Relationship Between Alcohol Use Categories and Noninvasive Markers of Advanced Hepatic Fibrosis in HIV-Infected, Chronic Hepatitis C Virus–Infected, and Uninfected Patients

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Background. It is unclear if the risk of liver disease associated with different levels of alcohol consumption is higher for patients infected with human immunodeficiency virus (HIV) or chronic hepatitis C virus (HCV). We evaluated associations between alcohol use categories and advanced hepatic fibrosis, by HIV and chronic HCV status.

Methods. We performed a cross-sectional study among participants in the Veterans Aging Cohort Study who reported alcohol consumption at enrollment (701 HIV/HCV-coinfected; 1410 HIV-monoinfected; 296 HCV-monoinfected; 1158 HIV/HCV-uninfected). Alcohol use category was determined by the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) questionnaire and alcohol-related diagnoses and was classified as nonhazardous drinking, hazardous/binge drinking, or alcohol-related diagnosis. Advanced hepatic fibrosis was defined by FIB-4 index >3.25.

Results. Within each HIV/HCV group, the prevalence of advanced hepatic fibrosis increased as alcohol use category increased. For each alcohol use category, advanced hepatic fibrosis was more common among HIV-infected than uninfected (nonhazardous: 6.7% vs 1.4%; hazardous/binge: 9.5% vs 3.0%; alcohol-related diagnosis: 19.0% vs 8.6%; $P < .01$) and chronic HCV-infected than uninfected (nonhazardous: 13.6% vs 2.5%; hazardous/binge: 18.2% vs 3.1%; alcohol-related diagnosis: 22.1% vs 6.5%; $P < .01$) participants. Strong associations with advanced hepatic fibrosis (adjusted odds ratio [95% confidence interval]) were observed among HIV/HCV-coinfected patients with nonhazardous drinking (14.2 [5.91–34.0]), hazardous/binge drinking (18.9 [7.98–44.8]), and alcohol-related diagnoses (25.2 [10.6–59.7]) compared with uninfected nonhazardous drinkers.

Conclusions. Advanced hepatic fibrosis was present at low levels of alcohol consumption, increased with higher alcohol use categories, and was more prevalent among HIV-infected and chronic HCV-infected patients than uninfected individuals. All alcohol use categories were strongly associated with advanced hepatic fibrosis in HIV/HCV-coinfected patients.

Keywords. alcohol; liver fibrosis; HIV; hepatitis C; FIB-4.

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Alcohol consumption is prevalent among human immunodeficiency virus (HIV)–infected [1–3] and chronic hepatitis C virus (HCV)–infected [4] patients and is an important contributor to progression of liver fibrosis in these groups [5, 6]. Excessive alcohol intake is associated with a range of hepatic manifestations, including hepatic inflammation, fibrosis, and steatosis, which can lead to cirrhosis and hepatic decompensation [7].

Despite the acknowledged impact of alcohol on the liver, few studies have evaluated the effects of different patterns of alcohol consumption on liver disease, particularly among persons with HIV or chronic HCV. Furthermore, it is unclear if the risk of liver disease associated with each level of alcohol use is higher for those with HIV or chronic HCV. Given the prevalence of alcohol consumption in these groups [1, 2, 4], it is important to determine if certain patterns of alcohol use—such as nonhazardous and binge drinking, which are traditionally not thought to contribute to hepatic fibrosis—are harmful to the liver, and more so for those infected with HIV or chronic HCV.

Although biopsy has been the gold standard for staging liver disease, it is not feasible to perform liver biopsies in large cohort studies because of the costs and risks to patients [8]. Noninvasive markers of hepatic fibrosis have been valuable for evaluating liver disease in population-based studies [9], particularly in HIV-infected cohorts [10–12]. The FIB-4 index (based on liver aminotransferases, platelet count, and age) is a noninvasive, validated measure of advanced hepatic fibrosis in patients with chronic liver disease, including alcoholic liver disease [13], viral hepatitis [14–17], and HIV/viral hepatitis coinfection [18], and can predict liver-related mortality among HCV-monoinfected [19–21] and HIV/HCV–coinfected patients [20, 21].

Our objective was to evaluate the association between alcohol use categories and advanced hepatic fibrosis, determined by FIB-4 index, by HIV and chronic HCV status among participants in the Veterans Aging Cohort Study (VACS), an ongoing cohort established to examine the effects of alcohol and comorbidities on health outcomes [22]. We hypothesized that for each category of alcohol use, the prevalence of advanced fibrosis would be greater in persons infected with HIV or chronic HCV compared with uninfected persons. We also examined associations between alcohol use categories and advanced hepatic fibrosis among HIV/HCV-coinfected, HIV-monoinfected, HCV-monoinfected, and HIV/HCV-uninfected patients, to gain insights into the effects of HIV, chronic HCV, and alcohol use on significant liver fibrosis.

PATIENTS AND METHODS

Study Design and Data Source

We conducted a cross-sectional study among participants receiving medical care at 1 of 8 VACS sites (Veterans Health Administration [VA] facilities in Atlanta, Georgia; Baltimore, Maryland; Bronx, New York; Houston, Texas; Los Angeles, California; Manhattan, New York; Pittsburgh, Pennsylvania; Washington, D.C.) [22]. VACS follows HIV-infected patients group matched in a 1:1 ratio to uninfected patients by age, sex, race/ethnicity, and clinical site. At enrollment, participants complete a standardized questionnaire that collects demographic information, alcohol use (determined using the Alcohol Use Disorders Identification Test-Consumption [AUDIT-C] questionnaire [23–25]), and other self-reported behaviors. VACS also extracts VA electronic medical record data, including body mass index (BMI), diagnoses (recorded using *International Classification of Diseases, Ninth Revision* [*ICD-9*] diagnostic codes), procedures, laboratory results, and VA-dispensed medications [26]. Approval was obtained by the institutional review boards at each participating VA medical center.

Study Participants

Patients enrolled in the VACS between 1 June 2002 and 30 September 2010 and reporting alcohol consumption on the AUDIT-C at enrollment were eligible for inclusion. Participants were excluded if they (1) denied alcohol use in the prior 12 months or (2) did not have laboratory results available to determine FIB-4 index at enrollment. We excluded patients who did not consume alcohol to avoid inclusion of sick abstainers (ie, persons who avoid drinking alcohol because of former alcohol abuse, knowledge of the presence of advanced hepatic fibrosis, or concerns regarding alcohol's interactions with prescribed medications), which could bias results [27].

Main Study Outcomes

The primary outcome was advanced hepatic fibrosis, determined by FIB-4 index. FIB-4 is calculated using aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, and age as follows: (age [years] × AST [U/L])/((platelet count [10^9/L]) × (ALT [U/L])$^{1/2}$) [18]. A FIB-4 index >3.25 has been shown to identify advanced hepatic fibrosis (Metavir stage F3 or F4) with a high degree of accuracy in patients with alcoholic liver disease (area under the receiver-operating characteristic curve [AUROC], 0.70–0.80) [13], viral hepatitis (AUROC, 0.85–0.91) [14–17], and HIV/viral hepatitis coinfection (AUROC, 0.77) [18]. FIB-4 was calculated using age at VACS enrollment and AST, ALT, and platelet count results measured closest to, but between 12 months before and 6 months after, enrollment. We used the established cutoff of FIB-4 index >3.25 to define advanced hepatic fibrosis [14–16, 18].

To further examine the relationship between alcohol use categories and liver disease, we evaluated 3 secondary outcomes: (1) significant liver fibrosis determined by AST-to-platelet ratio index (APRI) >1.5, (2) hepatic inflammation, and (3) hepatic decompensation. APRI is calculated using AST and platelet count: ([AST [U/L]/upper limit of normal [considered as 40 U/L])/platelet count (10^9/L)] × 100 [28]. An APRI >1.5 accurately identifies significant liver fibrosis (Metavir stage F2–F4) in chronic liver

diseases [13, 14, 17, 28–32]. Hepatic inflammation was defined by serum levels of either AST or ALT >40 U/L, as this cutoff reflects a clinically meaningful level of hepatocellular injury [33, 34]. Hepatic decompensation was defined by medical record–confirmed diagnoses of ascites, spontaneous bacterial peritonitis, esophageal variceal hemorrhage, or hepatic encephalopathy [35, 36].

Alcohol Use Categories

Alcohol use at enrollment was categorized using responses to AUDIT-C questions and diagnoses of alcohol-related conditions [37, 38]. AUDIT-C is a 3-item screening test evaluating alcohol consumption within the prior year (ie, frequency of alcohol use, quantity of alcohol consumed, and consumption of ≥6 drinks on 1 occasion [binge drinking]) [23]. This instrument has good operating characteristics for the detection of nonhazardous, hazardous, and binge drinking, but not for the diagnosis of alcohol abuse or dependence [23–25]. Diagnoses of alcohol-related conditions (defined by *ICD-9* codes 291.x, 303.x, and 305.0) have been shown to accurately identify active alcohol dependence/abuse [39]. Because neither AUDIT-C nor alcohol-related diagnoses can individually capture all levels of alcohol consumption, we used both measures to categorize alcohol use. The need, feasibility, and validity of using both psychometric and diagnostic measures of alcohol consumption have previously been established [40–43], and this methodology minimizes exposure misclassification. Participants reporting alcohol use on the AUDIT-C within the 12 months prior to enrollment were assigned, in a hierarchical manner, to 3 mutually exclusive alcohol consumption categories: (1) alcohol-related diagnosis, defined by an *ICD-9* diagnosis for alcohol dependence/abuse recorded between 12 months before and 6 months after VACS enrollment; (2) hazardous or binge drinking in those without an alcohol-related diagnosis, defined as an AUDIT-C score ≥4 or report of consumption of ≥6 drinks on any 1 occasion in the past year; and (3) nonhazardous drinking, defined as an AUDIT-C score <4 [37–39].

Demographic and Clinical Data

Demographic data collected at VACS enrollment included age, sex, and race/ethnicity. Clinical data collected between 12 months before and 6 months after enrollment included BMI, chronic HCV infection (detectable HCV RNA); active hepatitis B virus (HBV) infection (positive HBV surface antigen and/or detectable HBV DNA); history of other chronic liver diseases (*ICD-9* diagnosis of nonalcoholic fatty liver disease, autoimmune hepatitis, primary biliary cirrhosis, α-1 antitrypsin deficiency, or Wilson disease); diabetes mellitus (random glucose ≥200 mg/dL, diabetes *ICD-9* diagnosis, or antidiabetic medication use [44, 45]); HIV-related data (CD4 count; HIV RNA level; use of antiretroviral therapy [ART], defined as at least 3 antiretrovirals from 2 different classes [46]; and ART regimen); ALT; AST; and platelet count. Laboratory results measured closest to but between 12 months before and 6 months after enrollment were used in analyses. We evaluated for the presence of hepatic decompensation at VACS enrollment as previously described [47].

Statistical Analysis

Differences in characteristics by HIV and chronic HCV status were assessed using χ^2 tests for categorical data and *t* tests or Wilcoxon rank-sum tests, as appropriate, for continuous data. We determined differences in the prevalence of outcomes for each category of alcohol use, by HIV and chronic HCV status. Next, we used logistic regression to determine the adjusted odds ratio (OR) and 95% confidence interval (CI) of advanced hepatic fibrosis associated with alcohol use categories, stratified by HIV status. Models were adjusted for sex, race, BMI, diabetes, HBV infection, chronic HCV, and CD4 count and HIV RNA level (HIV-infected stratum). We did not control for age because age is a component of the FIB-4 index.

We then evaluated the prevalence of advanced fibrosis for each alcohol use category among HIV/HCV-coinfected, HIV-monoinfected, HCV-monoinfected, and HIV/HCV-uninfected participants. We determined adjusted ORs of advanced hepatic fibrosis associated with the alcohol use categories in these 4 groups. Associations were assessed with a 12-level HIV/HCV and alcohol use category variable (4 HIV/HCV groups × 3 alcohol levels). HIV/HCV-uninfected nonhazardous drinkers served as the reference group for all comparisons. Analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Participant Characteristics

Among the 7270 participants enrolled in VACS through September 2010, 4611 (63%; 2311 HIV-infected vs 2300 HIV-uninfected; $P = .7$) reported alcohol consumption within the 12 months prior to enrollment, and 5784 (80%; 3312 HIV-infected vs 2472 HIV-uninfected; $P < .001$) had laboratory data available to calculate FIB-4. The final study sample included 3565 current drinkers with available FIB-4 data (701 HIV/HCV-coinfected; 1410 HIV-monoinfected; 296 HCV-monoinfected; 1158 HIV/HCV-uninfected), of whom 1479 (41.5%) met criteria for nonhazardous drinking, 1232 (34.6%) for hazardous/binge drinking, and 854 (24.0%) for an alcohol-related diagnosis (Table 1). Compared with those excluded due to lack of FIB-4 data, patients included in the study sample were older; more commonly black, Hispanic, and infected with HIV or viral hepatitis; and less frequently obese (BMI > 30 kg/m^2). The groups were similar for all other characteristics listed in Table 1.

Compared to HIV-uninfected persons, those with HIV were younger (median, 48 vs 50 years), more commonly black (66.2% vs 62.4%), and more frequently infected with HBV (4.3% vs

Table 1. Characteristics of Participants Reporting Alcohol Use at Enrollment in the Veterans Aging Cohort Study, Overall and by HIV/Chronic Hepatitis C Virus Status

Characteristic	Overall (N = 3565)	HIV/HCV-Coinfected (n = 701)	HIV-Monoinfected (n = 1410)	HCV-Monoinfected (n = 296)	HIV/HCV-Uninfected (n = 1158)
Age, median (IQR)	49 (43–55)	50 (47–54)	47 (41–54)	51 (47–54)	50 (44–56)
Age ≥50 y	1706 (47.9)	382 (54.5)	553 (39.2)	159 (53.7)	612 (52.8)
Male sex	3439 (96.5)	687 (98.0)	1372 (97.3)	285 (96.3)	1095 (94.6)
Race/ethnicity					
White	764 (21.4)	81 (11.6)	364 (25.8)	31 (10.5)	288 (24.9)
Black	2305 (64.7)	529 (75.5)	869 (61.6)	222 (75.0)	685 (59.2)
Hispanic	364 (10.2)	62 (8.8)	127 (9.0)	36 (12.2)	139 (12.0)
Other	132 (3.7)	29 (4.1)	50 (3.5)	7 (2.4)	46 (4.0)
Alcohol category					
Nonhazardous	1479 (41.5)	242 (34.5)	719 (51.0)	60 (20.3)	458 (39.6)
Hazardous or binge	1232 (34.6)	249 (35.5)	512 (36.3)	70 (23.6)	401 (34.6)
Alcohol-related diagnosis	854 (24.0)	210 (30.0)	179 (12.7)	166 (56.1)	299 (25.8)
Hepatitis B virus infection[a]	117 (3.3)	37 (5.3)	54 (3.8)	13 (4.4)	13 (1.1)
Hepatitis C virus infection[b]	997 (28.0)	701 (100.0)	0 (0.0)	296 (100.0)	0 (0.0)
Hepatitis C RNA					
<400 000 IU/mL and/or <1 000 000 copies/mL		55 (7.8)		20 (6.8)	
≥400 000 IU/mL and/or ≥1 000 000 copies/mL		204 (29.1)		56 (18.9)	
Qualitative HCV RNA result only		442 (63.1)		220 (74.3)	
Other chronic liver disease	32 (0.9)	12 (1.7)	6 (0.4)	9 (3.0)	5 (0.4)
Diabetes mellitus	469 (13.2)	86 (12.3)	138 (9.8)	49 (16.6)	196 (16.9)
Body mass index					
Median (IQR)	26 (23–30)	24 (22–27)	25 (22–28)	26 (23–30)	29 (26–33)
≥30 kg/m^2	844 (23.7)	87 (12.4)	210 (14.9)	73 (24.7)	474 (40.9)
HIV RNA, log copies/mL, median (IQR)		2.8 (1.9–4.3)	2.9 (1.9–4.2)		
HIV RNA ≤400 copies/mL		336 (47.9)	624 (44.3)		
CD4 cell count, cells/μL, median (IQR)		345 (194–515)	375 (228–564)		
CD4 cell count					
<200 cells/μL		181 (25.8)	302 (21.4)		
200–500 cells/μL		333 (47.5)	656 (46.5)		
>500 cells/μL		187 (26.7)	452 (32.1)		
On antiretroviral therapy		578 (82.5)	1165 (82.6)		
Protease inhibitor		330 (47.1)	608 (43.1)		
Nonnucleoside reverse transcriptase inhibitor		221 (31.5)	525 (37.2)		
Nucleos(t)ide reverse transcriptase inhibitor		569 (81.2)	1157 (82.1)		

Data are presented as No. (%) unless otherwise specified.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; IU, international units.

[a] Defined by positive hepatitis B surface antigen and/or detectable hepatitis B virus DNA.

[b] Defined by detectable hepatitis C virus RNA.

1.8%) or chronic HCV (30.6% vs 18.9%), but less commonly had diabetes mellitus (10.6% vs 16.9%) or obesity (14.1% vs 37.6%). Twenty-three percent of HIV-infected patients had a CD4 count <200 cells/μL, and 83% received ART. As alcohol use category increased, the mean CD4 count decreased (nonhazardous: 417 cells/μL; hazardous/binge: 402 cells/μL; alcohol-related diagnosis: 384 cells/μL; test for trend, $P = .04$) and mean HIV RNA level increased (nonhazardous: 3.1 log

copies/mL; hazardous/binge: 3.2 log copies/mL; alcohol-related diagnosis: 3.3 copies/L; test for trend, $P = .01$).

Advanced Hepatic Fibrosis, by HIV and Chronic HCV Status

Overall, 271 (7.6%) participants had advanced hepatic fibrosis (FIB-4 >3.25). Advanced fibrosis was more prevalent among HIV-infected than -uninfected (210 [9.9%] vs 61 [4.2%]; $P < .001$) and chronic HCV-infected than -uninfected (182 [18.3%] vs 89 [3.5%]; $P < .001$) patients. Among HIV-infected and -uninfected (Table 2) and chronic HCV-infected and -uninfected (Table 2) participants, the prevalence of advanced hepatic fibrosis increased as the category of alcohol use increased, with the lowest prevalence among nonhazardous drinkers, an increased prevalence among participants who reported hazardous/binge drinking, and the highest prevalence among those with an alcohol-related diagnosis. For each category of alcohol use, HIV-infected (Table 2) or chronic HCV-infected (Table 2) patients more commonly had advanced hepatic fibrosis than uninfected patients. Similar patterns were observed for significant liver fibrosis, hepatic inflammation, and hepatic decompensation (Table 2).

In multivariable analyses, category of alcohol use remained independently associated with advanced hepatic fibrosis in HIV-infected ($P = .001$) and -uninfected ($P = .003$) persons (Table 3). Results were similar when the outcome was significant liver fibrosis (APRI >1.5; Supplementary Appendix 1).

The prevalence of advanced hepatic fibrosis increased with higher alcohol use category among HIV/HCV-coinfected, HIV-monoinfected, HCV-monoinfected, and HIV/HCV-uninfected patients (Figure 1). For each alcohol use category, the prevalence of advanced hepatic fibrosis was highest among HIV/HCV-coinfected participants. In multivariable analysis, the ORs of advanced hepatic fibrosis increased with greater severity of alcohol use categories within each of the 4 groups (Figure 2; Supplementary Appendix 2). The strongest associations with advanced hepatic fibrosis were observed among HIV/HCV-coinfected patients with nonhazardous drinking (OR, 14.2; 95% CI, 5.91–34.0), hazardous/binge drinking (OR, 18.9; 95% CI, 7.98–44.8), and alcohol-related diagnoses (OR, 25.2; 95% CI, 10.6–59.7) compared with uninfected nonhazardous drinkers.

Table 2. Prevalence of Hepatic Outcomes of Interest for Specified Alcohol Use Categories, by HIV and Chronic Hepatitis C Virus Infection Status, Among Patients Reporting Current Alcohol Use at Enrollment in the Veterans Aging Cohort Study (N = 3565)

			Markers of Advanced Hepatic Fibrosis[a,b]		Markers of Significant Liver Fibrosis[a,b]		Markers of Hepatic Inflammation[a,b]		Hepatic Decompensation[b,c]	
	No. at Risk		(FIB-4 >3.25)		(APRI >1.5)		(ALT or AST >40 U/L)			
Outcome	HIV$^-$	HIV$^+$	HIV$^-$	HIV$^+$	HIV$^-$	HIV$^+$	HIV$^-$	HIV$^+$	HIV$^-$	HIV$^+$
Prevalence of hepatic outcomes by HIV status										
Overall	1454	2111	61 (4.2)	210 (9.9)	51 (3.5)	168 (8.0)	480 (33.0)	908 (43.0)	11 (0.8)	34 (1.6)
Alcohol use category										
Nonhazardous	518	961	7 (1.4)	64 (6.7)	0 (0.0)	47 (4.9)	141 (27.2)	354 (36.8)	0 (0.0)	11 (1.1)
Hazardous or binge	471	761	14 (3.0)	72 (9.5)	11 (2.3)	57 (7.5)	156 (33.1)	318 (41.8)	2 (0.4)	8 (1.1)
Alcohol-related diagnosis	465	389	40 (8.6)	74 (19.0)	40 (8.6)	64 (16.5)	183 (39.4)	236 (60.7)	9 (1.9)	15 (3.9)
χ^2 test for trend P value			<.001	<.001	<.001	<.001	<.001	<.001	<.001	.002
	HCV$^-$	HCV$^+$	HCV$^-$	HCV$^+$	HCV$^-$	HCV$^+$	HCV$^-$	HCV$^+$	HCV$^-$	HCV$^+$
Prevalence of hepatic outcomes by chronic HCV status										
Overall	2568	997	89 (3.5)	182 (18.3)	55 (2.1)	164 (16.4)	686 (26.7)	702 (70.4)	18 (0.7)	27 (2.7)
Alcohol use category										
Nonhazardous	1177	302	30 (2.5)	41 (13.6)	14 (1.2)	33 (10.9)	293 (24.9)	202 (66.9)	7 (0.6)	4 (1.3)
Hazardous or binge	913	319	28 (3.1)	58 (18.2)	18 (2.0)	50 (15.7)	248 (27.2)	226 (70.8)	3 (0.3)	7 (2.2)
Alcohol-related diagnosis	478	376	31 (6.5)	83 (22.1)	23 (4.8)	81 (21.5)	145 (30.3)	274 (72.9)	8 (1.7)	16 (4.3)
χ^2 for trend P value			<.001	.005	<.001	<.001	.022	.093	.065	.018

Data are presented as No. (%) unless otherwise specified.

Abbreviations: ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a] χ^2 test for effect of HIV infection within alcohol category; $P < .01$.

[b] χ^2 test for effect of chronic HCV infection within alcohol category; $P < .01$.

[c] χ^2 test for effect of HIV infection within alcohol category; $P = .025$.

Table 3. Evaluation of the Association Between Alcohol Use Categories and Advanced Hepatic Fibrosis (Defined by FIB-4 Index >3.25), Controlling for Specified Variables, Among HIV-Infected and -Uninfected Patients Reporting Current Alcohol Use at Enrollment in the Veterans Aging Cohort Study (N = 3565)

	HIV-Infected (n = 2111)				HIV-Uninfected (n = 1454)			
	FIB-4 >3.25		Adjusted Odds Ratio[a]		FIB-4 >3.25		Adjusted Odds Ratio[b]	
Characteristic	No.	(%)		(95% CI)	No.	(%)		(95% CI)
Alcohol use category								
Nonhazardous	64	(6.7)	Ref.		7	(1.4)	Ref.	
Hazardous or binge	72	(9.5)	1.26	(.87–1.82)	14	(3.0)	1.98	(.78–5.04)
Alcohol-related diagnosis	74	(19.0)	2.05	(1.39–3.02)	40	(8.6)	4.00	(1.70–9.41)
Sex								
Men	207	(10.1)	Ref.		59	(4.3)	Ref.	
Women	3	(5.8)	0.58	(.17–2.01)	2	(2.7)	.86	(.19–3.93)
Race/ethnicity								
White	31	(7.0)	Ref.		8	(2.5)	Ref.	
Black	148	(10.6)	0.88	(.57–1.36)	39	(4.3)	1.08	(.48–2.84)
Hispanic	25	(13.2)	1.47	(.81–2.67)	11	(6.3)	2.07	(.78–5.52)
Other	6	(7.6)	0.72	(.27–1.88)	3	(5.7)	2.07	(.48–9.04)
Diabetes								
No	182	(9.6)	Ref.		52	(4.3)	Ref.	
Yes	28	(12.5)	1.39	(.88–2.20)	9	(3.7)	0.96	(.45–2.05)
Body mass index, kg/m^2								
<30	187	(10.3)	Ref.		48	(5.3)	Ref.	
≥30	23	(7.7)	0.89	(.55–1.45)	13	(2.4)	0.69	(.36–1.33)
HBV infection[c]								
No	193	(9.6)	Ref.		54	(3.8)	Ref.	
Yes	17	(18.7)	1.72	(.94–3.14)	7	(26.9)	4.13	(1.53–11.16)
Chronic HCV infection[d]								
No	80	(5.5)	Ref.		26	(2.2)	Ref.	
Yes	146	(20.8)	5.03	(3.62–6.97)	36	(12.2)	4.37	(2.50–7.64)
CD4 cell count, cells/μL								
≥200	121	(7.4)	Ref.					
<200	89	(18.4)	2.46	(1.78–3.40)				
HIV RNA, copies/mL								
<400	77	(8.0)	Ref.					
≥400	133	(11.5)	1.37	(.99–1.89)				

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a] Adjusted odds ratios for HIV-infected patients were determined using a multivariable logistic regression model that included terms for alcohol use category, sex, race/ethnicity, diabetes mellitus, body mass index, HBV infection status, chronic HCV infection status, CD4 cell count, and HIV RNA level at the time of enrollment in the Veterans Aging Cohort Study.

[b] Adjusted odds ratios for HIV-uninfected patients were determined using a multivariable logistic regression model that included terms for alcohol use category, sex, race/ethnicity, diabetes mellitus, body mass index, HBV infection status, and chronic HCV infection status at the time of enrollment in the Veterans Aging Cohort Study.

[c] Defined by positive hepatitis B surface antigen and/or detectable HBV DNA.

[d] Defined by detectable HCV RNA.

DISCUSSION

Our study found that advanced hepatic fibrosis by FIB-4 was present at low levels of alcohol consumption across groups stratified by HIV/HCV status. For each alcohol use category, advanced hepatic fibrosis was more common among HIV-infected than -uninfected and chronic HCV-infected than -uninfected patients. In addition, increasing categories of alcohol use were associated with a higher prevalence of advanced hepatic fibrosis among HIV/HCV-coinfected, HCV-monoinfected, HIV-monoinfected, and HIV/HCV-uninfected persons. Alcohol use category remained independently associated with

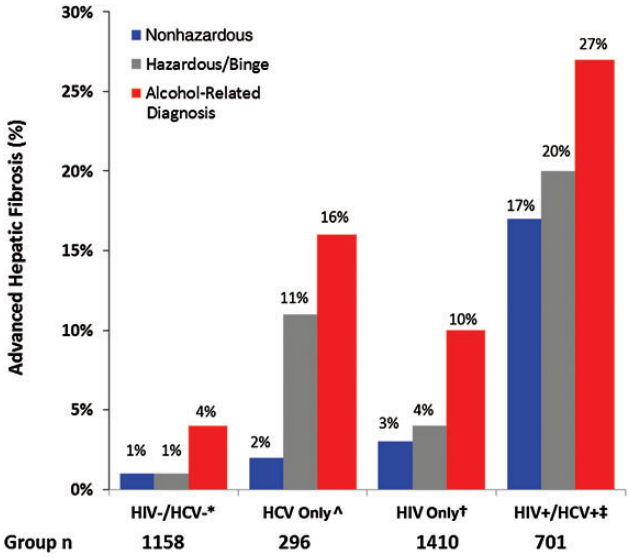

Figure 1. Prevalence of advanced hepatic fibrosis (defined by FIB-4 index >3.25) according to category of alcohol use (ie, nonhazardous drinking, hazardous or binge drinking, alcohol-related diagnosis), by human immunodeficiency virus (HIV) and chronic hepatitis C virus (HCV) infection status, in patients reporting current alcohol use at enrollment in the Veterans Aging Cohort Study (N = 3565). *χ^2 test for trend over categories of alcohol use for HIV/HCV-uninfected, $P = .019$. ^χ^2 test for trend over categories of alcohol use for HCV-monoinfected, $P < .001$. †χ^2test for trend over categories of alcohol use for HIV-monoinfected, $P = .0025$. ‡χ^2 test for trend over categories of alcohol use for HIV/HCV-coinfected, $P = .060$.

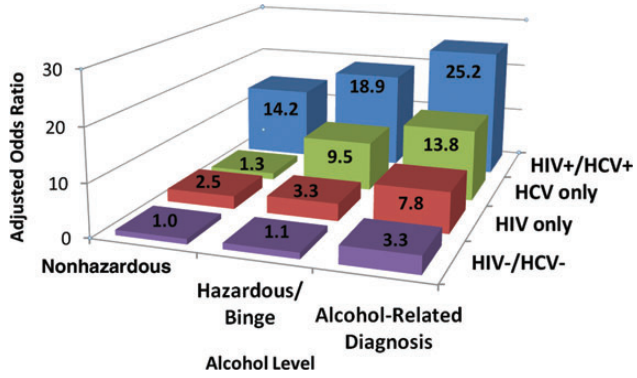

Figure 2. Odds ratio of advanced hepatic fibrosis (defined by FIB-4 index >3.25) for category of alcohol use (ie, nonhazardous drinking, hazardous or binge drinking, alcohol-related diagnosis), by human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection status, in patients reporting current alcohol use at enrollment in the Veterans Aging Cohort Study (N = 3565). Model adjusted for hepatitis B virus infection. Reference category is HIV/HCV-uninfected nonhazardous drinkers.

advanced hepatic fibrosis in both HIV-infected and -uninfected persons. Finally, when we evaluated associations between alcohol use categories and advanced hepatic fibrosis across groups stratified by HIV/HCV status, the strongest associations were observed among those with HIV/HCV coinfection. These results provide new data that suggest that there is a stepwise increased risk of advanced liver fibrosis with greater severity of alcohol use. They also demonstrate that all alcohol use categories are strongly associated with advanced hepatic fibrosis in HIV/HCV-coinfected patients.

The reasons for the higher prevalence of advanced hepatic fibrosis at each category of alcohol use among HIV-infected or chronic HCV-infected patients compared to uninfected persons remain unclear. In vitro data have demonstrated that HIV and HCV can each induce hepatocyte apoptosis [48], and the addition of alcohol may accelerate this process. Moreover, the hepatic inflammation and fibrosis induced by alcohol may be additive in the setting of HIV-associated immune dysfunction/dysregulation and HCV-related liver inflammation [49–51]. Alternatively, the hepatotoxicity of antiretroviral and nonantiretroviral drugs may be exacerbated by alcohol consumption in the setting of HIV or chronic HCV infection [52]. Future studies should evaluate the mechanisms by which alcohol contributes to liver disease progression in HIV-monoinfected, HCV-monoinfected, and HIV/HCV-coinfected patients.

Our results have several clinical implications. First, the 3-item AUDIT-C questionnaire could be administered by HIV practitioners during routine practice to ascertain and categorize patients' alcohol consumption [38]. Knowledge of the alcohol use category and its potential effects on various organ systems, such as the liver, might motivate patients to reduce or discontinue alcohol consumption. Second, given the strong associations between all alcohol use categories and advanced hepatic fibrosis among HIV/HCV-coinfected patients, clinicians should particularly counsel these patients to decrease their alcohol use, even with low levels of consumption. Finally, any patient with a FIB-4 >3.25 should be counseled to reduce or avoid alcohol consumption.

Our results extend the observations of 2 prior studies examining the relationship between alcohol consumption and advanced liver fibrosis in HIV-infected patients. Chaudhry et al [6] conducted a cross-sectional study within the Johns Hopkins HIV Clinical Cohort and observed that hazardous drinking was associated with an APRI >1.5 in HIV-monoinfected, but not HIV/HCV-coinfected, patients. Fuster et al [53] performed a cross-sectional analysis among HIV-infected patients with current or past alcohol problems enrolled in the HIV-Longitudinal Interrelationships of Viruses and Ethanol (HIV-LIVE) study. No association was observed between lifetime alcohol use and either FIB-4 >3.25 or APRI >1.5, regardless of HCV status. Differences in the way that alcohol use was categorized and the smaller samples of patients who reported alcohol consumption in those studies might account for the disparate results. Neither

study included HIV-uninfected patients, as was done in the present analysis.

Our study has several potential limitations. First, because cross-sectional studies evaluate exposure and disease status simultaneously, our analysis is limited in its ability to determine whether alcohol use category preceded or resulted from advanced hepatic fibrosis. Being informed about the presence of hepatic fibrosis, either through invasive or noninvasive modalities, may prompt patients to decrease or cease alcohol consumption. Because of this phenomenon of sick abstainers, we chose to exclude participants who did not report current alcohol use. Among current drinkers, reverse causality seems less likely. The cross-sectional design also did not permit us to evaluate changes in hepatic outcomes over time.

Second, we cannot exclude the possibility that some individuals were misclassified by FIB-4 due to conditions that can decrease the platelet count or that transiently increase liver aminotransferase levels. However, FIB-4 has been validated to identify advanced hepatic fibrosis among individuals with alcoholic liver disease [13], viral hepatitis [14–17], and HIV/viral hepatitis coinfection [18]. Further, we conducted parallel analyses evaluating APRI, liver inflammation, and hepatic decompensation and observed consistent results and relationships. Hepatic fibrosis would ideally be assessed with liver biopsy, but the acceptability, cost, and risk of liver biopsy in large cohorts of patients make such a study impractical. Further, liver biopsy itself is an imperfect measure as it is subject to sampling error and interobserver variability in histological assessment [54, 55]. Future studies could use other noninvasive modalities, such as transient elastography, to assess the degree of hepatic fibrosis [56].

Third, as with any observational study, there is the possibility of residual confounding. We were unable to account for lifetime history of alcohol consumption [57], but such measures are currently unable to classify patterns of alcohol use [58]. We also did not have durations of HIV or HCV infections and did not collect all potential hepatotoxic medications.

Finally, our study sample was predominantly comprised of male US veterans of black race, potentially limiting the generalizability of our results. Because liver fibrosis progression may differ by sex and race [59–61], future epidemiologic analyses should evaluate the relations between alcohol use categories and hepatic outcomes among women and persons of other races.

In summary, our findings suggest that increased category of alcohol use is associated with a correspondingly higher risk of advanced hepatic fibrosis. In addition, for each category of alcohol use, advanced hepatic fibrosis was more common among persons infected with HIV or chronic HCV than among uninfected individuals. Strong associations between all categories of alcohol use and advanced hepatic fibrosis were observed among HIV/HCV-coinfected patients. Future longitudinal studies should evaluate the mechanisms for the increased liver injury associated with alcohol consumption in the setting of HIV and chronic HCV infection and characterize the impact of nonhazardous alcohol consumption and binge drinking on liver fibrosis progression over time to help determine whether there is a safe level of alcohol exposure.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. The contents of this article do not represent the views of the Department of Veterans Affairs, the US Food and Drug Administration, or the United States government.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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