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Associations of Liver Disease with Alcohol Use among People Living with HIV and the Role of Hepatitis C: The New Orleans Alcohol Use in HIV Study

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Abstract

Aim: This cross-sectional analysis of the New Orleans Alcohol Use in HIV (NOAH) study assesses whether current and lifetime alcohol use in people living with HIV (PLWH) are associated with greater liver disease and how hepatitis C-viral (HCV) co-infection (HIV/HCV+) modifies the association.

Methods: Alcohol use was measured by Lifetime Drinking History (LDH), a 30-day Timeline Follow-back calendar, the Alcohol Use Disorder Identification Test, and phosphatidylethanol. Liver disease was estimated by alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST platelet ratio-index (APRI), fibrosis-4 index (FIB-4) and nonalcoholic fatty liver disease-fibrosis score. Associations between alcohol consumption and liver disease were estimated with multivariable logistic regression. Models were adjusted for age, sex, body-mass index, hepatitis B and HIV viral load.

Results: Participants ($N = 353$) were majority male (69%) and black (84%) with a mean age of 48.3 ± 10 years. LDH was significantly associated with advanced liver fibrosis (FIB-4 aOR = 22.22 [1.22–403.72]) only among HIV/HCV+ participants with an LDH of 100–600 kg. HIV/HCV+ partici-

pants had a higher prevalence of intermediate and advanced liver disease markers than HIV/HCV− ($P < 0.0001$). Advanced markers of liver disease were most strongly associated with hazardous drinking (≥40(women)/60(men) grams/day) (APRI aOR = 15.87 (3.22–78.12); FIB-4 aOR = 6.76 (1.81–7.16)) and PEth ≥400 ng/ml (APRI aOR = 17.52 (2.55–120.54); FIB-4 aOR = 17.75 (3.30–95.630).
Conclusion: Results indicate a greater association of current alcohol use with liver disease than lifetime alcohol use, which varied by HCV status. These findings stress the importance of reducing alcohol use in PLWH to decrease risk of liver disease and fibrosis.

INTRODUCTION

Increased uptake of effective combination antiretroviral therapy (cART) in recent years has allowed people living with HIV (PLWH) to extend survival approaching that of HIV-negative counterparts (Lee *et al*., 2001). This, in turn, has limited AIDS-related death and increased the opportunity for the development of chronic comorbidities associated with aging and lifestyle behaviors among PLWH. One of these comorbidities is chronic liver disease, which remains one of the leading causes of morbidity and mortality in PLWH (Chaudhry *et al*., 2009). The main contributor to this is hepatitis C virus (HCV) (Thornton *et al*., 2017), which affects an estimated 25% of PLWH in the USA (Centers for Disease Control, 2019). Both HIV and HCV are independently associated with liver disease progression, with coinfection of HIV and HCV further accelerating liver disease (Gaslightwala and Bini, 2006; Labarga *et al*., 2015).

Although there are numerous ways in which liver disease manifests, the most serious is liver fibrosis and when untreated, liver fibrosis advances to liver cirrhosis and in some cases to hepatocellular carcinoma (American Liver Foundation, 2019). The gold standard for the clinical assessment of hepatic fibrosis is liver biopsy (Gebo *et al*., 2002; American Association for the Study of Liver Disease, 2019). However, this procedure is invasive and subject to sampling error (Regev *et al*., 2002). In contrast, noninvasive markers of liver disease that utilize liver enzymes such as aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis-4 index score (FIB-4) correlate well with liver biopsy findings and have been validated for use in both HIV and HCV populations (Vallet-Pichard *et al*., 2007; Adler *et al*., 2008; Sebastiani *et al*., 2008). Studies have shown that subjects with HCV have increased risk of moderate to severe fibrosis, as indicated by these markers (Adler *et al*., 2008; Fuster *et al*., 2012). Increasing evidence suggests that HIV mono-infection can also induce fibrotic changes (Pembroke *et al*., 2017).

Alcohol use can further exacerbate liver injury produced by HIV and HCV alone or when co-infection exists (Rosenthal *et al*., 2003; Bilal *et al*., 2016). Both HIV+ and HCV− infected individuals demonstrate higher rates of hazardous drinking and alcohol use disorders (Hahn and Samet, 2010), which have been associated with greater susceptibility to viral disease progression (Chander *et al*., 2006; Baum *et al*., 2010) and development of chronic comorbidities. Alcohol consumption has been well documented to accelerate liver disease progression among those monoinfected with HCV (Muga *et al*., 2012), and a 2014 study found that heavy alcohol consumption may be more predictive of liver disease progression than HCV coinfection among patients with HIV (HIV/HCV) (Mankal *et al*., 2015). Indeed, higher Alcohol Use Disorder Identification Test (AUDIT-C) scores are associated with advanced hepatic fibrosis among HIV, HCV, HIV/HCV co-infected and noninfected individuals, with the greatest association being among HIV/HCV individuals (Lim *et al*., 2014).

Previous studies on the association between alcohol consumption and liver disease in PLWH that have focused on current drinking patterns, have failed to include biomarkers of alcohol assessment (Benhamou *et al*., 1999; Justice *et al*., 2006; Blackard *et al*., 2011). Furthermore, these studies reported conflicting data on the effect of alcohol consumption on liver disease among HIV/HCV patients (Benhamou *et al*., 1999; Blackard *et al*., 2011). Few studies have had sufficient data on participants' alcohol consumption patterns to effectively compare associations of long-term and current alcohol use with markers of liver disease in PLWH or have not seen an association between alcohol use and liver fibrosis in those with HIV and HIV/HCV coinfection (Blackard *et al*., 2011; Fuster *et al*., 2012; Muga *et al*., 2012).

The primary objective of this study was to assess whether lifetime drinking history (LDH) and current hazardous or harmful drinking, as defined by National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines, AUDIT and the biological marker phosphatidylethanol (PEth) were associated with liver disease as measured by APRI and FIB-4. We additionally examined the association of these alcohol use measures with indicators of liver injury such as abnormal AST and alanine aminotransferase (ALT) levels and nonalcoholic fatty liver disease fibrosis score (NAFLD-FS). Our secondary objective was to examine whether coinfection with HCV acts as an effect modifier in the association between alcohol consumption and liver disease markers in PLWH.

METHODS

Study population

This was a cross-sectional analysis of the New Orleans Alcohol Use in HIV (NOAH) study, a longitudinal study conducted by the Comprehensive Alcohol Research Center (CARC) at the Louisiana State University Health Sciences Center in New Orleans, Louisiana. The NOAH study is a translational investigation of alcohol use disorder, HIV, and ART in aging and exacerbation of comorbid conditions in an underserved cohort of PLWH. NOAH participants are adults (≥18 years old) with an HIV/AIDS diagnosis who are currently under care. Additional NOAH study methods have been previously published (Welsh *et al*., 2019). Of the 365 participants in the NOAH study, 353 had available information on liver disease markers and thus were included in the current analysis. There was no significant difference in demographic characteristics between those included and excluded due to missing liver disease markers (*P*-value ranged from 0.08 to 0.98). A medical record of a positive HCV ribonucleic acid (RNA) test was used to define diagnosis of HCV in this population, yielding a total of 56 (16%) participants who were co-infected with HIV and HCV.

Alcohol exposure

The primary exposure of interest, LDH, was defined as alcohol consumption over the life course and was measured in kilograms. This

drinking measure, aimed at quantifying long-term alcohol exposure and drinking patterns, was assessed through a structured interview in which the participant was asked about alcohol consumption patterns spanning from the first year of regular drinking to the present. A standard drink was equated to 14 g of alcohol, and the total grams of alcohol consumed was then converted to kilograms of alcohol consumed. When categorizing participants' LDH, the cut points used were <100, 100–600, and >600 kg. The reference category of <100 kg LDH was chosen using previously established evidence that alcoholic liver disease is less likely to develop below a lifetime alcohol ingestion of 100 kg, which equates to a daily alcohol intake of 30 g (or about 2 standard drinks/day) over a span of 10 years (Bellentani and Tiribelli, 2001). The second clinically relevant threshold of 600 kg was selected due to its approximate correspondence to a drinking pattern of >4 standard drinks a day for 28 years, as four standard drinks per day has been established as a threshold for advanced liver fibrosis in HCV infection (Fuster *et al*., 2013).

The 30-day Timeline Followback (TLFB) calendar was used to obtain estimates of daily alcohol consumption in the past 30 days by asking NOAH participants to retrospectively recount the number of drinks consumed on each day. These data were used to calculate alcohol consumption (in grams) per day and used to assess hazardous drinking as defined by NIAAA ≥40 g/day for females and ≥60 g/day for males.

The AUDIT, developed by the World Health Organization, consists of 10 questions that result in a score between 0 and 40 (Alcohol Use Disorders Identification Test, 2019). An AUDIT score <8 corresponds to a low risk for AUD, a score between 8 and 15 corresponds to a moderate risk for AUD, and a score ≥16 corresponds to a high risk of AUD.

Serum phosphatidylethanol (PEth) is a biological marker that reflects alcohol use within an approximate 3–4-week period. PEth is an abnormal phospholipid that is only formed in the presence of ethanol by the enzyme phospholipase D (Viel *et al*., 2012). As defined by previously established relevant thresholds (Afshar *et al*., 2017), participants were categorized as showing no indication of alcohol misuse (PEth <250 ng/ml), any misuse of alcohol (250–400 ng/ml) or severe misuse of alcohol.

Liver outcomes

AST to Platelet Ratio Index (APRI). Widely accepted as a noninvasive alternative to liver biopsy, APRI is a tool for the assessment of liver fibrosis. This measure is calculated using participants' AST level, platelet count, and the upper limit of normal AST levels (Wai *et al*., 2003). When calculating APRI score, the upper normal limit used was 40 for all participants based on recent data (Neuschwander-Tetri *et al*., 2004). An APRI score >0.4 was defined as intermediate liver fibrosis and advanced liver fibrosis was defined as an APRI >1.5.

Fibrosis-4 (FIB-4). Like APRI, FIB-4 is a noninvasive tool used to measure liver fibrosis. Calculated using participants' age, AST level, ALT level and platelet count, a FIB-4 index score of <1.45 has a negative predictive value of over 90% for advanced liver fibrosis and a score of >3.25 has a positive predictive value of 65% for advanced liver fibrosis and specificity of 97% (Sterling *et al*., 2006). Using these cut points, an FIB-4 index score >1.45 was classified as intermediate and a score >3.25 was classified as advanced liver fibrosis.

Additional Liver Enzymes. To further assess the association between alcohol consumption and liver dysfunction, liver enzyme levels indicative of hepatic damage were also measured. AST is also produced in smaller amounts by the heart, kidneys, brain and muscles, making it less specific for the diagnosis of liver disease. Although an upper limit of ALT 40 U/L was used in this study for determining APRI and FIB-4 associations, there is evidence that ALT levels in the historically "normal range" may suggest liver injury and that these thresholds appear to differ for females and males (Kim *et al*., 2004). Therefore, we performed a secondary analysis of abnormal ALT defined as >19 U/L for females and >30 U/L for males and AST >40 U/L as an indicator of liver injury for both females and males (Kim *et al*., 2008). Finally, because of the high prevalence of nonalcoholic fatty liver disease in HIV+ patients, we included the Non-Alcoholic Fatty Liver Disease Fibrosis Score (NAFLD-FS) (Angulo *et al*., 2007; Crum-Cianflone *et al*., 2009). This measure is derived from fasting glucose, age, AST levels, ALT levels, platelet count, body mass index (BMI) and albumin levels. We defined an NAFLD-FS of ≤−1.455 as normal, >−1.455 as intermediate and >0.676 as an indication of advanced liver fibrosis.

Statistical analysis

Descriptive statistics were used to summarize patient demographics in this population, stratified by LDH to evaluate differences in potential confounding variables among those with varying long-term alcohol exposure. To assess differences in current and lifetime drinking patterns among co-infected with HIV/HCV+ and those PLWH without HCV (HIV/HCV−), chi-squared tests were conducted to test for differences in proportions for LDH, TLFB, AUDIT and PEth categories. Bivariate analyses were also conducted to examine all markers of liver disease among HIV/HCV+ and HIV/HCV−.

Multinomial logistic regression was used to determine differences in intermediate and advanced indications of liver fibrosis (APRI, FIB-4, NAFLD-FS, ALT and AST). To assess the effect of alcohol use on liver disease, multinomial logistic regression was used and all models were adjusted for age, sex, BMI, hepatitis B virus (HBV), HIV viral load and current drinking (quantified by PEth) or conversely LDH. To assess potential effect modification by HCV, an interaction term was added to the lifetime alcohol use model and current alcohol use model. Results were then stratified by HCV status. All significance testing was conducted at an alpha level of 0.05 and all analyses were conducted using SAS 9.4.

RESULTS

The average age of participants was 48.3 with a standard deviation ±10.3 years, and the study population was 69.4% male and 83.9% black (Table 1). An estimated 38.3% of participants were normal weight and 28.9% were overweight as determined by BMI. The majority were current smokers (59.8%) and 16.7% were former smokers. More than 75% had an undetectable HIV viral load of ≤50 copies/ml. The overall prevalence of HBV in the sample was 5.1%. Only 0.9% of the NOAH study participants are co-infected with HCV and HBV. Those with an LDH >600 kg were more likely to be older ($P < 0.0001$), male ($P = 0.001$) and current smokers ($P = 0.002$) compared with those with an LDH <100 kg. There were no statistically significant differences in the distribution of race, BMI category, HIV viral load or diagnosis of HBV by the LDH categories.

The results of the bivariate analyses conducted to compare alcohol use measures among PLWH with and without HCV (HCV+/−) are shown in Fig. 1. The only alcohol consumption measure that was significantly different between HIV/HCV+ and HIV/HCV− was LDH ($P = 0.019$), with more HIV/HCV+ participants having an LDH >600 kg (26.8 vs. 13.8%) (Fig. 1A). Those with HIV/HCV+ coinfection had significantly higher rates of all noninvasive markers

Table 1. Demographics of included participants from the NOAH study

		All participants ($n = 353$)	LDH* <100 kg ($n = 155$)	LDH 100–600 kg ($n = 142$)	LDH >600 kg ($n = 56$)	*P*-value
Mean age (SD)		48.3 (10.3)	44.7 (11.0)	50.4 (9.4)	52.7 (7.2)	**<0.0001**
				% (*n*)		
Sex						**0.001**
	Female	30.6 (108)	40.6 (63)	23.2 (33)	21.4 (12)	
	Male	69.4 (245)	59.4 (92)	76.8 (109)	78.6 (44)	
Race						0.448
	Black	83.9 (296)	85.8 (133)	81.7 (116)	83.9 (47)	
	White	15.3 (54)	12.3 (19)	18.3 (26)	16.1 (9)	
	Other	0.8 (3)	1.9 (3)	-	-	
BMI category						0.099
	Underweight	4.3 (15)	3.9 (6)	3.6 (5)	7.3 (4)	
	Normal weight	38.3 (134)	34.2 (53)	45.0 (63)	32.7 (18)	
	Overweight	28.9 (101)	30.3 (47)	25.0 (35)	34.6 (19)	
	Obese	17.7 (62)	16.8 (26)	16.4 (23)	23.6 (13)	
	Extremely obese (>35)	10.9 (38)	14.8 (23)	10.0 (14)	1.8 (1)	
Smoking status						**0.002**
	Never	23.5 (83)	33.6 (52)	16.9 (24)	12.5 (7)	
	Former	16.7 (59)	14.2 (22)	19.7 (28)	16.1 (9)	
	Current	59.8 (211)	52.3 (81)	63.4 (90)	71.4 (40)	
Viral load						0.112
	≤50	75.6 (267)	71.0 (110)	78.9 (112)	80.4 (45)	
	51–200	8.2 (29)	7.7 (12)	7.8 (11)	10.7 (6)	
	201–1000	4.8 (17)	4.5 (7)	6.3 (9)	1.8 (1)	
	>1000	11.3 (40)	16.8 (26)	7.0 (10)	7.1 (4)	
Hepatitis B		5.1 (18)	5.2 (8)	7.0 (10)	-	0.128

LDH = lifetime drinking history; SD = standard deviation; BMI = body mass index.

Table 2. Adjusted* odds ratios of intermediate and advanced liver fibrosis by liver disease markers for lifetime alcohol use patterns, stratified by HCV status, the NOAH study

	Intermediate liver damage/fibrosis					Advanced liver fibrosis		
	ALT	AST	NAFLD-FS	APRI	FIB-4	NAFLD-FS	APRI	FIB-4
LDH			Odds ratios (95% CI)				Odds ratios (95% CI)	
<100 kg 100–600 kg	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
All	1.09 (0.58, 2.04)	1.76 (0.71, 4.37)	1.73 (0.91, 3.30)	1.04 (0.50, 2.16)	1.09 (0.55, 2.16)	1.49 (0.48, 4.68)	1.93 (0.37, 10.17)	2.67 (0.68, 10.49)
HCV+	1.36 (0.36, 5.18)	2.43 (0.52, 11.43)	0.89 (0.16, 4.90)	2.28 (0.54, 9.67)	4.65 (0.57, 38.13)	5.88 (0.31, 113.41)	-	**21.89 (1.19, 402.36)**
HCV−	1.05 (0.53, 2.09)	1.50 (0.51, 4.44)	1.93 (0.97, 3.87)	0.81 (0.35, 1.89)	0.94 (0.45, 1.97)	1.04 (0.29, 3.69)	1.41 (0.24, 8.22)	1.41 (0.28, 7.11)
>600 kg								
All	1.55 (0.70, 3.44)	2.46 (0.86, 7.06)	1.03 (0.46, 2.33)	0.86 (0.35, 2.15)	0.41 (0.16, 1.00)	0.50 (0.10, 2.58)	0.29 (0.02, 5.04)	0.22 (0.03, 1.75)
HCV+	3.82 (0.75, 19.53)	3.58 (0.67, 19.13)	0.41 (0.07, 2.42)	1.17 (0.25, 5.38)	0.31 (0.06, 1.75)	0.89 (0.03, 26.63)	-	0.19 (0.01, 5.72)
HCV−	1.13 (0.44, 2.91)	1.94 (0.50, 7.56)	1.31 (0.52, 3.29)	0.84 (0.28, 2.52)	0.48 (0.17, 1.33)	0.45 (0.07, 3.00)	-	0.31 (0.02, 3.90)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NAFLD-FS = non-alcoholic fatty liver disease fibrosis score; APRI = AST to platelet ratio index; FIB-4 = fibrosis-4.

*All models adjusted for age, sex, BMI, hepatitis-B virus status, smoking status, viral load and PEth concentration.

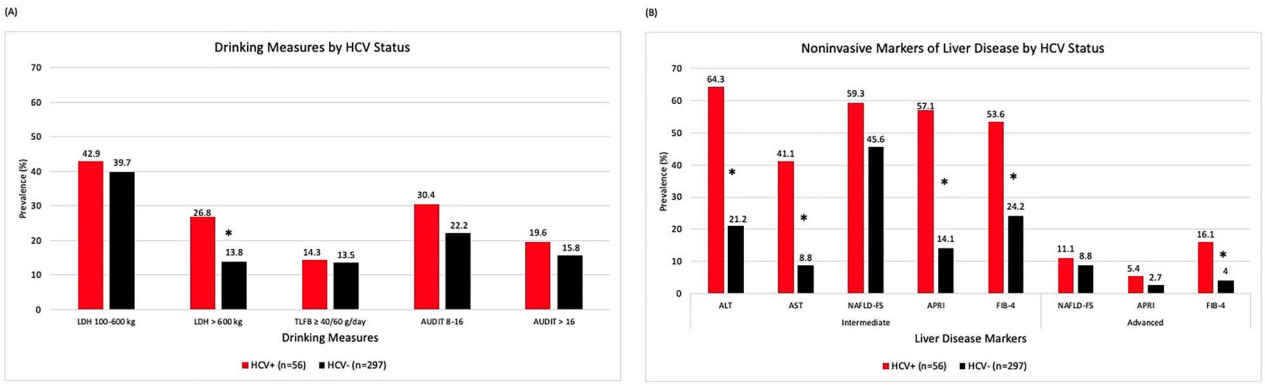

Fig. 1 Prevalence of current and lifetime drinking measures (**A**) and noninvasive markers of liver disease (**B**) among NOAH study participants, stratified by HCV status.

of liver disease than their HIV/HCV−counterparts ($P < 0.0001$) except for advanced liver fibrosis as measured by APRI and NAFLD-FS ($P > 0.05$). Prevalence of intermediate liver fibrosis ranged from 41.1 to 64.3% among those with HIV/HCV+ coinfection and 8.8–45.8% among HIV/HCV−.

Figure 2 illustrates the relationship between LDH and PEth and liver disease markers (APRI and FIB-4) by HCV status. Fig. 2A and 2B shows that HIV/HCV+ co-infected participants have higher liver disease markers than HIV monoinfected participants regardless of LDH. There is a positive association between PEth and APRI for both HIV/HCV+ co-infected and HIV/HCV−, and PEth and FIB-4 among HIV/HCV−.

Multinomial logistic regression analyses of LDH categories and liver disease markers showed very few statistically significant associations (Table 2). In stratified analyses, associations between LDH and markers of liver disease had higher magnitude among HIV/HCV+ participants, but again did not reach statistical significance for any measure of liver disease except for FIB-4. Compared to LDH <100 kg, LDH 100–600 kg had an association with advanced liver fibrosis (FIB-4 aOR = 21.89 (95% confidence interval [CI]: 1.19, 402.36).

Results for current alcohol use and liver disease markers are shown in Table 3. Among the entire sample, TLFB hazardous drinking was associated with intermediate liver disease [ALT aOR = 3.33 (1.58, 7.02); AST aOR = 5.74 (1.40, 7.85); APRI aOR = 2.44 (1.02, 5.81); NAFLD-FS aOR = 3.31 (1.40, 7.85)], and advanced liver fibrosis [APRI aOR = 15.87 (3.22, 78.12); FIB-4 aOR = 6.76 (1.81, 25.33)]. In contrast, in HIV/HCV− individuals, hazardous drinking was significantly associated with intermediate liver disease/fibrosis [ALT aOR = 2.94 (1.35, 6.39); AST aOR = 5.57 (2.15, 14.48); NAFLD-FS aOR = 4.55 (1.76, 11.73); APRI aOR = 2.90 (1.18, 7.16)] and advanced liver fibrosis [APRI aOR = 11.79 (2.17, 64.16); FIB-4 aOR = 7.68 (1.90, 31.08)]. While moderate AUD risk was not significantly associated with liver fibrosis (Appendix A), high risk of AUD (Table 3) was significantly associated with advanced fibrosis [APRI aOR = 7.07 (1.31, 38.26; FIB-4 aOR = 5.83 (1.44, 23.68)] and intermediate liver disease (AST aOR = 3.12 (1.22, 7.99)]. In stratified analysis, HIV/HCV+ participants with a high risk of AUD were significantly associated with intermediate liver disease [AST aOR = 8.81 (1.36, 57.19)]; and among HIV/HCV− participants, there was a ninefold increased odds of having an advanced liver fibrosis with APRI score (aOR = 8.91 (1.56, 50.90)) and a sevenfold increased odds with FIB-4 score (aOR = 7.08 (1.60, 31.25)). The interaction terms to assess effect modification for HCV status did not reach statistical significance.

Moderate risk of AUD was not significantly associated with any liver disease markers among HIV/HCV− or HIV/HCV+ co-infected participants (Appendix A). Any misuse of alcohol identified by PEth was significantly associated with intermediate liver disease as measured by APRI, FIB-4, ALT, and AST and advanced liver disease/fibrosis with APRI and FIB-4.

DISCUSSION

This study aimed to investigate whether current and lifetime alcohol use patterns are associated with markers of liver disease in a predominantly virally suppressed majority black cohort of PLWH. We found that advanced markers of liver disease were more strongly associated with hazardous drinking in the last 30 days. LDH was only significantly associated with advanced liver fibrosis as measured by FIB-4. Our results show that HIV/HCV+ co-infected individuals had a higher prevalence of intermediate or advanced fibrosis than HIV/HCV− participants, suggesting that HCV exacerbates liver damage in PLWH. However, the effects of HCV status were not consistent and the interaction term for HCV and alcohol did not reach statistical significance.

One of the main findings of our analysis is that current drinking patterns in the NOAH study were more associated with liver disease among both HIV/HCV− and HIV/HCV+ co-infected individuals than LDH. This was consistent with previous studies that have found significant associations between both AUDIT-C (Lim *et al*., 2014) and current hazardous drinking (Muga *et al*., 2012) with fibrosis markers. While all of the drinking measures that captured current alcohol use patterns were significantly associated with at least one of the markers of liver injury, TLFB hazardous drinking and PEth concentrations were significantly associated with most markers, with PEth concentrations showing slightly greater association. Among HIV/HCV+ co-infected patients, a PEth concentration >400 was significantly associated with intermediate liver disease (APRI and FIB-4) and was significantly associated with the presence of all liver disease markers in HIV/HCV− participants. Unlike the other measures of current and lifetime alcohol use utilized in this study, PEth is a biological marker and does not rely on self-report by

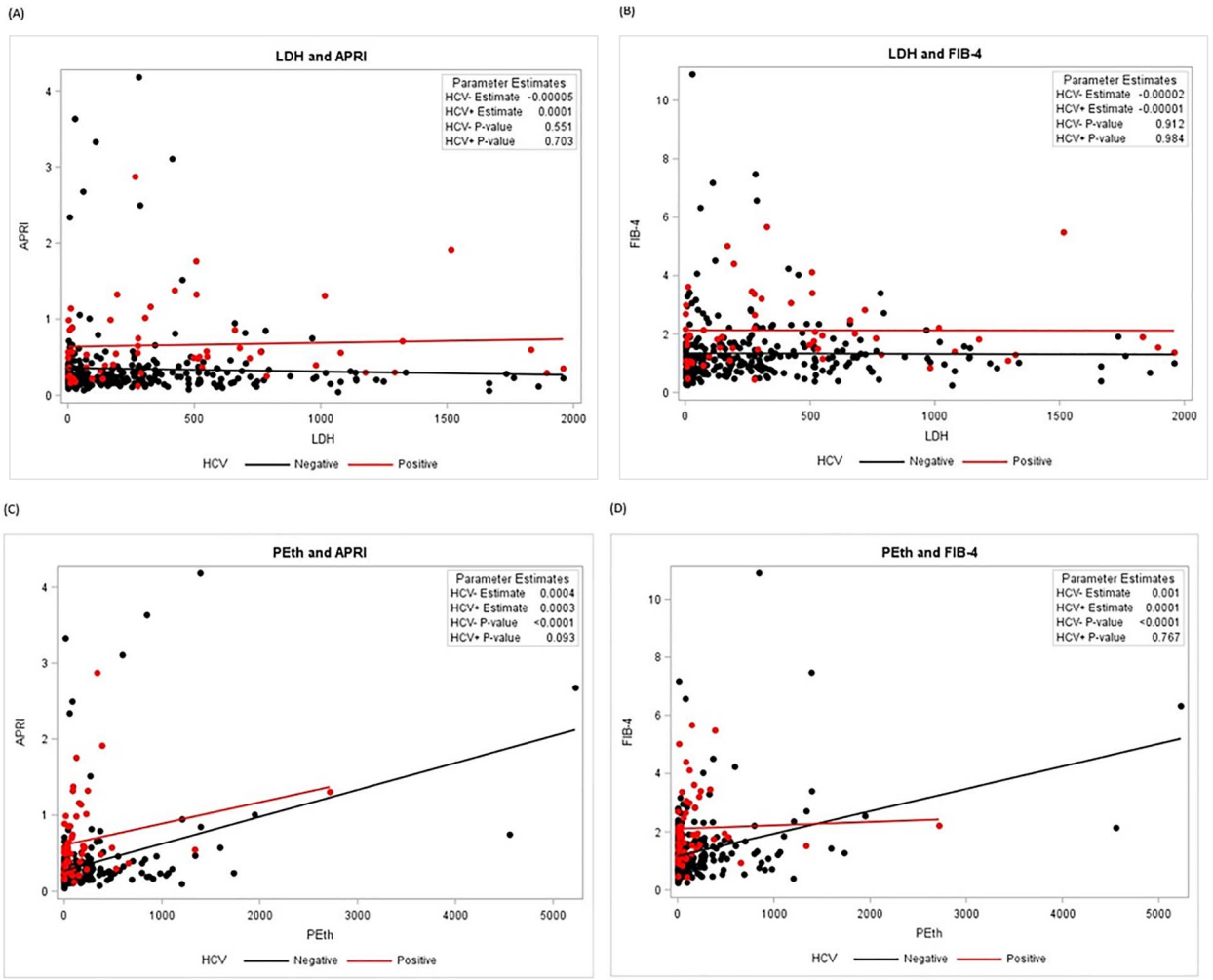

Fig. 2 Alcohol use measures and liver disease markers by HCV status among people living with HIV, NOAH study.

participants. While LDH, TLFB and AUDIT are all validated and widely used screening tools for alcohol use and abuse, they are still subject to both recall and stigma biases, both of which could have impacted our findings.

Our results are in partial contrast to those conducted by Fuster *et al*. that found no statistically significant associations between lifetime alcohol exposure and liver fibrosis markers in HIV/HCV+ patients (Fuster *et al*., 2013). Our primary exposure of interest, LDH, was significantly positively associated with advanced liver fibrosis (FIB-4 score) among those with HIV/HCV+ for LDH of 100–600 kg. In contrast to our hypothesis, PLWH with higher LDH (>600 kg) showed a lower association with liver fibrosis. We speculate that this is not suggestive that higher lifetime alcohol exposure is associated with lower risk of liver damage. Rather, we believe this is likely due to either discontinuation of current alcohol use because of health concerns related to lifetime alcohol exposure of this caliber (Shaper *et al*., 1988). Conversely, continued heavy alcohol use in healthier PLWH could erroneously have resulted in an apparent protective effect of increased alcohol consumption. This pattern of alcohol abstention parallels the "sick-quitter" hypothesis. This hypothesis, first proposed by Shaper *et al*., states that groups of abstainers in studies include many former drinkers who quit drinking because of illness or alcohol's interaction with prescription drugs (Shaper *et al*., 1988). While the hepatic injury done by alcohol can be reversed by this period of abstinence, the cumulative nature of LDH does not allow for the classification of exposure to be reduced, which could weaken the association.

Our finding could have also been affected by the standard calculation of lifetime drinking history that average alcohol consumption by decade and the heavier months or years of drinking are averaged over a larger period of time potentially decreasing the intensity of the consumption. While 600 kg of alcohol could equate to an average of two drinks a day for about 59 years, it could also be six drinks a day for roughly 20 years. These patterns of use correspond to significantly different levels of health risk for participants but would result in the same classification of LDH.

Strengths of our study include that this is the first study to our knowledge to examine four distinct drinking measures of alcohol use with noninvasive markers of liver disease in a population of PLWH both with and without HCV. In addition to the robust nature of exposure information, this study had the strength of access to a relatively virally suppressed cohort of PLWH. Approximately, 97% of participants are currently on ART and 75% had an undetectable HIV viral load. These participants were all under care in the New

Table 3. Adjusted* odds ratios of intermediate and advanced liver fibrosis by liver disease markers for current alcohol use patterns, stratified by HCV status, the NOAH study

	Intermediate liver damage/fibrosis					Advanced liver fibrosis		
	ALT	AST	NAFLD-FS	APRI	FIB-4	NAFLD-FS	APRI	FIB-4
	Odds ratios (95% CI)							
TLFB hazardous ≥40/60								
All	**3.33 (1.58, 7.02)**	**5.74 (2.33, 14.10)**	**3.31 (1.40, 7.85)**	**2.44 (1.02, 5.81)**	1.79 (0.74, 4.32)	4.08 (0.81, 20.60)	**15.87 (3.22, 78.12)**	**6.76 (1.81, 25.33)**
HCV+	-	6.98 (0.64, 75.60)	0.45 (0.05, 4.00)	1.06 (0.14, 8.11)	1.52 (0.17, 13.93)	6.48 (0.28, 149.68)	**67.55 (1.09, 765.63)**	3.68 (0.23, 60.33)
HCV−	**2.94 (1.35, 6.39)**	**5.57 (2.15, 14.48)**	**4.55 (1.76, 11.73)**	**2.90 (1.18, 7.16)**	1.81 (0.71, 4.62)	3.62 (0.56, 23.32)	**11.79 (2.17, 64.16)**	**7.68 (1.90, 31.08)**
AUDIT high risk > 16								
All	1.53 (0.72, 3.29)	**3.12 (1.22, 7.99)**	1.24 (0.56, 2.75)	1.38 (0.57, 3.37)	0.76 (0.31, 1.88)	1.40 (0.28, 7.07)	**7.07 (1.31, 38.26)**	**5.83 (1.44, 23.68)**
HCV+	5.18 (0.56, 48.25)	**8.81 (1.36, 57.19)**	0.73 (0.13, 4.27)	2.78 (0.51, 14.93)	0.49 (0.08, 2.90)	2.37 (0.12, 48.21)	4.43 (0.13, 147.70)	2.46 (0.19, 31.60)
HCV−	1.29 (0.57, 2.94)	2.30 (0.80, 6.67)	1.36 (0.58, 3.16)	1.49 (0.55, 4.05)	0.82 (0.31, 2.17)	1.14 (0.18, 7.25)	**8.91 (1.56, 50.90)**	**7.08 (1.60, 31.25)**
PEth severe misuse >400								
All	2.05 (0.93, 4.52)	**3.90 (1.45, 10.49)**	**5.51 (2.23, 13.62)**	**3.75 (1.55, 9.07)**	**3.96 (1.56, 10.07)**	**8.43 (1.32, 53.72)**	**17.52 (2.55, 120.5)**	**17.75 (3.30, 95.63)**
HCV+	0.29 (0.04, 2.10)	0.63 (0.08, 5.13)	**26.09 (1.97, 345.82)**	**1.40 (1.33, 1.48)**	**16.57 (1.12, 244.2)**	-	0.41 (0.35, 0.49)	-
HCV−	**2.77 (1.23, 6.25)**	**5.89 (2.03, 17.07)**	**4.42 (1.71, 11.42)**	**3.18 (3.12, 3.24)**	**3.16 (1.17, 8.51)**	**7.66 (1.18, 49.85)**	**26.20 (25.71, 26.70)**	**46.95 (6.15, 358.70)**

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NAFLD-FS = non-alcoholic fatty liver disease fibrosis score; APRI = AST to platelet ratio index; FIB-4 = fibrosis-4.

*All models adjusted for age, sex, BMI, hepatitis-B virus status, smoking status, viral load and lifetime drinking history.

Orleans metropolitan area. This provision makes our findings more clinically relevant in the age of higher rates of antiretroviral treatment and suppression among PLWH. Our population also differed from previous studies in that we included men and women, mostly African Americans that are in care.

There are several limitations to consider when interpreting the findings of this study. First and foremost, the 16% prevalence of HCV in this population of HIV+ individuals is lower than anticipated. This led to extremely wide confidence intervals on parameter estimates (or an inability to obtain estimates) for HIV/HCV+ co-infected individuals. This could have also impacted the ability to detect a statistically significant interaction term in our models as we explored effect modification by HCV status. An additional limitation is that our analysis was cross sectional in nature, which allowed us to only consider alcohol use and liver disease markers at one time point. This is an important consideration because all measures utilized either AST or ALT in their calculations, and these enzyme levels can fluctuate over time, possibly leading to outcome misclassification. To reduce this potential for misclassification, outcome status was also evaluated as categorical rather than continuous. As previously mentioned, another limitation stems from the self-report method of data collection to classify exposure status of LDH, TLFB and AUDIT. While there was a possibility for misclassification of exposure status resulting from participants' underreporting alcohol use, this misclassification would have likely diluted true associations. The final limitation of this study was that it only consists of HIV+ participants, precluding dissection of the relationship between HIV status, alcohol use and HCV. Future studies will expand recruitment to HIV− subjects.

Despite the limitations of the current study, there are several potential implications for clinical practice suggested by the findings. While HIV/HCV+ co-infected participants seem to engage less in hazardous or risky drinking than HIV/HVC- participants, they were still active alcohol consumers, despite a surplus of evidence on the detrimental effects of HIV, HCV, and alcohol use on the liver (Lim *et al.*, 2014; Mankal *et al.*, 2015). This suggests a need for additional counseling and information dissemination on the topic of alcohol use in this population. This study also highlights the necessity of using alcohol-related biological markers in this clinical setting. When biological markers are not feasible, clinicians should consider multiple alcohol measures in PLWH, both with and without concurrent HCV infection, when classifying disease risk. Very few of the alcohol use measures were significantly associated with all markers of liver disease in this population, so using the alcohol use measures to supplement one another has the potential to lead to more accurate identification of those at risk of developing liver disease, thus reducing the burden of advanced liver disease in this population.

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Table A1. Adjusted* odds ratios of intermediate and advanced liver fibrosis by liver disease markers by AUDIT and phosphatidylethanol (PEth), stratified by hepatitis-c viral (HCV) status, NOAH study.

	Intermediate liver damage/fibrosis					Advanced liver fibrosis		
	ALT	AST	NAFLD-FS	APRI	FIB-4	NAFLD-FS	APRI	FIB-4
	Odds ratio (95% CI)					Odds ratio (95% CI)		
AUDIT <8		Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Moderate risk 8–16								
All	0.65 (0.33, 1.29)	1.04 (0.43, 2.52)	0.85 (0.41, 1.75)	0.88 (0.41, 1.86)	0.56 (0.26, 1.21)	0.92 (0.27, 3.15)	0.73 (0.12, 4.65)	1.77 (0.47, 6.58)
HCV+	0.35 (0.10, 1.25)	0.49 (0.12, 2.02)	3.48 (0.62, 19.66)	0.84 (0.23, 3.05)	1.10 (0.21, 5.68)	4.05 (0.31, 53.19)	-	1.14 (0.11, 12.04)
HCV−	0.81 (0.38, 1.75)	1.61 (0.57, 4.57)	0.63 (0.29, 1.39)	0.83 (0.34, 2.05)	0.47 (0.19, 1.14)	0.66 (0.16, 2.66)	1.70 (0.23, 12.45)	3.67 (0.80, 16.93)
PEth <250		Ref.	Ref.				Ref.	Ref.
Any misuse 250–400								
All	**3.83 (1.49, 9.83)**	**7.70 (2.38, 24.94)**	1.45 (0.52, 4.04)	**4.86 (1.68, 14.11)**	**3.33 (1.05, 10.56)**	1.99 (0.31, 12.67)	**25.39 (3.15, 205.08)**	**17.52 (3.23, 95.18)**
HCV+	-	-	0.39 (0.03, 5.79)	-	-	-	-	-
HCV−	**3.73 (1.38, 10.08)**	**8.03 (2.20, 29.33)**	1.85 (0.59, 5.84)	**4.40 (4.31, 4.50)**	3.02 (0.92, 9.87)	2.66 (0.39, 18.36)	**3.83 (3.67, 4.00)**	**33.6 (4.00, 283.91)**
PEth <250		Ref.	Ref.				Ref.	Ref.
≥250								
All	**2.60 (1.36, 5.00)**	**5.00 (2.13, 11.69)**	**3.28 (1.59, 6.79)**	**4.13 (1.95, 8.75)**	**3.71 (1.70, 8.14)**	**4.57 (1.11, 18.87)**	**20.23 (3.54, 115.48)**	**17.92 (4.34, 74.01)**
HCV+	0.83 (0.16, 4.21)	1.78 (0.32, 10.02)	4.33 (0.68, 27.69)	1.79 (0.26, 12.10)	**14.54 (1.04, 203.45)**	-	19.98 (0.71, 559.91)	8.52 (0.34, 215.46)
HCV−	**16.83 (2.46, 115.13)**	**4.72 (2.14, 10.43)**	**3.09 (1.56, 6.15)**	**3.15 (1.45, 6.82)**	3.11 (1.37, 7.06)	**4.85 (1.13, 20.77)**	**6.54 (2.53, 16.88)**	**41.44 (6.48, 264.96)**

ALT = alanine aminotransferase; AST = aspartate aminotransferase; APRI = AST to platelet ratio index; FIB-4 = fibrosis-4; NAFLD FS = non-alcoholic fatty liver disease fibrosis score.

*All models adjusted for age, sex, BMI, hepatitis-B virus status, smoking status, viral load and lifetime drinking history.

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