events and/or liver enzymes could be implemented; however, this monitoring may not be available in resource-constrained settings. Patients should also receive education and counseling about the dangers of continued alcohol and substance use over the course of IPT, which could have beneficial effects on ART and IPT adherence in addition to reducing hepatotoxic effects. Additionally, PLHIV may benefit from gender-specific alcohol reduction interventions. With such measures the side effects of IPT may be minimized, which could support IPT adherence and retention among PLHIV.

References

Abebe, D., Debella, A., Dejene, A., Degefa, A., Abebe, A., Urga, K., Ketema, L., 2005. Khat chewing habit as a possible risk behaviour for HIV infection: A case-control study. Ethiop. J. Health Dev. 3, 174–181.

Al-hebshi, N., Al-haroni, M., Skaug, N., 2006. In vitro antimicrobial and resistance-modifying activities of aqueous crude khat extracts against oral microorganisms. Arch. Oral Biol. 3, 183–188.

Alemu, Y.M., Awoke, W., Wilder-Smith, A., 2016. Determinants for tuberculosis in HIV-infected adults in Northwest Ethiopia: a multicentre case–control study. BMJ Open 4, e009058.

Allen, L., Townsend, N., Williams, J., Mikkelsen, B., Roberts, N., Wickramasinghe, K., 2018. Socioeconomic status and alcohol use in low-and lower-middle income countries: a systematic review. Alcohol 23–31.

Azar, M.M., Springer, S.A., Meyer, J.P., Altice, F.L., 2010. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to anti-retroviral therapy and health care utilization. Drug Alcohol Depend. 3, 178–193.

Babor, T.F., Higgins-Biddle, J.C., Saunders, J.B., Monteiro, M.G., 2001. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Health Care, 2nd ed. World Health Organization. https://apps.who.int/iris/handle/10665/

67205.

Badje, A., Moh, R., Gabillard, D., Guéhi, C., Kabran, M., Ntakpé, J.-B., Le Carrou, J., Kouame, G.M., Ouattara, E., Messou, E., 2017. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. Lancet Glob. Health 11, e1080–e1089.

Bullers, S., Cooper, M.L., Russell, M., 2001. Social network drinking and adult alcohol involvement: a longitudinal exploration of the direction of influence. Addict. Behav. 2, 181–199.

Bultum, J.A., Yigzaw, N., Demeke, W., Alemayehu, M., 2018. Alcohol use disorder and associated factors among human immunodeficiency virus infected patients attending antiretroviral therapy clinic at Bishoftu General Hospital, Oromiya region, Ethiopia. PLoS One 3, e0189312.

Chapman, M.H., Kajihara, M., Borges, G., O'beirne, J., Patch, D., Dhillon, A.P., Crozier, A., Morgan, M.Y., 2010. Severe, acute liver injury and khat leaves. N. Engl. J. Med. 17, 1642–1644.

Cox, G., Rampes, H., 2003. Adverse effects of khat: a review. Adv. Psychiatr. Treat. 6, 456–463.

Davis, C.G., Thake, J., Vilhena, N., 2010. Social desirability biases in self-reported alcohol consumption and harms. Addict. Behav. 4, 302–311.

Freiman, J.M., Jacobson, K.R., Muyindike, W.R., Horsburgh, C.R., Ellner, J.J., Hahn, J.A., Linas, B.P., 2018. Isoniazid preventive therapy for people with HIV who are heavy alcohol drinkers in high TB-/HIV-burden countries: a risk-benefit analysis. J. Acquir. Immune Defic. Syndr. 4, 405–412.

Gelaye, B., Williams, M.A., Lemma, S., Deyessa, N., Bahretibeb, Y., Shibre, T., Wondimagegn, D., Lemenhe, A., Fann, J.R., Vander Stoep, A., 2013. Validity of the patient health questionnaire-9 for depression screening and diagnosis in East Africa. Psychiatry Res. 2, 653–661.

Giusto, A., Puffer, E., 2018. A systematic review of interventions targeting men's alcohol use and family relationships in low-and middle-income countries. Glob. Ment. Health 5, e10.

Hahn, J.A., Woolf-King, S.E., Muyindike, W., 2011. Adding fuel to the fire: alcohol's effect on the HIV epidemic in Sub-Saharan Africa. Curr. HIVAIDS Rep. 3, 172.

Hendershot, C.S., Stoner, S.A., Pantalone, D.W., Simoni, J., 2009. Alcohol use and anti-retroviral adherence: review and meta-analysis. J. Acquir. Immune Defic. Syndr. 2, 180.

Howard, A.A., Hirsch-Moverman, Y., Saito, S., Gadisa, T., Daftary, A., Melaku, Z., 2017. The ENRICH Study to evaluate the effectiveness of a combination intervention package to improve isoniazid preventive therapy initiation, adherence and completion among people living with HIV in Ethiopia: rationale and design of a mixed methods cluster randomized trial. Contemp. Clin. Trials Commun. 46–54.

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 9, 606–613.

Kwan, C.K., Ernst, J.D., 2011. HIV and tuberculosis: a deadly human syndemic. Clin. Microbiol. Rev. 2, 351–376.

Lönnroth, K., Williams, B.G., Stadlin, S., Jaramillo, E., Dye, C., 2008. Alcohol use as a risk factor for tuberculosis–a systematic review. BMC Public Health 1, 289.

Lyimo, R.A., Stutterheim, S.E., Hospers, H.J., de Glee, T., van der Ven, A., de Bruin, M., 2014. Stigma, disclosure, coping, and medication adherence among people living with HIV/AIDS in Northern Tanzania. AIDS Patient Care STDS 2, 98–105.

Meneses-Gaya, Cd., Zuardi, A.W., Loureiro, S.R., Crippa, J.A.S., 2009. Alcohol Use Disorders Identification Test (AUDIT): an updated systematic review of psychometric properties. Psychol. Neurosci. 1, 83–97.

Morojele, N.K., Nkosi, S., Kekwaletswe, C.T., Shuper, P.A., Manda, S.O., Myers, B., Parry, C.D., 2016. Utility of brief versions of the alcohol use disorders identification test (AUDIT) to identify excessive drinking among patients in HIV care in South Africa. J. Stud. Alcohol Drugs 1, 88–96.

Obot, I.S., Room, R., 2005. Alcohol, Gender and Drinking Problems: Perspectives from Low and Middle Income Countries. World Health Organization, Geneva. https://www.who.int/substance_abuse/publications/alcohol_gender_drinking_problems.pdf.

Rosenquist, J.N., Murabito, J., Fowler, J.H., Christakis, N.A., 2010. The spread of alcohol consumption behavior in a large social network. Ann. Intern. Med. 7, 426–433.

Rutstein, S.O., Johnson, K., MEASURE, O.M., 2004. The DHS Wealth Index. ORC Macro, MEASURE DHS. https://dhsprogram.com/pubs/pdf/cr6/cr6.pdf.

Saukkonen, J.J., Cohn, D.L., Jasmer, R.M., Schenker, S., Jereb, J.A., Nolan, C.M., Peloquin, C.A., Gordin, F.M., Nunes, D., Strader, D.B., 2006. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am. J. Respir. Crit. Care Med. 8, 935–952.

Saunders, J.B., Aasland, O.G., Babor, T.F., De la Fuente, J.R., Grant, M., 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction 6, 791–804.

Semu, M., Fenta, T.G., Medhin, G., Assefa, D., 2017. Effectiveness of isoniazid preventative therapy in reducing incidence of active tuberculosis among people living with HIV/AIDS in public health facilities of Addis Ababa, Ethiopia: a historical cohort study. BMC Infect. Dis. 1, 5.

Shuper, P.A., Neuman, M., Kanteres, F., Baliunas, D., Joharchi, N., Rehm, J., 2010. Causal considerations on alcohol and HIV/AIDS—a systematic review. Alcohol Alcohol. 2, 159–166.

Soboka, M., Tesfaye, M., Feyissa, G.T., Hanlon, C., 2014. Alcohol use disorders and associated factors among people living with HIV who are attending services in south west Ethiopia. BMC Res. Notes 1, 828.

Stuyt, R.J., Willems, S.M., Wagtmans, M.J., van Hoek, B., 2011. Chewing khat and chronic liver disease. Liver Int. 3, 434–436.

Vyas, S., Kumaranayake, L., 2006. Constructing socio-economic status indices: how to use principal components analysis. Health Policy Plan. 6, 459–468.

Wilsnack, R.W., Wilsnack, S.C., Kristjanson, A.F., Vogeltanz-Holm, N.D., Gmel, G., 2009. Gender and alcohol consumption: patterns from the multinational GENACIS project. Addiction 9, 1487–1500.

World Health Organization, 2018a. Global Status Report on Alcohol and Health 2018. . https://www.who.int/substance_abuse/publications/global_alcohol_report/gsr_2018/en/.

World Health Organization, 2018b. Global Tuberculosis Report 2018. . https://www.who.int/tb/publications/global_report/en/.

World Health Organization, 2018c. Latent Tuberculosis Infection: Updated and Consolidated Guidelines for Programmatic Management. https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/.