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## The Role of Current and Historical Alcohol Use in Hepatic Fibrosis Among HIV-infected Individuals

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### Abstract

We examined risk factors for advanced hepatic fibrosis (FIB-4 >3.25) including both current alcohol use and a diagnosis of alcohol use disorder among HIV-infected patients. Of the 12,849 patients in our study, 2,133 (17%) reported current hazardous drinking by AUDIT-C, 2,321 (18%) had a diagnosis of alcohol use disorder, 2,376 (18%) were co-infected with chronic hepatitis C (HCV); 596 (5%) had high FIB-4 scores >3.25 as did 364 (15%) of HIV/HCV coinfecting patients. In multivariable analysis, HCV (aOR 6.3, 95% CI 5.2–7.5), chronic hepatitis B (aOR 2.0, 95% CI 1.5–2.8), diabetes (aOR 2.3, 95% CI 1.8–2.9), current CD4 <200 cells/mm<sup>3</sup> (aOR 5.4, 95% CI

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#### Compliance with Ethical Standards:

Conflict of Interest: JJE has received grant support from ViiV Healthcare, Gilead Sciences, BMS and Janssen; he is a consultant for ViiV Healthcare, Gilead, BMS, Janssen and Merck. MS has received grant support from BMS, ViiV, Merck, Gilead, BMS Abbvie and Janssen; he is a consultant for Merck, Gilead and BMS. The remaining authors declare that they have no conflict of interest. This article does not contain any studies with animals performed by any of the authors. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent to participate in CNICS was obtained from all individual participants included in the study.

4.2–6.9) and HIV RNA >500 copies/mL (aOR 1.3, 95% CI 1.0–1.6) were significantly associated with advanced fibrosis. A diagnosis of an alcohol use disorder (aOR 1.9, 95% CI 1.6–2.3) rather than report of current hazardous alcohol use was associated with high FIB-4. However, among HIV/HCV coinfecting patients, both current hazardous drinkers (aOR 1.6, 95% CI 1.1–2.4) and current non-drinkers (aOR 1.6, 95% CI 1.2–2.0) were more likely than non-hazardous drinkers to have high FIB-4, with the latter potentially reflecting the impact of sick abstainers. These findings highlight the importance of using a longitudinal measure of alcohol exposure when evaluating the impact of alcohol on liver disease and associated outcomes.

## Keywords

HIV; liver fibrosis; alcohol; CNICS

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## Introduction

Decompensated liver disease has been a major cause of non-AIDS-related death among HIV-infected persons since the advent of combination antiretroviral therapy (1). While the contribution of chronic viral hepatitis to liver-related morbidity and mortality has been well established (1, 2), less is known about the impact of alcohol use on liver disease progression, relative to other known risk factors such as viral hepatitis or immune suppression in HIV-infected patients (3). Variability in definitions of alcohol use, outcome measurement and study populations in previous reports may have contributed to inconsistent findings (4–7). Understanding the relative influence of alcohol use, both current and historical, on the natural history of liver disease is essential given that it remains one of the more prevalent modifiable factors.

Due to the invasive nature and limitations of biopsy (8), noninvasive markers have been useful in determining advanced fibrosis in population-based studies. The Fibrosis-4 (FIB-4) index, derived from age, liver aminotransferases and platelet count, is more widely available than biopsy, and has been shown to predict liver-related events and death in patients with chronic hepatitis C virus infection (HCV), HIV and HIV/HCV co-infection (9–12).

In a large cohort of HIV-infected patients receiving care across the US, we sought to define the impact of current and historical alcohol use on hepatic fibrosis as measured by FIB-4 in the context of other comorbidities including viral hepatitis, diabetes and HIV disease markers. Accounting for other factors, we examined the effect of current alcohol use, measured systematically across sites using standardized clinical assessments, as well as a clinician-documented diagnosis of an alcohol use disorder on the development of advanced hepatic fibrosis.

## Methods

The Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) data repository captures comprehensive clinical data that include standardized diagnosis, medication, laboratory, and demographic information collected through electronic medical records and other institutional data systems at each site (13). Data are updated quarterly and

undergo extensive quality assurance procedures prior to data transmission, at the time of submission, and during integration into the CNICS repository (<http://www.uab.edu/cnics>). Additionally, patients complete standardized clinical assessments as part of routine clinical care that include questions on adherence and substance use in English or Spanish using touch-screen tablets (14). We conducted a cross-sectional study at seven clinical sites in the CNICS cohort among all patients who completed at least one clinical assessment from September 2005 to September 2015 and had at least one set of laboratory measurements available to calculate FIB-4. Institutional review boards at each site approved the study protocol.

Current alcohol use was assessed using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire (15). The AUDIT-C is collected as part of self-administered standardized clinical assessments which were introduced into routine care at CNICS sites at varying time points between 2007 and 2015. For the main analysis, we used data from the most recent clinical assessment for each patient. We defined current hazardous drinking as an AUDIT-C score  $\geq 5$  for men,  $\geq 4$  for women and categorized patients into current non-drinkers, non-hazardous drinkers and hazardous drinkers (16). Patients who had a diagnosis of alcohol abuse or dependence recorded by the treating clinician any time prior to the assessment date were classified as having an alcohol use disorder using a modified list of International Classification of Diseases, Ninth Revision diagnostic codes (291.x, 303.x and 305.0), which have been shown to be moderately sensitive and highly specific for alcohol use disorders (17, 18). The period of observation over which individuals could have an alcohol use disorder (AUD) diagnosis assigned was a median of 6 years and median of 23 encounters (5 and 85 encounters for 5<sup>th</sup> and 95<sup>th</sup> percentiles). We defined chronic HCV infection as ever having detectable HCV RNA or positive HCV antibody test and chronic hepatitis B (HBV) as the presence of detectable HBV DNA or positive HBV surface antigen before the assessment. Diabetes mellitus was defined as a diagnosis of diabetes mellitus recorded by the treating clinician and use of diabetes-related medication, or use of diabetes-specific medication, or a hemoglobin A1C  $\geq 6.5\%$  (19). Body mass index (BMI) was defined as underweight ( $<18.5$  kg/m<sup>2</sup>), normal range (18.5 to  $<25$  kg/m<sup>2</sup>), overweight (25–29 kg/m<sup>2</sup>) and obese ( $\geq 30$  kg/m<sup>2</sup>). Current CD4 cell count and plasma HIV RNA level (“viral load” [VL]) were the values closest to the date of the assessment. CD4 count was categorized as  $\geq 500$ , 200–499,  $<200$  cells/mm<sup>3</sup>, and undetectable (VL  $<500$  copies/mL) vs. detectable VL was a measure of effective ART.

We computed FIB-4 index according to the formula:  $(\text{age [years]} \times \text{AST [IU/L]}) / (\text{platelets [10}^9\text{/L]} \times (\text{ALT [IU/L]})^{1/2})$  (20) using the ALT, AST and platelet count closest to the assessment date. We defined high FIB-4 as a score exceeding 3.25, a threshold validated in other settings and predictive not only of advanced fibrosis, but of liver-related outcomes and overall mortality (9–11, 20–22).

We used  $\chi^2$  tests to examine bivariate associations and multivariable logistic regression to determine factors associated with advanced fibrosis by FIB-4 including chronic HCV, chronic HBV, current alcohol use, diagnosis of alcohol use disorder, diabetes, current CD4 count, current VL, sex and race. We did not include risk factor for HIV transmission in the model because of collinearity between injection drug use (IDU) and HCV, nor age as a

separate variable because it is a component of the FIB-4 index. BMI was not associated with FIB-4 and therefore omitted from the final model. We explored the possibility of effect modification of HCV status on FIB-4 by alcohol by (1) performing the analysis using different levels of alcohol use and (2) including an interaction term in the model. We evaluated our model stratified by HCV status and conducted sensitivity analyses that evaluated the maximum AUDIT-C score across multiple measurements per individual if more than one assessment was available. All analyses were performed using Stata 13 (College Station, TX).

## Results

Of the 13,386 patients in care from September 2005 to September 2015 at the seven CNICS sites that participated in clinical assessments, 12,849 individuals completed at least one assessment and had at least one set of lab measurements available to compute FIB-4. Study subjects were mostly men (83%) with a median age of 47 years, 47% were white, 35% were black, 11% had a current CD4 count  $<200$  cells/mm<sup>3</sup>, and 84% had a current VL  $<500$  copies/ml (Table 1). The study cohort was similar in baseline characteristics (age, sex, race, HCV co-infection and alcohol use disorder) to the overall cohort.

Of these, 3459 patients (27%) had FIB-4 indices  $>1.45$  indicative of at least moderate fibrosis (20) and 596 (5%) had a high FIB-4 score  $>3.25$  indicating advanced fibrosis. The majority (61%) of patients with high FIB-4 were HCV co-infected; 12% were HBV co-infected, 21% had diabetes mellitus, and 39% had a diagnosis of an alcohol use disorder.

Thirty-six percent of the study population identified themselves as current non-drinkers, 47% as current non-hazardous drinkers, and 17% as current hazardous drinkers by AUDIT-C scores. Eighteen percent of patients had a diagnosis of an alcohol use disorder with a greater proportion among HCV co-infected than HIV mono-infected patients (32% versus 15%,  $p<0.001$ ). Current hazardous drinking was more prevalent among patients with a diagnosis of alcohol use disorder than those without (30% vs. 14%,  $p<0.001$ ). However, patients with chronic HCV were more likely to report that they were currently not drinking than those without HCV (51% vs. 33%,  $p<0.001$ ).

In bivariate analysis, black race, chronic HCV, chronic HBV, diabetes, current CD4 count and current VL were associated with high FIB-4 while sex was not. Patients with a diagnosis of an alcohol use disorder were significantly more likely to have advanced fibrosis than those without a diagnosis (9.9% versus 3.5%,  $p<0.001$ ). There was no difference in the proportion of patients with high FIB-4 among those who reported current hazardous drinking compared with those who did not (4.7% versus 4.6%,  $p=0.90$ ). However, when we evaluated current alcohol use separating non-drinkers from non-hazardous drinkers, non-drinkers had just over 2-fold greater odds ( $p<0.001$ ) and hazardous drinkers a 1.5-fold greater odds ( $p=0.002$ ) compared with non-hazardous drinkers for high FIB-4. Notably, the relationship between FIB-4 and AUDIT-C examined as a continuous variable was not linear, but demonstrated a J-curve reflecting higher risk among current non-drinkers compared with non-hazardous drinkers for elevated FIB-4. The prevalence of alcohol use disorder (19% versus 13%,  $p<0.001$ ) and HCV infection (26% versus 14%,  $p<0.001$ ) was greater among

non-drinkers compared with non-hazardous drinkers potentially highlighting the significant number of current non-drinkers who had a prior history of extensive alcohol use and then stopped drinking.

In a multivariable model that included sex, race and both current alcohol use as well as an alcohol diagnosis among the overall study cohort (Table 2), we found that HCV infection (adjusted odds ratio [aOR] 6.3, 95% confidence interval [CI] 5.2–7.5), HBV infection (aOR 2.0, 95% CI 1.5–2.8), diabetes (aOR 2.3, 95% CI 1.8–2.9), current CD4 <200 cells/mm<sup>3</sup> (aOR 5.4, 95% CI 4.2–6.9) and current VL >500 copies/mL (aOR 1.3, 95% CI 1.0–1.6) were significantly associated with advanced fibrosis by FIB-4. In addition, a diagnosis of an alcohol use disorder was independently associated with high FIB-4 (aOR 1.9, 95% CI 1.6–2.3).

Current hazardous alcohol use compared with non-hazardous use was not associated with high FIB-4, but current non-drinking was independently associated with elevated FIB-4 in the overall cohort (aOR 1.3, 95% CI 1.1–1.6). However, when we stratified our model by HCV status (Table 3), neither current non-drinking nor current hazardous drinking were associated with high FIB-4 in HIV mono-infected patients while all of the aforementioned factors remained independently associated with high FIB-4 with the exception of black race (aOR 0.7, 95% CI 0.5–0.9). In contrast, among HIV/HCV coinfecting patients, both non-drinkers and hazardous drinkers had a greater risk of high FIB-4 (aOR 1.6, 95% CI 1.2–2.0 and aOR 1.6, 95% CI 1.1–2.4 respectively). There was no association between FIB-4 and hepatitis B or HIV VL among coinfecting patients possibly due to fewer individuals in those categories. Neither a history of an alcohol use disorder nor current alcohol use modified the effect of chronic HCV on FIB-4 (data not shown).

In sensitivity analyses, we examined all available AUDIT-C scores (69% of our cohort had at least two or more clinical assessments although 67% of these occurred during 2 years of follow-up) using the maximum AUDIT-C score, and again found no association between FIB-4 and current hazardous alcohol use as compared with non-hazardous use, and this lack of association was seen even among HIV-HCV coinfecting patients. Current non-drinking and all other covariates remained independently associated with high FIB-4 including alcohol use disorder (data not shown).

## Discussion

In our contemporary multi-site study of 12,849 HIV-infected patients in routine care, 596 (5%) had a high FIB-4 score >3.25 indicating advanced fibrosis. Over half (61%) of patients with high FIB-4 were HCV co-infected; 12% were HBV co-infected, 21% had diabetes mellitus, and 39% had a diagnosis of alcohol use disorder. Past and current alcohol use was prevalent in our cohort. A diagnosis of alcohol use disorder was independently associated with advanced hepatic fibrosis among both HIV-monoinfected and HIV/HCV coinfecting patients. However current hazardous alcohol use was not associated with high FIB-4 in the overall cohort, even when we evaluated all available AUDIT-C scores. We found the association of current hazardous use and high FIB-4 only in HIV/HCV coinfecting patients but not when all available AUDIT-C values were accounted for, suggesting that the link

between the most recent FIB-4 elevation and current hazardous drinking may reflect acute, transient alcohol-related injury rather than hepatic fibrosis per se. Notably, neither alcohol use disorder nor current alcohol use appeared to modify the effect of HCV on FIB-4.

While assessment of current alcohol use remains important in clinical care, our findings suggest that a diagnosis of an alcohol use disorder, which appears to capture more prolonged and severe exposure, may be a more specific marker for the cumulative use of alcohol harmful enough to promote hepatic fibrosis. Our findings suggest that we should go beyond a “snapshot” assessment of alcohol use and strive for a longitudinal or cumulative measure of alcohol exposure when evaluating patients and their risk of hepatic fibrosis. Indeed, HIV/HCV coinfecting patients who were current non-drinkers appeared to have a greater risk of advanced fibrosis compared with current non-hazardous drinkers. Others have shown a higher risk of adverse health outcomes in alcohol abstainers compared to light-to-moderate drinkers in the general population (23) as well as among people living with HIV (24). To our knowledge, our study is the first to demonstrate in HIV/HCV coinfecting individuals that current non-drinkers may be at greater risk for advanced fibrosis. These findings suggest a “sick quitter” phenomenon where a key subset of abstainers are not lifetime abstainers but former heavy drinkers (25) or those who quit for health reasons, which was certainly supported by the higher prevalence of alcohol use disorder and HCV infection among current non-drinkers compared with non-hazardous users in our cohort. A diagnosis of alcohol use disorder, however, is likely only the “tip of the iceberg” when used as a cumulative measure of alcohol use.

Alcohol use disorder was prevalent among HCV co-infected patients but this group reported current hazardous drinking less frequently than mono-infected patients. This finding may reflect a reluctance to disclose hazardous drinking or the impact of screening and much greater focus on counseling regarding the impact of alcohol in this at-risk population. Nearly half (49%) of HCV co-infected patients reported that they were still drinking, underscoring the importance of addressing alcohol use with patients so that they can modify behavior (26).

After controlling for traditional risk factors such as alcohol, viral hepatitis and diabetes, we found that advanced fibrosis by FIB-4 was significantly associated with detectable HIV VL and lower CD4 count, which have been linked with greater risk of significant hepatic fibrosis by transient elastography (4, 27) and liver decompensation in HCV/HIV co-infected patients (22, 28). This is consistent with findings that antiretroviral therapy can reduce the rate of fibrosis progression (29) and risk of liver-related mortality in HIV/HCV co-infected patients (30).

Given the cross-sectional nature of our analysis, we were unable to examine the temporal relationship between these factors and the development of fibrosis. Healthcare providers have been known to miss clinically significant alcohol use, particularly in patients who lack evidence of laboratory abnormalities (31), potentially introducing some measurement bias, the possibility of reverse causality and underestimation of alcohol use disorders. Current alcohol use was self-reported, and may have been underreported among patients with HCV infection and cirrhosis in whom alcohol use is ill advised. Longitudinal analyses of AUDIT



C scores were not possible since most subjects had 2 or fewer measures over a fairly limited timeframe. FIB-4 values can fluctuate due to comorbid conditions and acute medical events but the sample size of our cohort and predominantly outpatient origin of these lab results likely offset this variability. Despite these limitations, FIB-4 has been shown to predict death (9–12) and liver decompensation (22), and may surpass liver biopsy in this regard (21).

Our study was conducted in a large, diverse cohort of persons infected with HIV in the modern ART era with systematic collection of current alcohol use using a well-validated instrument. The size of our cohort allowed multiple comorbidities to be examined together to assess their relative importance with respect to hepatic fibrosis, capturing the clinical complexity of patients in real-world care settings. Our findings underscore the importance of addressing multiple modifiable factors, including alcohol use, to prevent or slow the progression of liver disease in HIV-infected individuals.

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**Table 1**

## Demographic and Clinical Characteristics of the Study Population

	<b>Total (N=12849)</b>	<b>Low FIB-4<sup>1</sup> (n=12253)</b>	<b>High FIB-4<sup>1</sup> (n=596)</b>
<b>Age, years (median, IQR)</b>	47 (38–51)	45 (37–51)	53 (47–58)
<b>Sex, male</b>	10698 (83)	10216 (83)	482 (81)
<b>Race</b>			
White	6049 (47)	5789 (47)	260 (44)
Black	4475 (35)	4227 (35)	248 (42)
Hispanic	1721 (13)	1655 (14)	66 (11)
Other	604 (5)	582 (5)	22 (4)
<b>HIV risk factor</b>			
MSM	7460 (58)	7238 (59)	222 (37)
IDU	2070 (16)	1832 (15)	238 (40)
Heterosexual	2926 (23)	2819 (23)	107 (18)
Other	393 (3)	364 (3)	29 (5)
<b>Chronic hepatitis C</b>	2376 (18)	2012 (16)	364 (61)
<b>Chronic hepatitis B</b>	716 (6)	646 (5)	70 (12)
<b>Diabetes mellitus</b>	1308 (10)	1183 (10)	125 (21)
<b>Current CD4 count (cells/mm<sup>3</sup>)</b>			
500	6971 (54)	6819 (56)	152 (25)
200–499	4468 (35)	4212 (34)	256 (43)
<200	1410 (11)	1222 (10)	188 (32)
<b>Current HIV RNA level<sup>2</sup></b>			
<500 copies/ml	10820 (84)	10389 (85)	431 (72)
<b>Current ART<sup>3</sup></b>	11435 (89)	10920 (89)	515 (86)
<b>Alcohol use disorder</b>	2321 (18)	2091 (17)	230 (39)
<b>Current alcohol use<sup>4</sup></b>			
No drinking	4637 (36)	4338 (35)	299 (50)
Non-hazardous	6079 (47)	5882 (48)	197 (33)
Hazardous	2133 (17)	2033 (17)	100 (17)

Values represent number (%) except for the category age. IQR: interquartile range, MSM: men who have sex with men, IDU: injection drug use, ART: antiretroviral therapy.

<sup>1</sup>FIB-4 index >3.25 represented high FIB-4. P-values were <0.005 for all comparisons between high and low FIB-4 groups except for sex (P=0.11) and current ART (P=0.04).

<sup>2</sup>Lab value closest to clinical assessment.

<sup>3</sup>As reported in the clinical assessment.

<sup>4</sup>Non-hazardous: AUDIT-C score <5 for men, <4 for women. Hazardous: AUDIT-C score ≥ 5 for men, ≥ 4 for women.

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**Table 2**

Factors Associated with Advanced Liver Fibrosis by FIB-4 >3.25

Factor	Bivariate Analysis			Multivariable Analysis		
	OR	95% CI	P Value	aOR	95% CI	P Value
Male sex	0.8	0.7–1.0	0.11	1.0	0.8–1.3	0.70
Race (ref: white)						
Black	1.3	1.1–1.6	0.003	0.9	0.7–1.1	0.36
Other	0.9	0.7–1.1	0.29	0.9	0.7–1.1	0.23
Chronic hepatitis C	8.0	6.7–9.5	<0.001	6.3	5.2–7.5	<0.001
Chronic hepatitis B	2.4	1.8–3.1	<0.001	2.0	1.5–2.8	<0.001
Diabetes mellitus	2.5	2.0–3.1	<0.001	2.3	1.8–2.9	<0.001
Alcohol use disorder	3.1	2.6–3.6	<0.001	1.9	1.6–2.3	<0.001
Current alcohol use <sup>a</sup> (ref: non-hazardous)						
No drinking	2.1	1.7–2.5	<0.001	1.3	1.1–1.6	0.006
Hazardous	1.5	1.1–1.9	0.002	1.3	0.9–1.6	0.09
Current CD4 count <sup>b</sup> , cells/mm <sup>3</sup> (ref: 500)						
200–499	2.7	2.2–3.3	<0.001	2.4	1.9–3.0	<0.001
<200	6.9	5.5–8.6	<0.001	5.4	4.2–6.9	<0.001
Current HIV viral load <sup>b</sup> , copies/ml (ref: <500)						
500	2.1	1.8–2.6	<0.001	1.3	1.0–1.6	0.02

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

<sup>a</sup>Non-hazardous: AUDIT-C score <5 for men, <4 for women. Hazardous: AUDIT-C score 5 for men, 4 for women.

<sup>b</sup>Closest to assessment date.

Factors Associated with Advanced Liver Fibrosis by FIB-4 >3.25 among HIV-Monoinfected and HIV/HCV Coinfected Individuals

Table 3

	HIV-Monoinfected (n=10473)		HIV/HCV Coinfected (n=2376)	
Factor	aOR	95% CI	aOR	95% CI
Male sex	0.9	0.6–1.3	0.57	0.8–1.5
Race (ref: white)				
Black	0.7	0.5–0.9	0.018	1.1 0.8–1.4
Other	0.7	0.5–1.0	0.034	1.1 0.8–1.6
Chronic hepatitis B	3.0	2.0–4.4	<0.001	1.3 0.8–2.0
Diabetes mellitus	2.2	1.5–3.2	<0.001	2.3 1.7–3.1
Alcohol use disorder	2.1	1.5–2.8	<0.001	1.8 1.4–2.3
Current alcohol use <sup>a</sup> (ref: non-hazardous)				
No drinking	1.1	0.8–1.5	0.50	1.6 1.2–2.0
Hazardous	1.0	0.7–1.4	0.92	1.6 1.1–2.4
Current CD4 count <sup>b</sup> , cells/mm <sup>3</sup> (ref: 500)				
200–499	3.2	2.2–4.6	<0.001	2.0 1.5–2.6
<200	8.4	5.7–12.2	<0.001	3.8 2.7–5.3
Current HIV viral load <sup>b</sup> , copies/ml (ref: <500)				
500	1.5	1.1–2.0	0.01	1.1 0.8–1.5

aOR, adjusted odds ratio; CI, confidence interval.

<sup>a</sup>Non-hazardous: AUDIT-C score <5 for men, <4 for women. Hazardous: AUDIT-C score 5 for men, 4 for women.

<sup>b</sup>Closest to assessment date.