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Journal

JAIDS: Journal of Acquired Immune Deficiency Syndromes, 91(5)

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Publication Date

2022-12-15

DOI

10.1097/QAI.0000000000003082

Peer reviewed

HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2023 December 15.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2022 December 15; 91(5): 460–468. doi:10.1097/QAI.0000000000003082.

Unhealthy Alcohol Use is Associated with sub-Optimal Adherence to Isoniazid Preventive Therapy in Persons with HIV in southwestern Uganda

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Abstract

Background: Unhealthy alcohol use is associated with increased progression to tuberculosis (TB) disease, but its effect on adherence to isoniazid (INH) preventive therapy (IPT) is not known.

Methods: This was a prospective study of persons with HIV (PWH) with latent TB in Southwestern Uganda reporting any current (prior 3 months) alcohol use or no alcohol consumption in prior year (2:1 ratio). All received INH. We defined sub-optimal adherence as <90% of days with at least one Medication Event Monitoring System (MEMS) cap opening, over the prior 90 days. Alcohol use was categorized as: none: no self-report, and phosphatidylethanol (PEth) <8 ng/mL; moderate: Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) 1–2 (women) or 1–3 (men), and/or PEth 8-<50 ng/mL; unhealthy: AUDIT-C ≥3 (women) or ≥4 (men), and/or PEth ≥50 ng/mL. We used generalized estimating equations logistic regression analyses to assess the association between the level of alcohol use and sub-optimal INH adherence.

Results: Three hundred and two persons were enrolled; 279 were on INH for three or more months. The prevalence of sub-optimal INH adherence was 31.3% at 3 months and 43.9% at 6 months. The odds of sub-optimal INH adherence were higher for unhealthy (adjusted odds ratio [aOR] 2.78 (95% CI: 1.62-4.76) and moderate [aOR] 1.59 (95% CI: 0.94-2.71) compared to no alcohol consumption.

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Conflicts of Interest:
The authors have no conflicts of interest to declare.

Conclusions: Sub-optimal adherence to INH at 3- and 6-months was high among PWH and associated with unhealthy alcohol use. Adherence support and/or alcohol reduction strategies are needed for this group at high risk for active TB.

Keywords

Adherence; Alcohol use; Isoniazid Preventive Therapy; Persons with HIV; Phosphatidylethanol; Uganda

INTRODUCTION:

The World Health Organization (WHO) recommends isoniazid (INH) as a major management strategy for the prevention of tuberculosis (TB) disease among persons with HIV (PWH)[1,2] Uganda is a high HIV/TB burden country,[1] with TB incidence estimated at 200 persons per 100,000 in 2019,[1] and an HIV prevalence of 5.8% among adults aged 15–49 years.[3] TB disease may result from infection with *Mycobacterium tuberculosis* leading to primary progression within the first two years or from later reactivation of latent TB infection (LTBI).[4–6] Reactivation occurs more often in people with compromised immune systems,[7] such as PWH, than in people with intact immune systems just as does primary progression to TB. In sub-Saharan Africa (SSA), the prevalence of LTBI in the general population ranges from 31–55%[8–10] and was estimated at 28% in PWH in Uganda.[11] TB preventive therapy with INH is important for PWH and has been reported to decrease mortality by 30–50% above and beyond the benefits of ART.[12–16] In addition, because TB is airborne, preventing TB in PWH also protects the families and community members of PWH. An effective IPT course encompasses INH initiation, optimal adherence, monitoring for any toxicities and treatment completion, hence initiating IPT among PWH may be insufficient without understanding how persons tolerate it, adhere and/or complete the course prescribed.

Several meta-analyses have found that alcohol use is associated with decreased ART adherence,[17,18] however while both infections are fatal if untreated, TB disease differs from HIV in that it is a short-term illness and curable, while HIV is lifelong and not curable. Thus, the impact of alcohol use on INH preventive therapy (IPT) adherence, whose time-limited course may make it easier to take than lifelong ART medications, is unclear. In Uganda, although about 60% of adults (age 15 years and older) report abstinence to alcohol in the prior 12 months, those who drink alcohol have a high average pure alcohol consumption.[19] Heavy alcohol users have a 2.5 increased risk for TB disease compared to others [20,21] and also have increased risk for poorer TB outcomes including mortality,[22] meaning prevention of disease may be particularly impactful. Approximately 25 to 30% of PWH in SSA and beyond engage in unhealthy alcohol use, that is, drinking above recommended safe limits.[23–27] Use of IPT among PWH with unhealthy alcohol use may be affected by reduced adherence as in those using ART with subsequent likelihood of reducing its' overall effectiveness.

There is sparse literature about how different levels of alcohol use affect adherence to TB preventive medicines among persons with or without HIV. We sought to: i) Determine

IPT adherence using Medication Event Monitoring System (MEMS) caps among PWH on ART in south-western (SW) Uganda overall and by level of alcohol use, and ii) evaluate factors associated with sub-optimal adherence to IPT. We hypothesized that participants with current unhealthy alcohol use would have higher odds of sub-optimal adherence to IPT.

METHODS

Study setting and population:

The data were collected during baseline and follow-up visits of the Alcohol Drinkers' Exposure to Preventive Therapy for TB (ADEPTT) Study, which is part of the Uganda Russia Boston Alcohol Network Alcohol Research Collaboration for HIV Research (URBAN ARCH) (NCT03302299). The study participants were PWH enrolled at the Immune Suppression Syndrome (ISS) clinic of Mbarara Regional Referral Hospital (MRRH) in SW Uganda from May 2017 to January 2020. The primary aim of the ADEPTT study was to estimate the rate of hepatotoxicity to 6 months INH treatment among PWH who are ≥18 years, have LTBI, and reported current (prior 3 months) alcohol use (n=200), with a comparison group not engaged in alcohol use in the prior year (n=100); and to examine the rate of hepatotoxicity by level of alcohol use.

Eligibility criteria

PWH were eligible if they were a patient at the MRRH ISS clinic, age ≥ 18 years, were fluent in English or Runyankole (the local language), were on a non-nevirapine containing ART regimen for at least six months, lived within 2 hours travel time from the clinic with no plans to move, showed no evidence of active TB infection based on WHO symptoms criteria, had no prior use of TB medicines for treatment and/or prevention of TB, reported either current (prior 3 month) alcohol use or abstaining for at least one year, including lifetime abstaining, had alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2x of the upper limit of normal (ULN), and were not pregnant (after September 2018) (because of a report on poor birth outcomes among women on IPT in pregnancy [28]). We placed a tuberculin skin test (TST) on each potential participant using 0.1 ml containing 5 tuberculin units of purified protein derivative (PPD). A TST was considered positive if ≥5 mm [29] within 72 hours of placement. Participants who had a positive TST were eligible to enroll.

Study procedures:

The follow-up visits were every 2 weeks in the first month followed by monthly until the IPT was completed (within 9 months of initiation). Participants were monitored for toxicity and adherence using clinical monitoring and laboratory liver enzyme tests at each study visit. For participants with adverse events such as hepatotoxicity, grading of the event determined the frequency of monitoring visits thereafter and/or cessation of IPT. IPT was stopped if a participant developed any Grade 3 or 4 adverse event[30] while on the INH. At baseline, 3- and 6-months, a structured questionnaire was administered by clinical research assistants. The laboratory measures done at baseline included a CD4 count, viral load count and dried blood spots (DBS) for phosphatidylethanol (PEth) test. PEth was repeated at 3- and 6-months for participants who self-reported alcohol use at any visit, or who tested

PEth-positive (≥8 ng/ml). The DBS were stored at −80°C until shipping to the United States Drug Testing Laboratory in Des Plaines, IL, USA for liquid chromatography with tandem mass spectrometry test for PEth, an abnormal phospholipid formed only in the presence of alcohol.[31] PEth testing measured the 16:0/18:1 homologue with a limit of quantification of 8 ng/mL, using standard procedures.[31] At baseline, 2-week's visit and monthly, ALT and AST were done. Dosing event histories from the MEMS bottle caps were downloaded and transferred to the MEMS Adherence Software at each study visit while on INH.

IPT:

INH was prescribed at a dose of 5mg/kg with a maximum adult dose of 300 mg/day and was given with pyridoxine to reduce the risk of developing peripheral neuropathy [32] at a starting dose of 25 mg per day and could be increased to 50 mg per day when symptoms of peripheral neuropathy were reported.

The main outcome variable: Sub-optimal adherence to IPT

We used electronic pill caps (Medication Event Monitoring System pill cap [MEMS CAP], Aardex version 6, Switzerland) that record each bottle cap opening (date and time). MEMS have been used as the standard for assessment of adherence[33,34] and in studies of adherence to ART [35–37] and to TB preventive treatment.[38,39] We collected MEMS data at all visits while on INH, however, for this analysis, the outcome sub-optimal adherence was defined as <90% of days with at least one MEMS cap opening in the prior 90 days, at 3- and 6-months.

Variables:

At baseline, we collected social demographic variables (age, gender, education level, marital status, literacy), and tobacco and other drug use using an interviewer administered structured interview. The interview also assessed social support using the Duke- UNC Functional social support scale with a mean score <3 defined as low social support,[40] HIV symptoms, social desirability using the Marlowe-Crowne social desirability scale (SDS),[41] and symptoms of depression, using the Centers for Epidemiologic Studies of Depression scale (CES-D) with a score of ≥16 indicating depression.[42] We collected self-reported prior 30-days adherence to ART using the single item rating scale,[43] dichotomized as excellent/very good, versus good/fair/poor/very poor (sub-optimal). ART adherence was measured at baseline, 3 months, 6 months, and then every 6 months until study end. For this analysis we used ART adherence at three and six months to coincide with when INH adherence was measured. Other variables were time since HIV diagnosis, time since ART start, and adverse events graded 1–4 (DAIDS Table).[30] For this analysis, Grade 2 or higher symptoms or liver enzyme elevations (LEEs) were included together: Grade 2 or higher symptoms or LEEs ≥2x ULN in the prior 3 months, versus none.

Main Independent variable (Predictor of Interest):

The main independent variable was level of alcohol consumption defined using a composite measure of self-report and PEth. For self-report, we used the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C),[44] modified for the prior 3 months to reflect alcohol consumption prior to each visit, with an AUDIT-C score ≥3 for women and ≥4 for

men considered positive.[45] Level of alcohol use was defined as: none (AUDIT-C = 0 and PEth <8 ng/mL); moderate (any self-report but AUDIT-C negative, i.e., 1–2 for women and 1–3 for men, and/or PEth ≥8 ng/mL and <50 ng/mL); unhealthy (AUDIT-C positive: a score of 3–12 for women and 4–12 for men and/or PEth ≥50 ng/mL).

Statistical methods:

We included all 3- and 6-months study visits for which the participants were on INH for the full prior 3 months, excluding visits after INH discontinuation due to Grade 3+ toxicities or other unrelated adverse events. We additionally excluded visits where the prior 90 days included the 2020 COVID-19 lockdown restrictions in Uganda instituted between mid-March to mid-May 2020 when participants were advised to pause their INH during the lockdown because we were unable to monitor their liver enzyme elevations per the normal study schedule. We conducted descriptive analyses of all variables, overall and by adherence (sub-optimal yes versus no). We calculated frequencies and proportions for categorical variables, and means and standard deviations and medians with interquartile ranges (IQR) for continuous variables.

We used generalized estimating equation (GEE) logistic regression models with exchangeable working correlations and report robust standard errors for unadjusted and adjusted analyses of sub-optimal adherence. The multivariable model included the following independent variables, chosen a priori: level of alcohol use (main independent variable of interest), age, gender, symptoms of depression, Grade 2+ adverse event, social support, ART adherence, and time on INH. These variables were chosen because of literature citing their association with adherence to either ART and/or TB treatment/IPT.[17,18,46–55] We conducted Spearman correlations for all pairs of covariates to assess for collinearity; all correlations were <0.50. We also ran the multivariable model stratified by social desirability score (low/moderate versus high), to explore whether the relationship between alcohol use and INH adherence differs by level of social desirability, which is common in self-reported behaviors.[56] SDS was dichotomized at the median (low/moderate: SDS ≤20 versus high: SDS >20).

Finally, we conducted two sensitivity analyses. First, we excluded the first 30 days of INH, to remove a possible effect of early repetitive openings of the MEMs that may occur when patients are aware they are being monitored as they start taking medications;[57] second, we imputed visit data (n=8 visits) for participants who missed visits (not due to an INH discontinuation). We used multiple imputation via chained equations with 20 imputed datasets, to impute missing data. The imputation model included all variables included in the primary analysis. We also conducted two exploratory analyses examining possible effect modification by age and sex. Stata version 14.2 was used for all analyses.

Ethical approvals and consent to participate:

The ADEPTT study activities were approved by the Ethics review boards of Mbarara University of Science and Technology, University of California San Francisco, and Boston University. Administrative approvals were also secured from the President's Office and

the Ugandan National Council for Science and Technology and from Clinicaltrials.gov (NCT03302299). All participants gave written informed consent to participate in the study.

RESULTS

Screening and baseline characteristics.

We approached 1434 participants for ADEPTT study screening; 242 were excluded for reasons that included (but were not mutually exclusive): having baseline elevated AST and/or ALT ≥2x the ULN (n=79), previous active TB (n=26) or use of any TB medicines or IPT (n=42), declining/failing to complete screening (n=43), being on nevirapine (n=36), living out of catchment area (n=23), pregnancy (n=10), having taken alcohol in the past year but not the past 3 months (n=8) and having current active TB or symptoms for active TB (n=2). 1211 participants received a TST and of these, 55 participants did not return for PPD reading within 72 hours and 848 were TST negative, leaving 308 participants eligible for study enrollment. Six persons declined enrollment leaving 302 participants (2 extra persons in the alcohol abstaining group were enrolled in error but retained for analyses). A comparison between the included 302 persons and the 1132 persons screened but not enrolled in the study did not show any differences by self-reported alcohol consumption, age, or gender.

Ninety-two percent (279/302) of participants completed at least one study visit at either 3- or 6-months on INH. Reasons for non-completion included disenrollment due ineligibility (n=1), discontinuation prior to 3 months because of liver or other toxicities (n=19), and loss to follow up (n=3). Of the 279, 50.9% were female, 80.7% reported very good to excellent adherence to ART in prior 30 days at baseline and 49.5% had high SDS (Table 1). The level of alcohol use was as follows: none: 27.6%; moderate: 21.9%; and unhealthy: 50.5%.

INH adherence at 3 months and 6 months

Sub-optimal adherence at 3 and 6 months was 31.3% and 43.9%, respectively. The mean percentage of days with at least one MEMS opening in prior 90 days at 3 and 6 months was 88.9 (standard deviation (SD):16.2) and 81.3 (SD 24.1) respectively (Table 2). At 3 and 6 months, 44.2% and 58.5% of participants within the unhealthy alcohol group had sub-optimal INH adherence, respectively; these proportions were 27.1% and 38.1% for those within moderate alcohol use and 19.8% and 29.8% for no alcohol use. The younger age and the non-literate participants had higher proportions with sub-optimal adherence at both 3 and 6 months.

Unadjusted Analysis

279 participants contributed 539 observations at 3- and 6-month timepoints. The participants in the moderate and unhealthy alcohol groups had odds of 1.56 (95% CI: 0.95-2.55) and 2.70 (95% CI: 1.68-4.36) of sub-optimal adherence respectively compared to those with no alcohol use. Other variables that appeared to be associated with sub-optimal adherence were age (OR: 1.05 per 1 year decrease (95% CI: 1.02-1.07)), sex (OR for males vs. females: 1.54 (95% CI: 1.01-2.34) and ART adherence (OR for very poor/poor/fair/good (sub-optimal adherence) vs. very good/excellent: 2.17 (95% CI: 1.35-3.48). Adherence decreased over

time; the 6- month's study visit had increased odds of sub-optimal INH adherence (OR: 1.72 (95% CI: 1.34-2.21) compared to the 3- months study visit. Participants who were not literate had increased odds for sub-optimal adherence compared to those who were literate (OR: 1.65 (95% CI: 1.03-2.63)), as did participants who reported low/moderate social desirability at baseline, compared to high (OR: 1.54 (95% CI: 1.01-2.35)). There were no significant differences in adherence among participants by education, marital status, baseline tobacco use, symptoms of depression, health status, with or without Grade 2+ LEE or symptoms and time since HIV diagnosis.

Multivariable analyses

In multivariable analysis, the global association of the level of alcohol use with sub-optimal adherence remained statistically significant; while the adjusted odds for those with moderate alcohol use compared to none was 1.59 (95% CI: 0.94-2.71), those with unhealthy alcohol use compared to none had an adjusted odds ratio [aOR] of 2.78, 95% CI: 1.62-4.76) (Table 3). Age, ART adherence, and months on INH remained associated with sub-optimal INH adherence, while gender was no longer associated with adherence in the adjusted analyses (Table 3).

Additional analysis excluding the first 30 days of INH showed similar results, as did the multiple imputation analysis (data not shown). Adjusted analysis stratified by SDS (median/low versus high) found that level of alcohol use, age, ART adherence, and months on INH were associated with sub-optimal INH adherence in both strata of SDS (Table 4). Finally, we found no evidence of effect modification by either age (interaction p=0.20) or sex (interaction p=0.60) (data not shown).

DISCUSSION

We found a high level of sub-optimal adherence to IPT among a study sample of PWH in southwestern Uganda, enriched for persons reporting current alcohol use, that is: 31.3% and 43.9% at 3 and 6 months of IPT respectively, with even greater proportions of sub-optimal adherence among those with unhealthy alcohol consumption (44.2% and 58.5% at 3 and 6 months, respectively). These proportions are similar to those reported for PWH in a South African study which found 28% with negative urine tests for INH metabolites,[58] another in PWH in Thailand that reported a 32.5% non-adherence to a 9-months IPT course using pill count,[59] and another study among PWH in Brazil and South Africa that recorded that 35% of their patients had no detectable urine INH metabolites.[46]

Our finding of sub-optimal IPT adherence among those with unhealthy alcohol use compared to those with no alcohol use is consistent with studies showing the effect of alcohol use on ART adherence[17,18,47–49] and TB treatment[50,51] which have also reported that unhealthy alcohol use affects adherence to medicines. As there is strong data citing the association between unhealthy drinking and increased likelihood of progression from LTBI to TB,[20,21] our data showing sub-optimal adherence to IPT among those engaging in unhealthy alcohol use raises concern that poor adherence at the preventive stage may contribute to the increased risk of progression from LTBI to TB disease in this group. Given that a high proportion of PWH in Uganda and other SSA countries engage in unhealthy

alcohol use,[23–27] sub-optimal adherence in this group likely impedes the efforts to realize the strategic goal of TB prevention among PWH. There is need to explore why persons who drink alcohol have more barriers to adherence to medicines and further study and/or optimize use of strategies that have been suggested to improve adherence to medicines among such persons such as contingency management such as incentivizing[60] or improve on methods prior endorsed by WHO such as directly observed treatment (DOTs) strategy for TB treatment.

We also found that participants who reported sub-optimal adherence to ART had increased odds of sub-optimal adherence to IPT compared to those who reported very good/excellent adherence to ART, suggesting that the challenges to ART adherence may extend to IPT adherence; the shorter course of medicines for 6 months does not seem to help improve adherence. However, we did find that adherence to IPT declined over time, with a higher proportion of PWH having sub-optimal adherence at 6 months compared to the 3 months timepoint. This was consistent with another study.[46] These changes over time may be attributed to fatigue that may occur with ingesting medicines over time and suggests that shorter courses of TB preventive therapy such as use of either 3 months of both INH and Rifapentine (abbreviated as 3HP) or 1 month of HP which may have increased opportunities for improved adherence especially among persons who use alcohol with increased risk of low adherence.[61,62]

Other studies in SSA cited other reasons that may reduce adherence to IPT including: toxicity to the drugs, lack of family and/ or household support and health system related factors like drug stock outs, poor health worker-patient relationships leading to poor prior patients' education and patient preparation for the treatment[53] and feeling depressed.[54] We found that decreasing age was associated with higher odds of sub-optimal IPT adherence. Although the literature on IPT and age is sparse, we found consistency with some studies examining adherence to ART[52,55] but not all.[63] Our study and analyses were however, neither designed to specifically evaluate any association between age or depression and IPT adherence. All the study participants were given the same education message about the reason for IPT before the initial dose of INH.

This study had several limitations and strengths. Although MEMS is considered the near gold standard measure,[33] it does not inform us about the actual ingestion of the pill hence may not provide perfect information on adherence to medications.[39,64] Additionally, device manipulation, repeated opening or failure to return the bottles at the set follow-up visits may affect its accuracy. Our study did not record any participant with device manipulation but we had thirteen instances of MEMS bottle/cap misplacement reported either as lost or stolen or destroyed by children and one case of low battery. The lost or malfunctioning MEMS were replaced as soon as the study team received the report. Regardless of the limitations mentioned, the MEMS adherence data that we compiled for prior 3 months encompassed a longer window of IPT adherence compared to some studies that used either self-reported adherence and/or pill count in prior recent days-1 month[53,65,66] and reported higher adherence levels; our study reported higher levels of sub-optimal adherence suggesting that the longer window and the MEMS may be more valid ways to measure adherence. Another limitation of our study is that we recruited participants based on alcohol

use (2 persons reporting current alcohol use for each 1 person reporting alcohol abstinence); as such, our estimates of sub-optimal adherence may not be representative of a general population sample of PWH. Additionally, our study did not collect any qualitative data that may help to distinguish the contributing factors for sub-optimal use among ART and/or IPT use as well as point us to the perceptions of the PWH towards HIV and/or latent TB. We strengthened our study by the use of PEth to augment self-reported alcohol use, which may be under-reported due to social desirability bias,[67–69] as in previous studies.[67,70] Our study had very high retention of participants.

Given that unhealthy alcohol use is associated with a 2.5 fold risk of active TB [20,21] which causes substantial morbidity and mortality, and what we found showing that those consuming alcohol at high levels were less likely to adhere to TPT, TPT programs should emphasize alcohol reduction to improve TPT adherence, to reduce the risk of active TB and of onward TB transmission to the community and families.

In summary, in a sample of PWH on ART in southwestern Uganda enriched for those reporting current alcohol use, about one-third to two-fifths had sub-optimal adherence to IPT at 3- and 6-months, with poorer adherence among those engaging in unhealthy alcohol use. We also found poorer IPT adherence among those reporting poorer ART adherence and adherence declined over the course of IPT. These results underscore the urgent need to assess and address alcohol use to increase IPT adherence among PWH and consider shorter TB preventive courses to have an impact on a highly fatal but preventable disease, TB among PWH who consume alcohol.

Acknowledgments:

I acknowledge all the co-authors of this work for their substantial contribution to the conception and design of study, its' performance (WM, CN, RF, DC, NE, JA, BL, KR and JH), data analysis (RF, LF, DC and JH), and reporting of the work (WM, RF, DB, CN, JA, LF, NE, KR, BL and JH). We also acknowledge the ISS clinic staff at Mbarara Regional Hospital, the study participants and the research assistants attached to the ADEPTT clinical trial for the immense work collecting the data used.

Sources of Funding

This study was funded by NIH/NIAAA U01 AA020776 (PI: Hahn), NIH/NIAAA K24 AA022586 (PI: Hahn), NIH/NIAAA U24AA020779 (PI: D Cheng)

Data Availability Statement:

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author and/or the senior author (Dr Judith A. Hahn: judy.hahn@ucsf.edu) on reasonable request.

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Table 1.

Study participant characteristics at baseline (n = 279).*

	N (%)
Age (median [IQR])	40 [34–47]
Gender	
Female	142 (50.9)
Male	137 (49.1)
More than a primary education	
No	203 (72.8)
Yes	76 (27.2)
Married/cohabitating	
No	88 (31.7)
Yes	190 (68.4)
Literate: able to read whole sentence?	
No	76 (27.2)
Yes	203 (72.8)
Low social support	
No	184 (66.0)
Yes	95 (34.1)
ART adherence, prior 30 days	
Excellent/very good	225 (80.7)
Good/fair/poor/very poor	54 (19.4)
Alcohol use**, prior 3 months	
None	77 (27.6)
Moderate	61 (21.9)
Unhealthy	141 (50.5)
Tobacco use, prior 30 days at baseline	
No	245 (87.8)
Yes	34 (12.2)
Self-reported health status	
Good/fair/poor/very poor	149 (53.4)
Excellent/very good	130 (46.6)
Depression	
No	249 (89.3)
Yes	30 (10.8)
Social desirability (median [IQR])	20 [18–22]
Low/moderate (≤20)	141 (50.5)
High (>20)	138 (49.5)
Years since HIV diagnosis (n=265) (median [IQR])	7 [5–12]

*includes only study participants who were on INH for 3 months or more.

**Alcohol use: None: no self-report and PEth < 8; Moderate: any self-report but AUDIT-C negative, and/or 8 ng/mL <= PEth < 50 ng/mL; Unhealthy: AUDIT-C positive and/or PEth >= 50 ng/mL.

Table 2.

Participant characteristics by INH adherence at 3 and 6 months.

	3 months (n=275)		6 months (n=264)	
	≥ 90% N (%) (n=189)	< 90% N (%) (n=86)	≥ 90% N (%) (n=148)	< 90% N (%) (n=116)
Alcohol use *, prior 3 months				
None	79 (82.3)	17 (19.8)	73 (70.2)	31 (29.8)
Moderate	43 (72.9)	16 (27.1)	26 (61.9)	16 (38.1)
Unhealthy	67 (55.8)	53 (44.2)	49 (41.5)	69 (58.5)
Age (median [IQR])	40 [35–49]	38 [32–44]	41 [35–49]	38 [32–44]
Gender				
Female	102 (72.9)	38 (27.1)	83 (61.9)	51 (38.1)
Male	87 (64.4)	48 (35.6)	65 (50.0)	65 (50.0)
Depression				
No	182 (68.7)	83 (31.3)	140 (56.7)	107 (43.3)
Yes	7 (70.0)	3 (30.0)	8 (47.1)	9 (52.9)
Grade 2+ LEEs or symptoms [a]				
No	160 (70.2)	68 (29.8)	135 (58.2)	97 (41.8)
Yes	29 (61.7)	18 (38.3)	13 (40.6)	19 (59.4)
Low social support				
No	126 (69.6)	55 (30.4)	97 (55.1)	79 (44.9)
Yes	63 (67.0)	31 (33.0)	51 (58.0)	37 (42.1)
ART adherence, prior 30 days				
Good/fair/poor/very poor	13 (39.4)	20 (60.6)	15 (42.9)	20 (57.1)
Excellent/very good	176 (72.7)	66 (27.3)	133 (58.1)	96 (41.9)
More than a primary education				
No	137 (68.5)	63 (31.5)	106 (55.2)	86 (44.8)
Yes	52 (69.3)	23 (30.7)	42 (58.3)	30 (41.7)
Married/cohabitating				
No	57 (67.1)	28 (32.9)	48 (56.5)	37 (43.5)
Yes	131 (69.3)	58 (30.7)	99 (55.6)	79 (44.4)
Literate: able to read whole sentence?				
No	44 (57.9)	32 (42.1)	32 (48.5)	34 (51.5)
Yes	145 (72.9)	54 (27.1)	116 (58.6)	82 (41.4)
Tobacco use, prior 30 days at baseline				
No	170 (70.5)	71 (29.5)	129 (55.8)	102 (44.2)
Yes	19 (55.9)	15 (44.1)	19 (57.6)	14 (42.4)
Health status				
Good/fair/poor/very poor	98 (71.0)	40 (29.0)	66 (55.0)	54 (45.0)
Excellent/very good	91 (66.4)	46 (33.6)	82 (56.9)	62 (43.1)

	3 months (n=275)		6 months (n=264)	
	≥ 90% N (%) (n=189)	**< 90% N (%) (n=86)**	**≥ 90% N (%) (n=148)**	**< 90% N (%) (n=116)**
Social desirability				
Low/moderate	89 (64.0)	50 (36.0)	67 (50.8)	65 (49.2)
High	100 (73.5)	36 (26.5)	81 (61.4)	51 (38.6)
Years since HIV diagnosis at baseline (median [IQR])	8 [5–12]	7 [4–10]	8 [5–12]	7 [4–10]

[*] Alcohol use: None: no self-report and PEth < 8; Moderate: any self-report but AUDIT-C negative, and/or 8 ng/mL <= PEth < 50 ng/mL; Unhealthy: AUDIT-C positive and/or PEth >= 50 ng/mL

[a] Grade 2 or higher symptoms or liver enzyme elevations (LEEs) ≥2x upper limit of normal, in the prior 3 month

Table 3.

Unadjusted and Adjusted Odds Ratios (OR) [*] and 95% Confidence Intervals (CI) for INH adherence <90% in the prior 3 months (n = 539 observations; n = 279 participants).

	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Alcohol use [**], prior 3 months		<0.01		<0.01
None	1.00		1.00	
Moderate	1.56 (0.95, 2.55)		1.59 (0.94, 2.71)	
Unhealthy	2.70 (1.68, 4.36)		2.78 (1.62, 4.76)	
Age (per 1 year decrease)	1.05 (1.02, 1.07)	<0.01	1.05 (1.02, 1.08)	<0.01
Gender		0.04		0.38
Female	1.00		1.00	
Male	1.54 (1.01, 2.34)		1.25 (0.76, 2.05)	
Depression		0.51		0.37
No	1.00		1.00	
Yes	1.28 (0.61, 2.67)		1.47 (0.64, 3.36)	
Grade 2+ LEEs or symptoms [a]		0.21		0.17
No	1.00		1.00	
Yes	1.36 (0.84, 2.19)		1.42 (0.86, 2.35)	
Low social support		0.96		0.58
No	1.00		1.00	
Yes	0.99 (0.63, 1.55)		0.87 (0.54, 1.41)	
ART adherence, prior 30 days		<0.01		<0.01
Good/fair/poor/very poor	2.17 (1.35, 3.48)		2.45 (1.46, 4.14)	
Excellent/very good	1.00		1.00	
Study visit		<0.01		<0.01
3 months	1.00		1.00	
6 months	1.72 (1.34, 2.21)		1.86 (1.39, 2.49)	
More than a primary education		0.68		
No	1.00		-	
Yes	0.91 (0.57, 1.45)		-	
Married/cohabitating		0.90		
No	1.00		-	
Yes	0.97 (0.62, 1.53)		-	
Literate: able to read whole sentence?		0.04		
No	1.65 (1.03, 2.63)		-	
Yes	1.00		-	
Tobacco use, prior 30 days at baseline		0.40		
No	1.00		-	
Yes	1.32 (0.69, 2.54)		-	

	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Health status		0.94		
Good/fair/poor/very poor	1.00		-	
Excellent/very good	1.01 (0.70, 1.47)		-	
Social desirability		0.05		
Low/moderate	1.54 (1.01, 2.35)		-	
High	1.00		-	
Time since HIV diagnosis at baseline (per year)	0.93 (0.88, 0.98)	<0.01	-	

*GEE logistic regression models, exchangeable working correlation with robust empirical std errors

**Alcohol use: None: no self-report, PEth < 8; Moderate: any self-report but AUDIT-C negative; 8 <= PEth < 50; Unhealthy: AUDIT-C positive or PEth >= 50

^{a}Grade 2 or higher symptoms or liver enzyme elevations (LEEs) ≥2x upper limit of normal, in the prior 3 months

Table 4.

Adjusted Odds Ratios (OR)* and 95% Confidence Intervals (CI) for INH adherence <90% in the prior 3 months (n = 539 observations; n = 279 participants) – stratified by social desirability score at baseline.

	Low/moderate SDS[x]		High SDS[xx]	
	Adjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Alcohol use**, prior 3 months		0.03		0.04
None	1.00		1.00	
Moderate	1.81 (0.81, 4.06)		1.37 (0.65, 2.86)	
Unhealthy	3.03 (1.33, 6.94)		2.60 (1.22, 5.54)	
Age (per 1 year decrease)	1.04 (1.00, 1.07)	0.04	1.06 (1.01, 1.10)	0.01
Gender		0.58		0.54
Female	1.00		1.00	
Male	1.21 (0.62, 2.38)		1.27 (0.59, 2.76)	
Depression		0.51		0.64
No	1.00		1.00	
Yes	1.30 (0.59, 2.87)		1.76 (0.16, 19.12)	
Grade 2+ LEEs or symptoms[a]		0.47		0.21
No	1.00		1.00	
Yes	1.29 (0.64, 2.63)		1.61 (0.77, 3.37)	
Low social support		0.75		0.60
No	1.00		1.00	
Yes	0.90 (0.47, 1.73)		0.81 (0.38, 1.76)	
ART adherence, prior 30 days		0.02		0.01
Good/fair/poor/very poor	2.41 (1.13, 5.15)		2.47 (1.21, 5.05)	
Excellent/very good	1.00		1.00	
Study visit		<0.01		<0.01
3 months	1.00		1.00	
6 months	1.96 (1.27, 3.01)		1.76 (1.17, 2.66)	

*GEE logistic regression models, exchangeable working correlation with robust empirical std errors

[x] n = 271 observations; n = 141 participants

[xx] n = 268 observations; n = 138 participants

**Alcohol use: None: no self-report, PEth < 8; Moderate: any self-report but AUDIT-C negative; 8 <= PEth < 50; Unhealthy: AUDIT-C positive or PEth >= 50

[a] Grade 2 or higher symptoms or liver enzyme elevations (LEEs) ≥2x upper limit of normal, in the prior 3 months