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Direct and Indirect Effects of Heavy Alcohol Use on Clinical Outcomes in a Longitudinal Study of HIV Patients on ART

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Abstract

Objectives—In a cohort of patients receiving care for HIV, we examined longitudinally the impact of past 30-day frequency of heavy drinking (consuming 5+ drinks on one occasion) on HIV-related (detectable viral load and CD4+ T-cell count) and non-HIV-related (hemoglobin and biomarkers of kidney function and liver fibrosis) clinical outcomes and the extent to which these effects were due to reduced antiretroviral therapy (ART) adherence.

Methods—Data came from the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy. Between March 2004 and June 2006, 533 individuals receiving ART were

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recruited and followed every 6 months for six years. Using longitudinal mediation analysis, we estimated natural direct effects (NDE) of heavy drinking frequency (never, 1–3 times, or 4+ times in the past 30 days) on clinical outcomes and natural indirect effects (NIE) mediated via ART adherence.

Results—A one-level increase in heavy drinking frequency had a significant negative NDE on CD4+ T-cell counts (−10.61 cells/mm^3; 95% CI [−17.10, −4.12]) and a significant NIE through reduced ART adherence of −0.72 cells/mm^3 (95% CI [−1.28, −0.15]), as well as a significant NIE on risk of detectable viral load (risk ratio = 1.03; 95% CI [1.00, 1.05]). Heavy drinking had a significant detrimental NIE on a combined index of 5-year mortality risk and detrimental NDE and total effect on a biomarker of liver fibrosis.

Conclusions—Heavy drinking has deleterious effects on multiple clinical outcomes in people living with HIV, some of which are mediated through reduced ART adherence.

Keywords

Alcohol; HIV; adherence; viral load; liver function; VACS Index

Introduction

Recent estimates indicate that 61% of persons living with HIV (PLWH) in the United States (U.S.) have consumed alcohol in the past year with 14.6% reporting drinking heavily (4 or more alcohol drinks on a single day for women; 5 or more drinks for men) at least once in the past 30 days (1). Two longitudinal studies have found that having of an alcohol use disorder or engaging in high levels of alcohol consumption predict increased risk of all-cause mortality in PLWH (2–3); in fact, the relative risk of mortality associated with heavy drinking appears to be especially high in PLWH compared to those without HIV (3). Understanding how alcohol use contributes to excess mortality in PLWH is an important topic for clinical research.

A large number of studies have documented that higher levels of drinking in PLWH are associated with decreased adherence to ART (4–8). Although definitions of heavy drinking have varied across studies, a comprehensive meta-analysis found that at-risk drinkers (women drinking >7 drinks per week or 4+ drinks in any day; men drinking >14 drinks per week or 5+ drinks on any day) were much less likely to be adherent (aOR = 0.47, 95% CI, [0.41, 0.55]) than nondrinkers (5). Heavy drinking, in particular, appears to be more strongly associated with non-adherence than the number of drinks consumed per week (6).

Given the association between heavy drinking and poor ART adherence, it is not surprising that a number of studies have found that heavy drinking is associated with poor health, including elevated plasma HIV RNA viral load (VL) and lower CD4+ T-cell counts (4, 9–11). Many of these studies have been cross-sectional. However, a longitudinal study found that high levels of alcohol consumption (4 or more drinks per day for men, 3 or more per day for women) predicted virologic rebound in those on ART who had initially had an undetectable viral load (12), and another found that drinking 2 or more drinks per day strongly predicted CD4+ T-cell count declines to less than 200 cells/mm^3 (13). None of

these studies formally tested whether the associations between heavier drinking and poorer HIV outcomes were due to reduced ART adherence.

When examining the effect of alcohol use on the health of PLWH, it is also important to consider non-HIV-related biomarkers that predict mortality in this population. In particular, the Veterans Aging Cohort Study (VACS) demonstrated that an index of mortality risk (the VACS Index), which incorporated non-HIV biomarkers including liver function (termed Fibrosis 4 [FIB-4]), kidney function, hemoglobin, and hepatitis C status, significantly improved survival prediction compared with an index using only age and HIV biomarkers (VL and CD4+ T-cell count; 14–17). Greater alcohol consumption and heavy drinking have been associated with higher VACS Index scores in cross-sectional analyses (3, 18), but no longitudinal studies to date have reported on the effect of heavy drinking on VACS Index scores over time.

It is not clear which components of the VACS Index are most likely to be impacted by drinking. Heavy drinking may have differential associations with non-HIV components of the VACS Index leading to poorer values on some components and improved values on others. Specifically, heavy drinking has been associated with increased liver fibrosis and cirrhosis (19–22) in PLWH who are co-infected with HCV, and hazardous drinking has been associated with a greater aspartate aminotransferase-to-platelet ratio index, a biomarker of risk for fibrosis and cirrhosis (23). However, some studies have not found these associations (24–25). No studies to date have reported whether heavy drinking in PLWH is associated with the two other non-HIV-related biomarkers in the VACS Index, altered kidney function and hemoglobin. In the general population, consumption of seven or more drinks per week has been associated with a lower risk of reduced kidney function as assessed by estimated glomerular filtration rate (eGFR) (26), and greater drinking frequency and quantity have been associated with lower risk of chronic kidney disease (27). Among the general population, greater alcohol use has been associated with higher hemoglobin values (28) but with a reduction in total red blood cell counts (29). Examining how heavy drinking impacts these biomarkers in PLWH is important to understanding how heavy drinking impacts VACS Index scores as a whole.

Study Aims

This study addresses a number of limitations in the empirical literature on the health impact of heavy drinking in PLWH. Previous research on this topic has typically used cross-sectional data or examined alcohol use at one time point to predict future clinical outcomes. Such studies do not capture the dynamic nature of alcohol consumption over time, leading to uncertainties about potential causal effects that are best addressed with longitudinal analyses. In addition, the role of ART adherence in the association between heavy drinking and health outcomes in PLWH also has not been fully integrated into most study analyses, and previous studies that examined alcohol's effect on adherence in PLWH have not formally tested the extent to which alcohol consumption *directly* impacts clinical outcomes or *indirectly* affects outcomes through reducing ART adherence (12). Finally, most studies have examined only one or two clinical outcomes in a single analysis, despite the importance

of considering other clinical outcomes, such as those included in the VACS Index, in addition to VL and CD4+ T-cell count.

The purpose of our study was to examine longitudinally the impact of heavy drinking on HIV- and non-HIV-related outcomes in PLWH using data from the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (30) (the 'SUN' Study). We analyzed frequency of heavy drinking as a time-dependent predictor (i.e., a predictor that changes over time) of outcomes while controlling both for time-independent confounders (static variables such as gender, race) and time-dependent confounders (e.g., illicit drug use, depression). We tested effects of heavy drinking on two HIV clinical biomarkers (CD4+ and VL), the three non-HIV-related biomarkers in the VACS Index (liver function, kidney function, and hemoglobin), and overall VACS Index scores. We used a causal modeling approach for observational data to test the extent to which heavy drinking had direct effects on outcomes versus indirect effects through reduced ART adherence.

Methods

The SUN Study, a prospective longitudinal cohort study, monitored the clinical course of HIV-infected individuals treated with combination ART in four U.S. cities (Denver, Minneapolis, Providence, and St. Louis). The study population has been previously described in detail (30). Between March 2004 and June 2006, seven hundred participants were enrolled and assessed at six-month intervals that coincided with scheduled clinic appointments over six years; for the purposes of these analyses, which modeled effects of ART non-adherence, we only included those 533 participants who were receiving ART at the baseline study visit. The institutional review boards of the Centers for Disease Control and Prevention and all participating institutions approved the study protocol. All eligible potential participants read and signed the informed consent document.

Participants

Patients who routinely received care at seven HIV specialty clinics were recruited to participate. Patients were eligible if they were capable of providing informed consent, were at least 18 years of age, had documented HIV infection, had attended at least two appointments at the clinic of enrollment, and had been treated only with combination ART. Patients who were pregnant or incarcerated were also excluded. Because a goal of the study was to examine patient outcomes over at least a 5-year period, patients also were excluded if they were expected to survive for less than two years or in the preceding 60 days had had an AIDS-defining illness or received chemotherapy or immune-modulating therapy.

Procedure

At each visit, we conducted clinical assessments, medical record abstractions, and audio computer-assisted self-interviews (ACASI). We also collected blood and urine specimens. Laboratory data were routinely collected and recorded at each clinical visit. Basic demographic information and medication lists (including dose, frequency, duration) were extracted from the medical record.

Measures

Serum biomarkers—HIV biomarkers included VL and CD4+ T-cell count. Non-HIV biomarkers included indices of liver fibrosis, kidney function, and hemoglobin: We used FIB-4 to estimate the extent of liver fibrosis; FIB-4 incorporates aspartate aminotransferase, alanine aminotransferase, platelets, and age, and has both high negative and positive predictive values for the presence of advanced fibrosis (31–32). We used the Modified Diet in Renal Disease equation to evaluate renal function (33) by estimated glomerular filtration rate (eGFR) based on creatinine, age, sex, and race. We recorded hemoglobin levels as grams per deciliter (g/dL). Finally at every visit, we calculated a VACS Index score for each participant by summing weighted point values for each of the following components: age, VL, CD4+ T-cell count, FIB-4, eGFR, hemoglobin, and HCV serostatus (14, 16).

ACASI variables—We used questions from the Behavioral Risk Factor Surveillance System (http://www.cdc.gov/brfss/) to assess frequency of drinking, typical quantity of drinking, and frequency of drinking five or more drinks over the past 30 days. We assessed ART adherence by asking the number of missed doses in the past three days, which then was dichotomized for our analyses as either no missed doses or having missed at least one dose, given that missing more than one dose was quite rare. We also assessed 30-day frequency of cigarette smoking and use of marijuana, cocaine, inhaled nitrites (poppers), heroin, injection drugs, amphetamines, methamphetamines and club/party drugs. Finally, we used the Primary Care Evaluation of Mental Disorders (PRIME-MD) to assess for major depressive disorder (34).

Data Analysis

The primary outcomes of interest at each assessment included VL and CD4+ T-cell count, other components of the VACS Index (FIB-4, eGFR, and hemoglobin), and the VACS Index score. VL was dichotomized as being detectable (>75 cells/mm^3) versus undetectable. FIB-4 was log-transformed to better approximate a normal distribution. We conducted mediation analyses to estimate the natural direct (NDE) and natural indirect effects (NIE) of past-30-day heavy drinking frequency on HIV and clinical outcomes using the approach of Valeri and VanderWeele (35). In the context of our study, NDE was defined as the effect of heavy drinking on health outcomes if ART adherence was kept at the ‘natural’ level in the absence of heavy drinking (i.e., what adherence would be expected to be if an individual had no heavy drinking), and NIE was defined as the effect of drinking-induced changes in ART adherence on health outcomes while drinking status was maintained at ‘heavy drinking’. The NDE and NIE allow for clearer causal interpretations than other mediation approaches and have become increasingly used over the past decade (35–39).

To take advantage of the longitudinal nature of the study, we estimated the NDE and NIE of heavy drinking using structural equations models (39–40) as depicted in Figure 1. Specifically, we denote the clinical outcomes of interest by Y, ART adherence by M, and heavy drinking status by A. The subscripts t, t-, and (t−1) denote outcomes at current visit, in the past thirty days, and at the previous visit, respectively. Time-independent confounders at baseline are denoted by X_0; for these analyses we chose *a priori* to include: demographics variables (age, gender, race/ethnicity, education level); hepatitis B (HBV) or HCV

coinfection, which could impact liver function; and study site given that participants were nested within site. In Figure 1, $C_{(t-1)}$ denotes the confounding effects due to time-dependent factors. We decided *a priori* to include as time-dependent confounders both behavioral (drug use and depression) and demographic (employment status) factors that can change over time and may be related to ART adherence and/or heavy drinking; drug use was represented with two dichotomous variables representing (a) any of marijuana use and (b) any use of drugs other than marijuana. Given the observed overlap between heavy drinking and cigarette smoking and the potential impact of smoking on various health outcomes, current smoking status (dichotomous) at the last visit was a included as time-dependent confounder. We also included heavy drinking status at the last visit so that the effect of current heavy drinking was not confounded with past heavy drinking. We adjusted for time-independent confounders X_0, time-dependent confounders $C_{(t-1)}$, and clinical outcomes at the last visit $Y_{(t-1)}$ in all models. The NDE is represented by the path that goes from A_{t-} directly to Y_t, whereas the NIE is the effect of A_{t-} on Y_t that goes through its effect on M_{t-}.

We analyzed heavy drinking frequency as an ordinal variable. Justice et al. (3) found that heavy drinking frequency showed a roughly linear association with increased mortality risk, when comparing monthly heavy drinking to weekly heavy drinking to daily heavy drinking. Because of the low number of participants who drank heavily more than 4 days in the past month in the current sample, we collapsed past 30-day heavy drinking frequency into three levels (0, 1–3, and > 4 days). We assumed that there was a roughly linear increasing dose effect over these three categories of heavy drinking. These linear assumptions were verified using residual plots for continuous outcomes (e.g. eGFR and VACS), and Hosmer-Lemeshow test for binary outcomes (e.g. detectable VL and ART adherence).

We allowed that heavy drinking and ART adherence could have an interacting effect on outcomes. Depending on the distributional properties of the outcome, different regression models were chosen: a log-linear model was fit to the dichotomized VL outcome and linear models were fit to the continuous outcomes (CD4+ T-cell count, log FIB-4, eGFR, hemoglobin, and VACS). The log-linear model for detectable VL differs from the linear model for log FIB-4, where the log in the former is a ‘link function’ while in the later, the log is a transformation of the continuous outcome.

To account for within-person correlations due to repeated measures, we calculated standard errors and p-values using the bootstrap method with 1,000 resamples whereby each participant was the basic resampling unit. In all analyses, we assumed that data were missing at random (41–42); that is, we assumed that conditional on baseline confounders X_0, time-dependent confounders $C_{(t-1)}$ at last visit, and clinical outcome $Y_{(t-1)}$ at the last visit, those with missing values were comparable to the participants who completed the visit. All analyses were carried out using STATA Version 12.1 (StataCorp. 4905 Lakeway Dr., College Station, TX 77845), and a significance level of less than 0.05 was used.

Results

Descriptive Analyses

The demographic and clinical characteristics of participants at baseline are shown in Table 1; these characteristics are further broken down by frequency of heavy drinking at baseline. Being male, smoking cigarettes, and using marijuana were particularly strongly associated with greater frequency of heavy drinking.

Figure 2 shows study retention, heavy drinking frequency, and ART adherence over the course of follow-ups. Panel 2a shows the proportion of the sample who completed the assessment, missed the assessment, or were lost/dropped out of the study at each follow-up. Overall, 24 participants died during follow up, 39 were lost, 52 moved and therefore received care at a new clinic, and 82 withdrew from the study. At visit six (three years post-enrollment), data for approximately 30% of the participants were missing. At the end of year six, data were missing for 44% of the original sample (n=296; Figure 2a). Heavy drinking frequency at baseline was not significantly associated with a higher rate of study dropout: OR = 1.17 (p=0.45) for 1–3 times/month and OR = 1.22 (p=0.53) for 4+ times/month compared to not drinking heavily.

Drinking behaviors were fairly stable over the study period (Figure 2b). Cross-sectional analyses demonstrated that at each visit about 70% of participants did not drink heavily, 20% drank heavily one to three times monthly, and approximately 10% drank heavily four or more times in the last month. At baseline (visit 0), about 16% of participants self-reported missing at least one ART dose in the past three days. During follow-up visits, 14–20% of participants reported missing at least one dose in the past three days, while 77–84% of participants reported 100% adherence with their regimen; 1–7% had missing ART adherence data (Figure 2c) primarily due to participants not being prescribed ART at a given visit.

Biomarker values and VACS Index scores are summarized in Figure 3. About 25% of study participants had detectable VL (defined as plasma HIV RNA > 75 cells/mm^3) at baseline. The prevalence of having a detectable VL dropped sharply to 12% (McNemar's Test: $p <$ 0.01) at the first visit then followed a nonlinear pattern so that at the end of year six the prevalence of detectable VL was approximately 19%. The mean CD4+ T-cell count increased by 25% over time, indicating improving immune function; longitudinal regression analyses (results not shown) indicated that the increase in CD4+ T-cell count was statistically significant. Although log FIB-4 and VACS Index scores increased numerically over time, suggesting greater fibrosis and greater risk of mortality, these increases were not significant. The mean eGFR and hemoglobin concentration exhibited little change.

Natural Direct and Indirect Effects

A precondition for having a significant indirect effect of heavy drinking frequency on biomarkers and clinical outcomes through reduced ART adherence is that heavy drinking has a significant effect on ART adherence. Results confirmed that condition. The linear effect over the three categories of heavy drinking frequency (0, 1–3, and > 4 times in the past 30 days), adjusting for baseline and time-varying confounders including heavy drinking in the prior assessment period, was a risk ratio of 1.12 (p = 0.004). Thus, the relative risk of

reporting ART nonadherence increased 12% with each one-level increase in heavy drinking frequency.

Table 2 shows the estimated NDE and NIE of heavy drinking frequency on biomarker outcomes, assuming that there was a linear increasing dose effect over the three categories of heavy drinking frequency. The parameter estimates in the table show the NDE and NIE associated with a one-level increase in heavy drinking frequency, e.g., "1–3 times/month" versus "never", or "> 4 times/month" versus "1–3 times/month." Increased frequency of past 30-day heavy drinking had a significant NIE (risk ratio = 1.03, 95% confidence interval [CI] = 1.00, 1.05) on increasing the risk of a detectable VL through its association with decreased past 3-day ART adherence. More frequent heavy drinking had both a significant NDE of −10.61 cells/mm^3 (95% CI [−17.10, −4.12]) and a significant NIE of −0.72 (95% CI [−1.28, −0.15]) cells/mm^3 on lowering CD4+ T-cell count, though the NDE was substantially larger in value. Heavy drinking frequency had a significant NDE and total effect of increasing FIB-4 values. Heavy drinking had no significant effects on eGFR. Heavy drinking had a significant NDE and a total effect on increasing hemoglobin values. Finally, heavy drinking frequency had a significant NIE on increasing VACS Index scores through its association with ART adherence.

We repeated analyses of FIB-4 comparing patients with and without HBV or HCV coinfection since alcohol consumption could have had a differential impact on liver function in those groups. Among co-infected patients, heavy drinking frequency had a significant NDE (estimate = 1.02, 95% confidence interval (CI) [1.01, 1.03], $p = 0.02$); the NDE among patients who were not co-infected was nonsignificant (estimate = 1.00, 95% CI [0.99, 1.01], $p = 0.19$). The NIE of heavy drinking frequency on FIB-4 in both groups was nonsignificant.

Discussion

We analyzed data from a longitudinal observational study using causal inference methods to estimate the effects of past 30-day heavy drinking frequency on HIV-specific and non-HIV-specific outcomes in PLWH and to estimate the extent to which those effects were due to reduced ART adherence. We found that greater frequency of heavy drinking in PLWH had a significant direct effect on reduced CD4+ T-cell counts and a significant direct effect on increased liver fibrosis, as indexed by FIB-4 scores. Greater heavy drinking frequency also had an indirect effect on increased risk of detectable viral load, reduced CD4+ T-cell counts, and higher VACS Index scores through its association with decreased ART adherence. Greater heavy drinking frequency was associated with higher hemoglobin levels over time, which also has been noted in the general population (28).

An association between heavy drinking and higher VL has been established in prior research (10), and the association between heavy drinking and reduced ART adherence is well supported in the literature (5). What our results clarify is that the effect of heavy drinking on VL is due primarily to its association with reduced ART adherence rather than to a direct effect on viral replication or reduction in ART effectiveness. Given that many PLWH may avoid taking ART when drinking, in part due to concern about interactive toxicities between

alcohol and ART (8, 43), clinicians should address such concerns directly, clearly indicating that ART adherence regardless of drinking is important for maintaining viral suppression.

Our study findings are consistent with the literature that generally supports an adverse effect of heavy drinking on CD4+ T-cell counts in PLWH (10, 13). We found that heavy drinking was associated with lower CD4+ T-cell counts, in part through its association with reduced ART adherence but primarily due to a direct effect on this biomarker. Heavy drinking is known to suppress the immune system, and this effect has been shown to be due not to only its toxicity to immune system cells (dendritic cells), which play a critical role in immune function, but also to reduced antigen-specific T-cell proliferation (44–46). Thus, especially for PLWH whose immune systems have not been fully reconstituted, avoiding heavy drinking may have direct clinical benefits.

Some (19–23) but not all (24–25) studies have shown associations between alcohol use and liver function. Our results suggest that viral hepatitis co-infection may be a key variable to consider when examining this association. Specifically, although we found significant direct and total effects of heavy drinking on liver fibrosis, as indexed by FIB-4 scores, subgroup analyses indicated that this effect was due primarily to a direct effect of heavy drinking in persons with HBV/HCV co-infection. The associations between viral liver disease (HBV and HCV), heavy alcohol use, increased fibrosis and increased mortality have been well supported in the literature (47), and this study clarifies that such effects in PLWH are not due to reduced ART adherence.

We did not find a significant effect of alcohol on kidney function (eGFR). In healthy men, regular moderate alcohol consumption has not been associated with lower eGFR (26, 27). Our results are consistent with those findings: in this sample of PLWH with a median age of 41 years, kidney function did not appear to be harmed by drinking. Likewise, our findings on hemoglobin were consistent with studies in the general population that have found a significant but small positive correlation between greater alcohol use and higher hemoglobin (28). Alcohol enhances dietary iron absorption and has harmful effects on hepatocytes leading to an inappropriate release of ferritin into the plasma, and thereby contributes to an increase in hemoglobin. While one might make an assumption that increased hemoglobin is beneficial, a prior study found that both low and high hemoglobin levels can predict higher mortality (48). Further study is needed to determine whether the effects of alcohol on hemoglobin in PLWH are beneficial or harmful in terms of survival.

A recent cross-sectional analysis study indicated that greater frequency of heavy drinking in PLWH was associated with higher scores on an index of 5-year mortality risk, the VACS Index (3). The current study extended that work in a longitudinal analysis that also considered how much of the association of drinking with the VACS Index is due to indirect effects through reduced ART adherence. Controlling for prior drinking and VACS Index scores, greater heavy drinking frequency had a significant positive indirect effect on the VACS Index through reduced ART adherence. Given the strong ability of the VACS Index to predict all-cause mortality (14–17) in PLWH, these results are especially concerning. Although heavy drinking had a direct effect on lowering CD4+ T-cell counts and increasing FIB-4 values, which would result in greater VACS Index scores, the overall direct effect of

heavy drinking on VACS Index scores was nonsignificant. This result was likely due to the direct effect of heavy drinking on raising hemoglobin levels, which would result in lower VACS Index scores. Future studies should examine more closely whether heavy drinking's effect on raising hemoglobin alters interpretation of the VACS Index.

Strengths and Limitations

To our knowledge, this prospective study is the first to examine the natural direct and indirect effects of heavy alcohol use over time on HIV-specific and other clinical outcomes in PLWH. While previous cross-sectional studies have demonstrated the impact of heavy alcohol use on VL and CD4+ T-cell counts, none have captured the dynamic nature of alcohol use and examined its influence on multiple outcomes while also including ART adherence as a mediator in the model. We used lagged analyses that accounted not only for baseline time-independent confounders but also potential time-dependent confounders (depression, other drug use, smoking, and employment) that could change over time and impact alcohol use, ART adherence, and health. Thus, this study provides particularly rigorous control of potential confounds when examining alcohol's effects on health.

This study also has limitations. Our cohort was largely non-Hispanic white gay, bisexual and other men who have sex with men with a low prevalence of HCV coinfection (12%) and limited illicit drug use (0.8% heroin use), and thus may not be representative of the larger population of HIV-infected adults in the United States. The study also had consistent attrition over time leading to more modest sample sizes at longer follow-up times. We relied on self-reports of alcohol use and ART adherence, which could lead to underreporting; however, these data were collected in a confidential manner with providers blinded to all answers, which should reduce social desirability bias in reporting. ART adherence was assessed with only a 3-day timeframe and therefore had to be dichotomized given limited range in responses. It is also possible that the 3-day timeframe would have spanned weekends for some participants and not for others, which could add variability in the measure of adherence for which we cannot control. At the time of this study, the Behavioral Risk Factor Surveillance System did not have separate questions for heavy drinking for men vs. women; therefore, all participants were asked about frequency of drinking 5+ drinks per occasion, which is higher than the 4+ drinks/occasion cutoff that is now typically used for women. This limitation may have resulted in heavy drinking frequency being especially strongly associated with male gender.

Conclusions

Heavy drinking in PLWH deleteriously affects multiple clinical biomarkers, including HIV VL, CD4+ T-cell counts, and estimated liver fibrosis. Reductions in heavy drinking are likely to benefit PLWH, both by reducing direct negative effects of heavy drinking on the body and by increasing adherence to ART. Prior research indicates that alcohol use leads to physical injury and increased mortality risk at lower levels in PLWH compared with those without HIV (3). Taken together, HIV clinicians may use these data in discussions with PLWH to encourage reduced heavy drinking. In particular, brief motivational interventions have been shown to reduce drinking in PLWH (49, 50). Our findings suggest that reducing

the frequency of heavy drinking, even if it is not eliminated, may benefit overall health outcomes in PLWH in a dose-dependent manner.

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References

1. Centers for Disease Control and Prevention. HIV Surveillance Special Report 16. Jan. 2016 Behavioral and Clinical Characteristics of Persons Receiving Medical Care for HIV Infection—Medical Monitoring Project, United States, 2013 Cycle (June 2013–May 2014).
2. DeLorenze GN, Weisner C, Tsai AL, et al. Excess mortality among HIV-infected patients diagnosed with substance use dependence or abuse receiving care in a fully integrated medical care program. Alcohol Clin Exp Res. 2011; 35:203–210. [PubMed: 21058961]
3. Justice AC, McGinnis KA, Tate JP, et al. Risk of mortality and physiologic injury evident with lower alcohol exposure among HIV infected compared with uninfected men. Drug Alcohol Depend. 2016; 161:95–103. [PubMed: 26861883]
4. Chander G, Lau B, Moore RD. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. J Acquir Immune Defic Syndr. 2006; 43:411–417. [PubMed: 17099312]
5. Hendershot CS, Stoner SA, Pantalone DW, et al. Alcohol use and antiretroviral adherence: review and meta-analysis. J Acquir Immune Defic Syndr. 2009; 52(2):180–202. [PubMed: 19668086]
6. Braithwaite RS, McGinnis KA, Conigliaro J, et al. A temporal and dose response association between alcohol consumption and medication adherence among veterans in care. Alcohol Clin Exp Res. 2005; 29(7):1190–97. [PubMed: 16046874]
7. Cohn SE, Jiang H, McCutchan JA, et al. Association of ongoing drug and alcohol use with non-adherence to antiretroviral therapy and higher risk of AIDS and death: results from ACTG 362. AIDS Care. 2011; 23(6):775–785. [PubMed: 21293986]
8. Kalichman SC, Grebler T, Amaral CM, et al. Intentional non-adherence to medications among HIV positive alcohol drinkers: prospective study of interactive toxicity beliefs. J Gen Intern Med. 2013; 28(3):399–405. [PubMed: 23065532]
9. Samet JH, Cheng DM, Libman H, et al. Alcohol consumption and HIV disease progression. J Acquir Immune Defic Syndr. 2008; 46(2):194–199.
10. Azar MM, Springer SA, Meyer JP, et al. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. Drug Alcohol Depend. 2010; 112(3):178–93. [PubMed: 20705402]
11. Shacham E, Agbebi A, Stamm K, et al. Alcohol consumption is associated with poor health in HIV clinic patient population: a behavioral surveillance study. AIDS Behav. 2011; 15(1):209–13. [PubMed: 20013042]
12. Marcellin F, Lions C, Winnock M, et al. Self-reported alcohol abuse in HIV-HCV co-infected patients: a better predictor of HIV virological rebound than physician's perceptions (HEPAVIH ARNS CO13 cohort). Addiction. 2013; 108(7):1250–1258. [PubMed: 23421419]
13. Baum MK, Rafie C, Lai S, et al. Alcohol use accelerates HIV disease progression. AIDS Res Hum Retroviruses. 2010; 26(5):511–8. [PubMed: 20455765]
14. Justice AC, McGinnis KA, Skanderson M, et al. Towards a combined prognostic index for survival in HIV infection: the role of "non-HIV" biomarkers. HIV Med. 2009; 11:143–151. [PubMed: 19751364]
15. Tate JP, Justice AC, Hughes MD, et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS. 2013; 27(4):563–572. [PubMed: 23095314]

16. Justice AC, Freiberg MS, Tracy R. and the VACS Project team et al. Does an index composed of clinical data reflect effects of inflammation, coagulation, and monocyte activation on mortality among those aging with HIV? Clin Infectious Diseases. 2012; 54(7):984–994.
17. Justice AC, Modur SP, Tate JP, et al. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. J Acquir Immune Defic Syndr. 2013; 62(2):149–163. [PubMed: 23187941]
18. Wang EA, McGinnis KA, Long JB, et al. Incarceration and health outcomes in HIV-infected patients: the impact of substance use, primary care engagement, and antiretroviral adherence. Am J Addiction. 2015; 24(2):178–184.
19. Carton JA, Collazos J, de la Fuente B, et al. Factors associated with liver fibrosis in intravenous drug users coinfected with HIV and HCV. Antivir Ther. 2011; 16(1):27–35. [PubMed: 21311106]
20. Fuster D, Tsui JI, Cheng DM, et al. Impact of lifetime alcohol use on liver fibrosis in a population of HIV-infected patients with and without hepatitis C coinfection. Alcohol Clin Exp Res. 2013; 37(9):1527–35. [PubMed: 23647488]
21. Muga R, Sanvisens A, Fuster D, et al. Unhealthy alcohol use, HIV infection and risk of liver fibrosis in drug users with hepatitis C. PloS One. 2012; 7(10):e46810. [PubMed: 23056462]
22. Lim JK, Tate JP, Fultz SL, et al. Relationship between alcohol use categories and noninvasive markers of advanced hepatic fibrosis in HIV-infected, chronic hepatitis C virus-infected, and uninfected patients. Clin Infect Dis. 2014; 58(10):1449–1458. [PubMed: 24569533]
23. Chaudhry AA, Sulkowski MS, Chander G, et al. Hazardous drinking is associated with an elevated aspartate aminotransferase to platelet ratio index in an urban HIV-infected clinical cohort. HIV Med. 2009; 10(3):133–42. [PubMed: 19207596]
24. Tsui JI, Cheng DM, Libman H, et al. Risky alcohol use and serum aminotransferase levels in HIV-infected adults with and without hepatitis C. J Stud Alcohol Drugs. 2013; 74(2):266–70. [PubMed: 23384374]
25. Blackard JT, Welge JA, Taylor LE, et al. HIV mono-infection is associated with FIB-4—A noninvasive index of liver fibrosis—in women. Clin Infect Dis. 2011; 52(5):674–680. [PubMed: 21248367]
26. Schaeffner ES, Kurth T, de Jong PE, et al. Alcohol consumption and the risk of renal dysfunction in apparently healthy men. Arch Intern Med. 2005; 165:1048–1053. [PubMed: 15883245]
27. Funakoshi Y, Omori H, Onoue A, et al. Association between frequency of drinking alcohol and chronic kidney disease in men. Environ Health Prev Med. 2012; 17(3):199–204. [PubMed: 21879343]
28. Milman N, Pedersen AN. Blood haemoglobin concentrations are higher in smokers and heavy alcohol consumers than in non-smokers and abstainers: should we adjust the reference range? Ann Hematol. 2009; 88(7):687–694. [PubMed: 19039534]
29. Whitehead TP, Clarke CA, Bayliss RI, et al. Mean red cell volume as a marker of alcohol intake. J R Soc Med. 1985; 78(10):880–881. [PubMed: 4045896]
30. Vellozzi C, Brooks J, Bush T. and the SUN Study Investigators et al. The study to understand the natural history of HIV and AIDS in the era of effective therapy (SUN Study). Am J of Epidemiol. 2009; 169(5):642–652. [PubMed: 19074775]
31. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006; 43:1317–1325. [PubMed: 16729309]
32. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. Hepatology. 2007; 46:32–36. [PubMed: 17567829]
33. Stevens LA, Coresh J, Greene T, et al. Assessing kidney function-measured and estimated glomerular filtration rate. N Engl J Med. 2006; 354:2473–2483. [PubMed: 16760447]
34. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999; 282(18):1737–1744. [PubMed: 10568646]

35. Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure–mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods. 2013; 18(2):137–150. [PubMed: 23379553]
36. Lange T, Hansen JV. Direct and indirect effects in a survival context. Epidemiology. 2011; 22(4): 575–581. [PubMed: 21552129]
37. Imai K, Keele L, Yamamoto T. Identification, inference and sensitivity analysis for causal mediation effects. Stat Sci. 2010; 25(1):51–71.
38. VanderWeele TJ. Marginal structural models for the estimation of direct and indirect effects. Epidemiology. 2009; 20(1):18–26. [PubMed: 19234398]
39. Pearl J. Direct and indirect effects. Proceedings of the seventeenth conference on uncertainty in artificial intelligence. 2001:411–420.
40. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. Epidemiology. 1992; 13(2):143–155.
41. Little, RJ., Rubin, DB. Statistical analysis with missing data. Hoboken: John Wiley & Sons, Inc; 2002.
42. Daniels, MJ., Hogan, JW. Missing data in longitudinal studies: Strategies for Bayesian modeling and sensitivity analysis. Boca Raton: Chapman and Hall/CRC Press; 2008.
43. Pellowski JA, Kalichman SC, Kalichman MO, Cherry C. Alcohol-antiretroviral therapy interactive toxicity beliefs and daily medication adherence and alcohol use among people living with HIV. AIDS Care. 2016:1–8.
44. Eken A, Ortiz V, Wands JR. Ethanol inhibits antigen presentation by dendritic cells. Clin Vaccine Immunol. 2011; 18(7):1157–1166. [PubMed: 21562114]
45. Szabo G, Mandrekar P, Dolganiuc A, Catalano D, Kodys K. Reduced alloreactive T-cell activation after alcohol intake is due to impaired monocyte accessory cell function and correlates with elevated IL-10, IL-13, and decreased IFNgamma levels. Alcohol Clin Exp Res. 2001; 25(12): 1766–1772. [PubMed: 11781510]
46. Barr T, Helms C, Grant K, Messaoudi I. Opposing effects of alcohol on the immune system. Prog Neuropsychopharmacol Biol Psychiatry. 2016; 65:242–251. [PubMed: 26375241]
47. Fuster D, Cheng DM, Quinn EK, et al. Chronic hepatitis C virus infection is associated with all-cause and liver-related mortality in a cohort of HIV-infected patients with alcohol problems. Addiction. 2014; 109(1):62–70. [PubMed: 24112091]
48. Skjelbakken T, Wilsgaard T, Forde OH, et al. Haemoglobin predicts total mortality in a general young and middle-aged male population. The Tromso Study. Scand J Clin Lab Invest. 2006; 66(7): 567–576. [PubMed: 17101548]
49. Hasin DS, Aharonovich E, O'Leary A, et al. Reducing heavy drinking in HIV primary care: a randomized trial of brief intervention, with and without technological enhancement. Addiction. 2013; 108(7):1230–1240. [PubMed: 23432593]
50. Chander G, Hutton HE, Lau B, Xu XQ, McCaul ME. Brief intervention decreases drinking frequency in hiv-infected, heavy drinking women: Results of a randomized controlled trial. JAIDS. 2015; 70(2):137–145. [PubMed: 25967270]

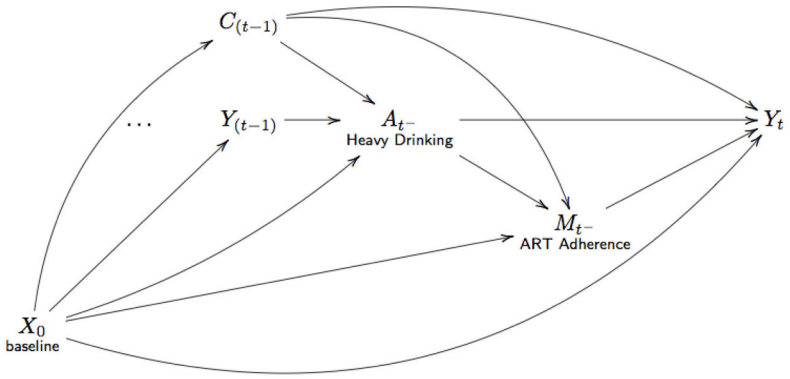

Figure 1.

Causal diagram of the natural direct effect of past 30-day heavy drinking on biomarker outcome Y_t and the natural indirect effect of heavy drinking on Y_t that goes through antiretroviral (ART) adherence.

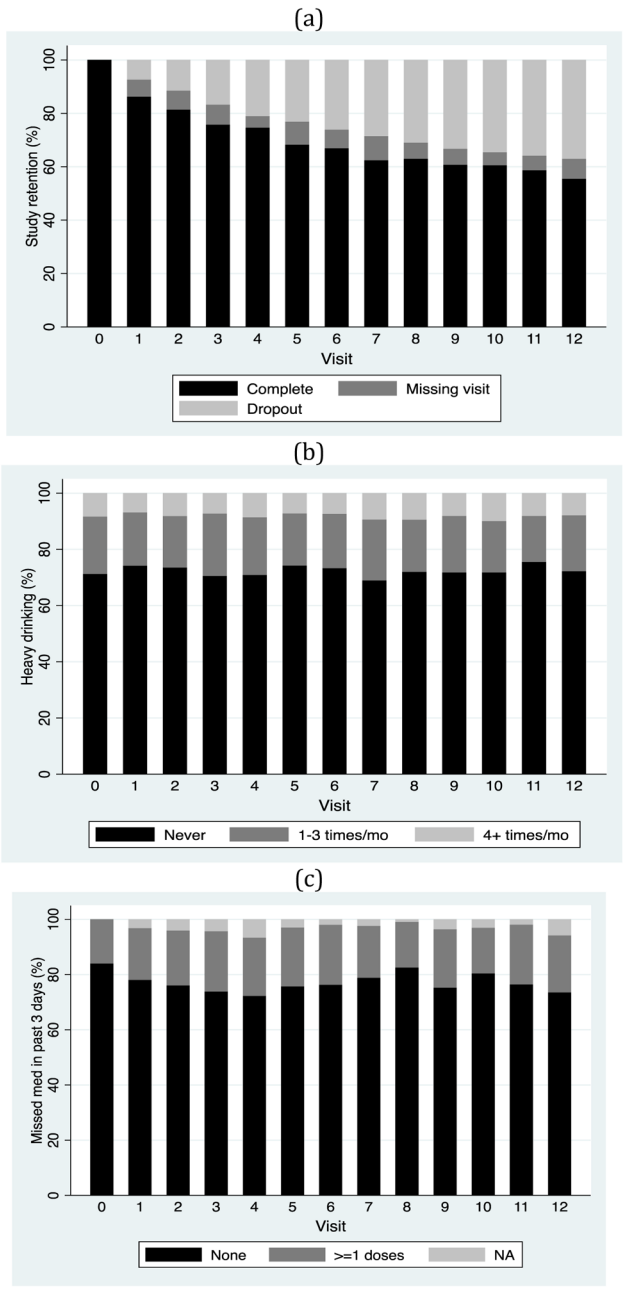

Figure 2.

Study retention (a), past 30-day heavy drinking frequency (b), and ART adherence (c) at each study visit in 533 participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy Study, 2004–2012. Heavy drinking is defined as drinking 5 or more drinks in one day. Visit 0 = enrollment and Visit 1 = 6 months after enrollment, with subsequent visits occurring at 6-month intervals. NA = not available due to the participant not being on ART at that study visit or in rare cases missing data.

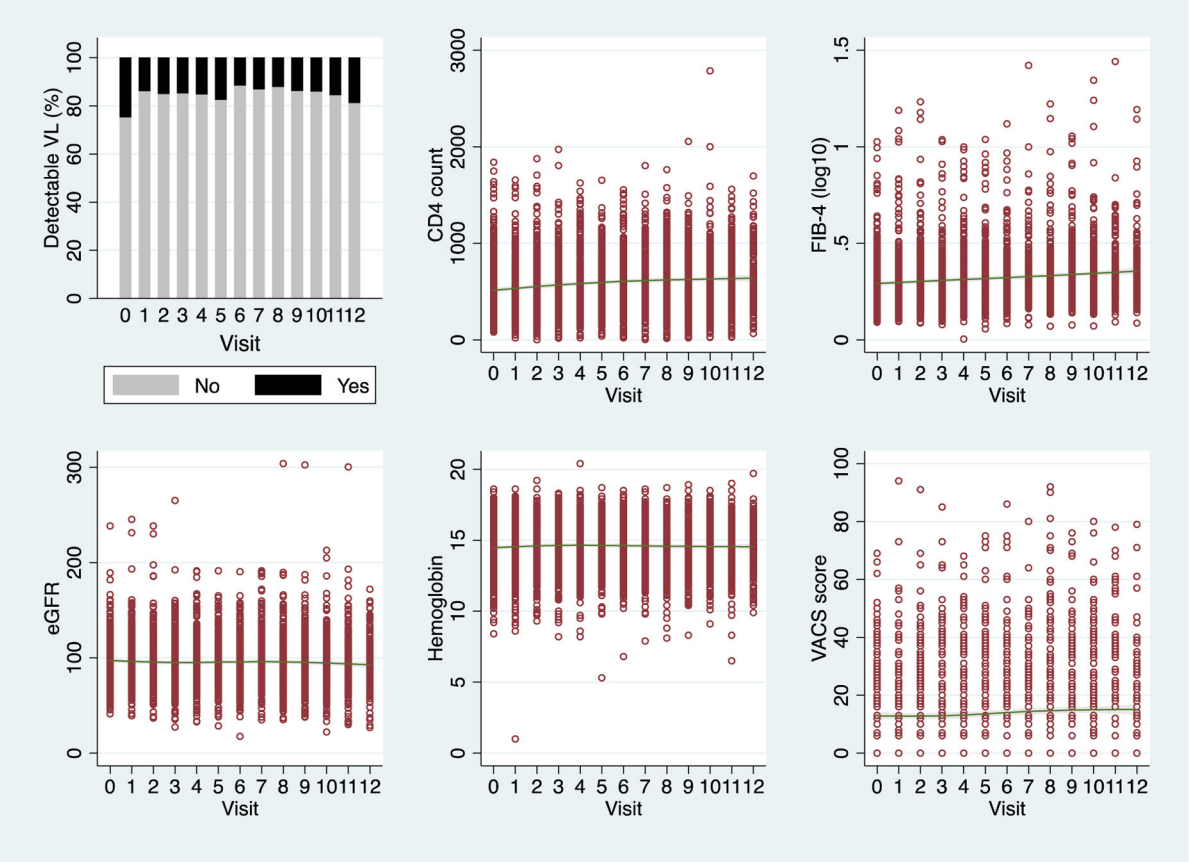

Figure 3.

Trajectories of biomarker outcomes and the VACS Index over study visits in 533 participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy Study, 2004–2012. VL = viral load. ART = antiretroviral therapy. FIB-4 = Fibrosis 4. eGFR = estimated glomerular filtration rate. VACS = Veterans Aging Cohort Study. Visit 0 = enrollment and Visit 1 = 6 months after enrollment, with subsequent visits occurring at 6-month intervals

Table 1

Baseline demographic, clinical, and behavioral characteristics of 533 participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy Study recruited from 2004–2006.

Characteristic	Total N = 533		Heavy drinking in the past 30 days[1]					
			Never (*n* = 377)		1–3 times (*n* = 108)		4 times or more (*n* = 44)	
Age, median (range)	41	(20–66)	42	(20–66)	40	(20–62)	41	(23–53)
Male gender, n (%)	416	(78.0)	281	(74.5)	92	(85.2)	42	(95.5)
Race/ethnicity, n (%)								
White, non-Hispanic	320	(60.0)	229	(60.7)	61	(56.5)	30	(68.2)
Black, non-Hispanic	147	(27.6)	107	(28.4)	30	(27.8)	8	(18.2)
Hispanic	52	(9.8)	31	(8.2)	14	(13.0)	5	(11.4)
Other	14	(2.6)	10	(2.7)	3	(2.8)	1	(2.3)
Education, n (%)								
Less than High School	60	(11.3)	40	(10.6)	14	(13.0)	5	(11.4)
High School	433	(81.2)	307	(81.4)	85	(78.7)	38	(86.4)
Graduate	39	(7.3)	29	(7.7)	9	(8.3)	1	(2.3)
Missing	1	(0.2)	1	(.27)	0	(0)	0	(0)
Employment status, n (%)								
Full time	256	(48.0)	182	(48.3)	47	(43.5)	26	(59.1)
Part-time	61	(11.4)	40	(10.6)	20	(18.5)	1	(2.3)
Current major depression by PRIME-MD, n (%)	73	(13.7)	49	(13.0)	15	(13.9)	9	(20.5)
Current smoker, n (%)	230	(43.2)	147	(39.0)	53	(49.1)	29	(65.9)
Substance use in the past 30 days, n (%)								
Marijuana	123	(23.1)	67	(17.8)	36	(33.3)	20	(45.6)
Inhaled nitrites (poppers)	89	(16.7)	55	(14.6)	24	(22.2)	9	(20.5)
Cocaine	53	(9.9)	28	(7.4)	17	(15.7)	8	(18.2)
Club drugs/methamphetamine	12	(2.3)	7	(1.9)	3	(2.8)	2	(4.6)
Injection drugs	6	(1.1)	4	(1.0)	0	(0)	2	(4.6)
Heroin	4	(0.8)	2	(.53)	1	(.93)	1	(2.3)
Amphetamines	2	(0.4)	2	(.53)	0	(0)	0	(0)
HIV transmission risk factor, n (%)								

Characteristic	Total N = 533		Heavy drinking in the past 30 days[1]					
			Never (*n* = 377)		1–3 times (*n* = 108)		4 times or more (*n* = 44)	
Sex with male	378	(70.9)	260	(69.0)	85	(78.7)	31	(70.5)
Sex with female	76	(14.3)	48	(12.7)	15	(13.9)	13	(29.6)
Injection drug use	33	(6.2)	24	(6.4)	5	(4.6)	3	(6.8)
Blood transfusion history	16	(3.0)	14	(3.7)	2	(1.9)	0	(0)
Occupational exposure	19	(3.6)	17	(4.5)	1	(.93)	1	(2.3)
Other or unknown risk	57	(10.7)	48	(12.7)	4	(3.7)	5	(11.4)
Nadir CD4+ T-cell count, median (range)	174	(0–1020)	174	(0–1020)	177	(2–672)	185	(5–657)
Number of years on ART, median (range)	2.91	(.02–10.2)	2.97	(.02–10.2)	2.64	(.03–9.48)	3.05	(.36–9.69)
Hepatitis C IgG antibody positive, n (%)	65	(12.2)	48	(12.7)	9	(8.3)	7	(15.9)
Hepatitis B surface antigen positive, n (%)	28	(5.3)	18	(4.8)	7	(6.5)	3	(6.8)
Detectable VL, n (%)	131	(24.6)	94	(24.9)	26	(24.1)	10	(22.7)
CD4+ T-cell count, median (range)	458	(81–1840)	469	(81–1840)	391	(116–1748)	468	(108–1562)
FIB-4, median (range)	.85	(.23–9.6)	.87	(.23–9.6)	.77	(.23–7.7)	.80	(.37–2.3)
eGFR, median (range)	95	(41–238)	94	(41–238)	98	(41–161)	99	(64–189)
Hemoglobin, median (range)	14.6	(8.4–18.6)	14.5	(8.4–18.6)	14.9	(9.4–18.0)	15.0	(11.4–17.7)
VACS, median (range)	10	(0–69)	10	(0–69)	8	(0–50)	6	(0–35)

Note. PRIME-MD = Primary Care Evaluation of Mental Disorders; IgG = Immunoglobulin G. FIB-4 = Fibrosis 4. eGFR = estimated glomerular filtration rate.

[1]Four participants had missing data on this variable at baseline.

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Table 2

Natural direct and indirect effects of heavy drinking frequency on biomarkers and the VACS Index over 6 years of follow-up in 533 participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy Study, 2004–2012

		Estimate	p-value	95% Conf. Interval	
Detectable VL *(a)*	NDE	1.13	0.06	0.99	1.27
	NIE	1.03	0.03	1.00 *(c)*	1.05
	Total Effect	1.16	0.02	1.00 *(c)*	1.31
CD4+ T-cell count	NDE	−10.61	<0.01	−17.10	−4.12
	NIE	−0.72	0.01	−1.28	−0.15
	Total Effect	−11.33	<0.01	−17.80	−4.85
FIB-4 *(b)*	NDE	1.01	0.03	1.00 *(c)*	1.01
	NIE	1.01	0.17	1.00 *(d)*	1.01
	Total Effect	1.01	0.02	1.00 *(c)*	1.01
eGFR	NDE	−0.01	0.98	−0.82	0.80
	NIE	−0.02	0.14	−0.05	0.01
	Total Effect	−0.03	0.94	−0.84	0.78
Hemoglobin	NDE	0.07	<0.01	0.03	0.11
	NIE	0.00	0.58	0.00	0.00
	Total Effect	0.07	<0.01	0.03	0.11
VACS	NDE	−0.17	0.48	−0.64	0.30
	NIE	0.05	0.02	0.01	0.09
	Total Effect	−0.12	0.62	−0.59	0.35

Note. Model assumes that heavy drinking frequency has a continuous dose effect. VL = viral load. ART = antiretroviral therapy. FIB-4 = Fibrosis 4. eGFR = estimated glomerular filtration rate. VACS = Veterans Aging Cohort Study. NDE = natural direct effect. NIE = natural indirect effect. The NIE is the effect of heavy drinking frequency on the biomarker outcome that is due to its association with reduced ART adherence. *p*-values and 95% confidence intervals are calculated based on the bootstrap standard errors. Analyses were adjusted for smoking status, marijuana use status, other drug use status, depression status, employment status, and heavy drinking status at the last visit; and age, gender, race/ethnicity, education level, hepatitis B (HBV) or HCV coinfection, and study site at baseline.

*(a)*The effect estimates and confidence intervals are in the scale of risk ratio.

*(b)*The effect estimates and confidence intervals are transformed back to the original scale of FIB-4, i.e., the interpretation should be in terms of multiplicative effects.

[c]The lower limit of the confidence interval is greater than 1.

[d]The lower limit of the confidence interval is less than 1.