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Hazardous drinking is associated with elevated aspartate aminotransferase to platelet ratio index in an urban HIV clinical cohort

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Abstract

Objectives: To determine the relationship between alcohol consumption and liver fibrosis as assessed by aspartate aminotransferase to platelet ratio index (APRI) in HIV-infected adults and to explore the relative contributions of alcohol and hepatitis C virus (HCV) to APRI among HIV/HCV co-infected adults.

Methods: We performed a cross-sectional analysis of data from an observational clinical cohort. Alcohol consumption was categorized according to National Institute on Alcohol Abuse and Alcoholism guidelines. We defined significant liver disease as APRI>1.5, and used multinomial logistic regression to identify correlates of increased APRI.

Results: Among 1358 participants, 10.4% reported hazardous drinking. 11.6% had APRI>1.5, indicating liver fibrosis. Hazardous drinking was associated with increased APRI (Adj. RRR 2.30, 95% CI: 1.26-4.17). Other factors associated with increased APRI were: male gender; viral hepatitis; and HIV transmission category of injection drug use. Among co-infected individuals, 18.3% had APRI>1.5, and hazardous drinking was not associated with APRI. Among nonHCV-infected individuals, 5.3% had APRI>1.5, and hazardous drinking was associated with increased APRI (Adj. RRR 3.72, 95%CI: 1.40-9.87).

Conclusions: Hazardous drinking is an important modifiable risk factor for liver fibrosis, particularly among non-HCV-infected patients. Clinicians and researchers must address alcohol use as the burden of liver disease increases among HIV-positive individuals.

Keywords

alcohol; APRI; liver fibrosis; viral hepatitis

INTRODUCTION

In the era of highly active antiretroviral therapy (HAART) liver disease is emerging as a major cause of morbidity and mortality among HIV infected individuals (1). Evidence suggests that viral hepatitis contributes most to liver disease among HIV-infected individuals (1-3). The role of exogenous agents, including hepatotoxic drugs and alcohol, is less well-defined. Acute drug-

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induced toxicity from antiretroviral medications (4) has been demonstrated, although the impact of long term use is still unclear. Limited data exist specifically evaluating the role of alcohol on liver disease progression among persons living with HIV.

Alcohol use among HIV-infected individuals is associated with poor adherence (5-10,) HIV disease progression (11), and inadequate viral suppression (10-12). Research among HIV-infected persons exploring the association of alcohol consumption with medical comorbidities (13) and health services utilization (14) is ongoing.

In evaluating the consequences of alcohol consumption in HIV, it is important to consider that individuals who are coinfected with chronic viral hepatitis and HIV may be uniquely susceptible to alcohol's effects. Much evidence regarding HIV and Hepatitis C virus (HCV) coinfection suggests poorer outcomes in both infections (15,16). Data for chronic hepatitis B (HBV) infection suggest increased incidence of liver-related disease among HIV/HBV-coinfected patients, but do not suggest poorer HIV outcomes (17).

Despite considerable data on HIV/viral hepatitis coinfection, there is little known about the effects of alcohol consumption on liver disease progression in these patients. Alcohol consumption in HCV monoinfection is associated with liver disease progression (16,18). One study of coinfected patients found that alcohol consumption was associated with increased HCV viral load and blunted CD4 response to therapy (19).

Currently, liver biopsy is considered the gold standard for staging of liver fibrosis (20). However, there are limitations to biopsy, including inherent risks of the procedure (21) and sampling error (22). A number of surrogate markers of liver fibrosis have been validated for staging of HCV-related liver disease in persons with and without HIV (23-25) as noninvasive alternatives to liver biopsy. The objectives of this study were 1) to determine the relationship between self-reported alcohol consumption and liver disease as assessed by aspartate aminotransferase (AST) to platelet ratio index (APRI) score, a non-invasive marker of liver fibrosis, in HIV-infected adults receiving medical care; and 2) to explore the relative contributions of alcohol and viral hepatitis-related liver disease to APRI among persons coinfected with HIV and HCV.

METHODS

Study Participants

The Johns Hopkins HIV Clinical Cohort (JHHCC) is an open cohort of approximately 6000 HIV-infected adults. All patients receiving care within the Johns Hopkins AIDS Service are eligible to participate. Data collected on enrollees include demographic, clinical, diagnostic, laboratory, and pharmacy data. Information from the clinical record is abstracted regularly by trained staff, and supplemented by laboratory, radiology, clinical diagnoses and procedure data that are obtained electronically. A description of the background, development, and data collection methods for the Johns Hopkins HIV cohort has been published elsewhere (26).

Survey

Since 1998, surveys addressing drug and alcohol use have been offered and administered to enrollees on a semiannual basis. Between November 1998 and July 2000, face-to-face surveys were conducted by a trained interviewer. Beginning in July 2000 the format changed was changed to an audio computer-assisted self-interview (ACASI). Assistance is available to participants who need or request it. The survey takes about 15 minutes to complete. Alcohol-related questions address quantity and frequency of alcohol consumed over the prior six months. A description of survey collection methods has been published elsewhere (27). In this study we included all cohort participants with documented HCV and HBV testing who had

completed at least one survey. Written informed consent is obtained to enroll participants, and the refusal rate is less than two percent. This study has been approved by the Johns Hopkins University School of Medicine Institutional Review Board.

Definitions

Alcohol consumption was categorized into three groups: (0) no alcohol consumption; (1) non-hazardous drinking, no more than 14 drinks per week and no more than 4 drinks per occasion for men or no more than 7 drinks per week and no more than 3 drinks per occasion for women; (2) hazardous drinking, more than 14 drinks per week or more than 4 drinks per occasion for men or more than 7 drinks per week or more than 3 drinks per occasion for women. Binge drinking was classified as drinking more than 4 drinks per occasion for men or more than 3 drinks per occasion for women. These classifications for hazardous and binge drinking were derived from the United States National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines. One standard drink in the United States contains 14g of alcohol (28).

All laboratory testing was performed by licensed clinical laboratories. Coinfection with HCV and HBV was defined as having tested positive for anti-HCV antibody or hepatitis B surface antigen, respectively. Testing for HCV and HBV is routine for all enrolled patients. Opportunistic infections (OI) were defined using the 1993 Centers for Disease Control and Prevention classification (29). CD4 lymphocyte nadir was defined as the lowest value recorded since time of enrollment into the study. HIV transmission category is recorded at time of enrollment into the cohort, and categories are as follows: injection drug use (IDU); men who have sex with men (MSM); heterosexual sex; or other. The groups are not mutually exclusive and more than one transmission risk may be selected.

Outcome variable

Our primary outcome measure was APRI. The APRI is a non-invasive marker of liver fibrosis initially proposed and developed by Wai et al (23) for use in chronic HCV-infected individuals that has been validated in HIV/HCV coinfected patients (30,31). Using commonly available blood tests it provides a surrogate marker of fibrosis. Wai et al demonstrated that an APRI of > 1.5 predicted significant fibrosis (Ishak stage ≥ 3) with an area under receiving operator characteristic curve (AUC) of 0.80, and cirrhosis (Ishak score of 5 or 6) with an AUC of 0.89 (23). Other investigators have validated the use of APRI in chronic hepatitis C (32-35) either alone or in combination with other biomarkers. Shastry et al evaluated 50 HIV/HCV coinfected patients with liver biopsies and found that APRI was useful in excluding advanced liver fibrosis (31). There is some evidence to suggest that APRI may be of more limited value in liver fibrosis due to causes other than chronic HCV (36,37).

We identified laboratory results for AST and platelets, as well as HIV RNA, alanine aminotransferace (ALT), total bilirubin, and albumin at the time closest to the available survey date. These tests are generally performed at least every three months. For AST and platelets, we included test results within 30 days of survey administration. We calculated APRI using the standard formula:

$$\text{APRI}=\frac{\text{AST level}/\text{Upper limit of normal}}{\text{Platelet count}\ \left(10^9/\text{L}\right)}\times 100$$

There were several different clinical laboratories that performed testing, and each lab determined their own upper limit of normal. We defined 40 U/L as the upper limit of normal for AST. We analyzed APRI as a categorical outcome (APRI<0.4, APRI 0.4-1.5, APRI >1.5). We defined minimal liver disease as an APRI score <0.4 and significant liver disease as an

APRI>1.5. Intermediate scores were categorized as indeterminate for the purpose of this analysis.

Statistical Analysis

All statistical analysis was performed using Stata version 9.1 for windows (StataCorp, College Station, Texas, USA). We included the most recent survey for each individual and laboratory data closest to the date of this survey. We assessed and compared participant characteristics by hazardous drinking categories using Wilcoxon Rank Sum test for continuous variables, and Pearson's chi-square test for categorical variables. We performed bivariate analyses using multinomial logistic regression to test preselected covariates and their association with APRI category, including age, sex, race, time enrolled in cohort, use of HAART, antiretroviral medication class, history of OI, history of drug use, current drug use, presence of viral hepatitis, HIV RNA, CD4 lymphocyte nadir, and HIV transmission risk. Then we performed multivariate multinomial logistic regression analysis including in our final model significant correlates of APRI category from among our predetermined covariates, and additionally adjusting for age and self-reported race/ethnicity. We then performed the described multivariate multinomial logistic regression analyses in two subgroups: HIV/HCV coinfected participants, and non-HCV-infected HIV-infected participants. This was done to test observed relationships in both of these important clinical groups and help shed light on the relative contributions of alcohol consumption and HCV to APRI. We report relative risk ratios (RRR) for increased APRI with 95% confidence intervals.

RESULTS

1358 surveys each representing one individual were included in our analysis. Participant characteristics are summarized in Table 1. The majority of study participants were men (65.6%). The median age of our participants was 38.5 years. 67.2% of the overall group reported consuming no alcohol at all in the prior six months, 22.4% reported nonhazardous drinking, and 10.4% reported hazardous drinking. 44.9% had a history of IDU, and about one-half of participants were documented to be seropositive for HCV. 8.2% of participants had chronic HBV infection. Participant characteristics are representative of the overall Johns Hopkins HIV cohort.

All patients

In the overall cohort of 1358 individuals, 51.3% had APRI< 0.4, 37.1% had APRI between 0.4 and 1.5, and 11.6% had APRI>1.5, indicating significant liver fibrosis.

The results of our bivariate and multivariate analyses of the overall cohort are shown in Table 2. In the multivariate analysis, factors associated with increasing RRR of increased APRI across both APRI categories were: male gender, presence of viral hepatitis (HBV or HCV), HIV transmission category of IDU, and hazardous drinking (Adj. RRR 1.78, 95% CI: 1.15-2.76 for APRI between 0.4 and 1.5, Adj. RRR 2.30, 95% CI: 1.26-4.17 for APRI >1.5). Nonhazardous drinking was not associated with APRI differences. HIV viral suppression (HIV RNA<400 copies/mL) and CD4 nadir greater than 350 cells/mm^3 was inversely associated with increasing APRI across both categories. Other covariates examined and not found to be associated with APRI include use HAART at the time of APRI, specific class of antiretroviral therapy, history of opportunistic infections (OI) and current drug use (data not shown).

HIV/HCV coinfected subgroup

In the HIV/HCV coinfected group of 662 individuals, 31.7% had APRI< 0.4, 50.2% had APRI between 0.4 and 1.5, and 18.3% had APRI>1.5.

The results of the above multivariate analysis performed in the subgroup of HIV/HCV coinfected patients are presented in Table 3. In this analysis, CD4 nadir > 350 cells/mm^3 was protective for increased APRI. No effect was seen for HIV viral suppression in this group. Male gender was associated with APRI between 0.4 and 1.5, but not APRI>1.5.

HIV-monoinfected subgroup

In the HIV-infected, non-HCV-infected group of 696 individuals, 70.0% had APRI< 0.4, 24.7% had APRI between 0.4 and 1.5, and 5.3% had APRI>1.5.

Among non-HCV infected patients, in the multivariate analysis, hazardous drinking was associated with APRI>1.5 (Adj. RRR 3.72, 95%CI: 1.40-9.87) Nonhazardous drinking was not associated with APRI. Other correlates of increased APRI in this subgroup were transmission category IDU, and chronic HBV infection. HIV suppression (HIV-1 RNA<400 copies) was protective for increased APRI.

DISCUSSION

We evaluated the contribution of alcohol consumption to liver fibrosis as estimated by APRI in HIV-infected persons with and without viral hepatitis, and demonstrated that self reported hazardous alcohol consumption was independently associated with increased APRI. We did not identify an association between nonhazardous drinking and APRI, suggesting a threshold effect. Our results suggest that alcohol consumption is an important determinant of liver disease progression, particularly among patients *without* viral hepatitis, a group of patients who may not routinely be evaluated for liver disease in clinical practice.

In the HAART era, liver disease is emerging as a major cause of morbidity and mortality (1, 3). A study of mortality in a cohort encompassing over 23,000 HIV-individuals in Europe, the United States, and Australia found that liver disease was the most frequent cause of non-AIDS related mortality (1). These investigators did not routinely collect information about alcohol consumption. Even among studies which account for alcohol use, this has generally been done by physician report or chart review. Data suggest that providers often miss diagnosing alcohol-use disorders, particularly in cases of decreased disease severity (11). As a result, alcohol has not been adequately evaluated as a contributor to liver disease in this population.

Alcohol use is common among HIV-infected individuals as it is in the general population. In the year 2000, alcohol was the third leading cause of death in the US (38). In one US-based national survey of HIV infected individuals, the prevalence of any alcohol consumption was estimated to be 53%: 15% of drinkers were classified as heavy drinkers (39). In our study, one-third of individuals reported alcohol consumption; of those, about one-third were hazardous drinkers. As mentioned, alcohol consumption is not adequately addressed by health care providers (11,40). Although the role alcohol consumption plays in liver disease progression is not clearly defined, our results suggest that it contributes substantially to liver disease. As a modifiable risk factor, it deserves further attention from both health care providers and researchers.

Evidence suggests that brief interventions in health care settings can help decrease alcohol consumption in patients not explicitly seeking treatment for alcohol (41), and effective behavioral and pharmacologic therapies for alcohol dependence exist (42). Data aimed at reducing drinking specifically among HIV patients are limited, but one study suggested that an HIV primary care intervention was efficacious and sustainable (43).

In addition to the association between hazardous alcohol consumption and APRI, we noted several other relationships. As expected, having a diagnosis of viral hepatitis (HCV, HBV) was

significantly associated with liver fibrosis. We also observed that both a higher CD4 nadir and HIV suppression were inversely associated with liver fibrosis, suggesting that more advanced HIV disease is associated with more advanced liver disease. These results are consistent with a recent study of liver fibrosis in HIV/HCV coinfected individuals that found an independent association between HIV viremia and the rate of fibrosis progression, and further found that HIV suppression slowed fibrosis progression (44).

SUBGROUP ANALYSES

HIV/HCV coinfected—Among HIV/HCV coinfected patients in our sample, 18.3% had APRI>1.5, indicating significant liver fibrosis, compared with 5.3% in the non-HCV infected group. This difference in prevalence highlights the magnitude of the contribution of viral hepatitis to liver fibrosis among these individuals. Alcohol use disorders frequently coexist in patients with hepatitis C (18). Still, data about the effects of alcohol consumption on outcomes in coinfected patients are scarce. One study found alcohol consumption to be associated with increased HCV viral load and blunted CD4 response to therapy (19). Another study comparing HCV monoinfected individuals with HIV/HCV coinfected individuals found that those who drank more than 80g of alcohol daily had increased risk of death independent of HIV (15).

In this group, we did not observe a significant association between hazardous alcohol consumption and liver fibrosis as measured by APRI. Given the relatively high prevalence of APRI > 1.5 in this subgroup, this suggests that other unmeasured factors contribute relatively more to liver fibrosis than alcohol in this group. Only 74 of 662 HIV/HCV infected patients (11%) reported hazardous alcohol consumption, which may have limited our ability to detect an effect for alcohol in this sample.

HIV-infected, non-HCV-infected patients—Among non-HCV-infected patients, APRI>1.5, indicating potential significant liver fibrosis, was evident although much less common (5.3%) than in the coinfected group. In this group, hazardous drinking was a major correlate of increased APRI, suggesting that this is a population where interventions addressing hazardous alcohol consumption could have a substantial impact on reducing morbidity from liver disease.

Higher CD4 nadir appeared to be protective for liver fibrosis as measured by APRI in the overall cohort and in the coinfected group. This trend was evident, but not significant among non-HCV-infected patients, suggesting that immunosuppression plays an important role in progressive liver fibrosis due to chronic HCV, but may not contribute similarly to liver fibrosis from non-infectious causes such as alcohol. Others have commented that HCV acts as an opportunistic infection among HIV-infected persons (45). Weber et al also found that degree of immunosuppression was clearly associated with all-cause, AIDS, and liver-related mortality (1).

Limitations—There are several potential limitations to our study. One is self-report of alcohol data. Social desirability bias is minimized as much as possible by use of ACASI technology, and recall bias is minimized by using a six month recall window, but it remains likely that actual alcohol consumption is underestimated. Another possible limitation is the phenomenon of “sick abstainers,” or drinkers who may decrease alcohol consumption as their illness progresses. This should however, bias our results towards the null. Additionally, we did not examine the effects of drinking patterns. Finally, lifetime history of alcohol consumption is not captured in this cross-sectional study. Substance use patterns often fluctuate. Lucas et al. found that changes over time in substance use patterns were correlated with adherence to medications, HIV suppression, and change in CD4 count (27). Lifetime use or changes in

alcohol consumption over time may be important to liver disease progression and this area should be further explored.

Our survey does not ask about the size or alcohol content of drinks consumed. For patients who are filling out the survey for the first time, guidance is provided explaining the size of a standard drink, although this is not part of the survey itself. This may have led to some hazardous drinkers being classified as non-hazardous. However, it is unlikely that anyone is *overestimating* their alcohol consumption. It is likely that differences between the heaviest drinkers and the non-drinkers would persist even if some truly heavier drinkers were misclassified as non-hazardous. We did not observe any dose effect or significant APRI effect for non-hazardous drinkers. Had we observed a dose effect, it might have been more vulnerable to the bias of underestimating alcohol consumption. However, given the suggestion of a threshold effect with heavier drinking, we believe the results of our analysis are valid.

Another potential limitation in our study is that APRI has not been extensively validated as a marker of non-HCV associated liver fibrosis. There is some evidence to suggest that it may be of more limited value in chronic HBV-infected individuals (36) and in patients with liver fibrosis related to alcohol consumption (37). Further investigation is needed to identify whether APRI as a predictor of significant fibrosis is reliable in all populations, and on the relative contributions of liver disease and alcohol-related platelet abnormalities in this index. However, as previously published, APRI has been validated among coinfected individuals in our cohort of patients (24), a result that is relevant to this analysis. Additionally, we did not limit our HIV/HCV subgroup analysis to patients with confirmed HCV viremia, so we could not account for spontaneous clearance of HCV, and did not have data on which of these patients had been treated for HCV, which would likely impact liver fibrosis.

Additionally, there is the potential that alcohol or other disease characteristics may impact the individual components of the APRI ratio. Alcohol consumption has been demonstrated to have various effects on hematalogic parameters, including platelet counts (46) and has effects on AST independent of liver disease (47) which may elevate APRI for reasons not reflecting liver pathology. Alcohol's effects on these hematologic and biochemical parameters in the presence of liver disease is not fully known (47). HIV itself also has hematologic effects, including thrombocytopenia, which is often multifactorial, but may be immune-modulated (48). We attempted to account for this by controlling for CD4 nadir and viral suppression, but cannot completely control for HIV effects on platelets.

Finally, we did not collect data on body mass index (BMI), glucose intolerance, or lipid parameters, which are associated with nonalcoholic fatty liver disease (49), likely another important contributor to liver fibrosis that warrants exploration.

Conclusions—This study examines the relationship between alcohol consumption and progression of liver disease among HIV infected individuals, a sizable proportion of whom are coinfected with viral hepatitis. As several recent studies have demonstrated, liver disease is an important comorbidity in patients with HIV. Consistent with the literature, we found that viral hepatitis was a major contributor to liver disease, and that and immunosuppression also plays a role in liver disease progression. Importantly, we also demonstrated that alcohol abuse is a significant, independent risk for the presence of liver fibrosis. Mehta et al demonstrated low referral rates and limited effectiveness for HCV treatment in a subset of the JHHCC (50). Thus, identifying additional modifiable risk factors in disease progression is an important goal in addressing the growing burden of liver disease. Alcohol consumption is a major modifiable risk factor for liver disease, and is has already been shown to adversely impact adherence and disease progression in HIV.

Alcohol consumption is prevalent, and tends to be under-identified by health care providers, but evidence suggests that interventions to address alcohol in health care settings can work. Further work is necessary measuring the impact of alcohol on laboratory, pathological, and clinical outcomes of liver disease in HIV-infected and coinfected individuals to assess the true burden of alcohol-related liver disease and to determine whether any safe level of alcohol consumption exists. Still, our findings and the mounting evidence of the magnitude of liver-related morbidity and mortality suggest that addressing alcohol consumption will be an essential undertaking among both researchers evaluating HIV outcomes and clinicians caring for HIV-infected patients.

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Table 1

Participant characteristics. N=1358. No. (%)

Participant characteristics	All n=1358 (100)	No alcohol consumption n=913	Non-hazardous alcohol consumption n=304	Hazardous alcohol consumption N=141
Median Age (IQR) †	38.5 (33.0-44.2)	38.8 (33.5-45.0)	38.2 (32.8-42.8)	36.5 (31.9-41.6)
Self-reported race #				
Black	1081 (79.6)	763 (83.6)	223 (73.4)	95 (67.4)
White	258 (19.0)	139 (15.2)	79 (26.0)	40 (28.4)
Other	19 (1.4)	11 (1.2)	2 (0.6)	6 (4.2)
Gender#				
Female	467 (34.4)	339 (37.1)	74 (24.3)	54 (38.3)
Male	891 (65.6)	574 (62.9)	230 (75.7)	87 (61.7)
Hepatitis C virus seropositive#				
No	696 (51.3)	449 (49.2)	180 (59.2)	67 (47.5)
Yes	662 (48.7)	464 (50.8)	124 (40.8)	74 (52.5)
Hepatitis B surface antigen positive				
No	1247 (91.8)	843 (92.3)	275 (90.5)	129 (91.5)
Yes	111 (8.2)	70 (7.7)	29 (9.5)	12 (8.5)
HIV transmission category				
IDU	610 (44.9)	428 (46.9)	120 (39.5)	62 (44.0)
MSM#	342 (25.2)	186 (20.4)	116 (38.2)	40 (28.4)
Heterosexual sex	699 (51.5)	485 (53.1)	138 (45.4)	76 (53.9)
HAART#	626 (46.1)	397 (43.5)	171 (56.3)	58 (41.1)
History of OI	749 (55.2)	521 (57.1)	158 (52.0)	70 (49.7)
Median CD4 nadir (IQR) †	114 (21-260)	106 (17-246)	132 (25-277)	148 (40-321)
Median platelet count (IQR)	210 (159-264)	208 (157-261)	217 (161-267)	217 (161-271)
Median AST (IQR) †	32 (23-51)	32 (22-50)	30 (23-50)	41 (25-73)
Median ALT (IQR) †	27 (18-44)	27 (17-42)	27 (18-40)	33 (18-58)
Median albumin (IQR) †	4.0 (3.5-4.4)	4.0 (3.6-4.3)	4.1 (3.6-4.4)	3.9 (3.4-4.4)

Abbreviations: IQR, interquartile range; IDU, injection drug use; MSM, men who have sex with men; OI, opportunistic infection; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Alcohol categories: 0, no alcohol consumption; 1, no more than 14 drinks per week and no more than 4 drinks per occasion for men or no more than 7 drinks per week and no more than 3 drinks per occasion for women; 2, more than 14 drinks per week or more than 4 drinks per occasion for men or more than 7 drinks per week or more than 3 drinks per occasion for women.

† $p<0.05$ by Kruskal-Wallis analysis of ranks

# $p< 0.05$ by Pearson's Chi square test

Table 2

Results of multivariate multinomial logistic regression (RRR with 95%CI). Correlates of increased APRI in a cohort of HIV-infected individuals, adjusted for age and self-reported race. Reference category is APRI<0.4. n=1358

Participant Characteristic	Unadjusted RRR for RRR for 0.4<APRI<1.5	Adjusted RRR for 0.4<APRI<1.5	Unadjusted RRR for APRI>1.5	Adjusted RRR for APRI>1.5
Gender				
Female	1.00	1.00	1.00	1.00
Male	1.51 (1.18-1.93)	1.61 (1.22-2.14)	1.35 (0.93-1.94)	1.45 (0.95-2.20)
HCV ab+				
No	1.00	1.00	1.00	1.00
Yes	4.48 (3.50-5.72)	3.32 (2.35-4.68)	7.52 (5.03-11.25)	4.73 (2.71-8.25)
HBsAg+				
No	1.00	1.00	1.00	1.00
Yes	1.64 (1.07-2.23))	1.66 (1.04-2.67)	2.41 (1.38-4.20)	2.60 (1.40-4.83)
HIV transmission category IDU?				
No	1.00	1.00	1.00	1.00
Yes	3.65 (2.87-4.66)	1.74 (1.23-2.45)	5.82 (3.98-8.50)	2.29 (1.35--3.89)
CD4 nadir				
≤50	1.00	1.00	1.00	1.00
51-200	0.87 (0.65-1.15)	0.80 (0.59-1.10)	1.10 (0.73-1.67)	1.02 (0.65-1.62)
201-350	0.66 (0.48-0.91)	0.62 (0.44-0.89)	0.85 (0.53-1.37)	0.80 (0.48-1.34)
>350	0.60 (0.41-0.86)	0.44 (0.29-0.67)	0.38 (0.19-0.75)	0.24 (0.11-0.51)
HIV RNA<400				
No	1.00	1.00	1.00	1.00
Yes	0.63 (0.50-0.79)	0.65 (0.50-0.85)	0.43 (0.30-0.62)	0.45 (0.30-0.68)
Alcohol category				
0 (no consumption)	1.00	1.00	1.00	1.00
1 (non-hazardous)	0.91 (0.69-1.21)	0.99 (0.72-1.36)	0.87 (0.56-1.35)	0.95 (0.59-1.55)
2 (hazardous)	1.54 (1.04-2.27)	1.78 (1.15-2.76)	2.00 (1.18-3.37)	2.30 (1.26-4.17)

Abbreviations: RRR, relative risk ratio; 95%CI, 95% confidence interval; APRI, aspartate aminotransferase to platelet ratio index; HCV-Ab, Hepatitis C antibody; HBSAg, hepatitis B surface antigen; IDU, injection drug use.

Alcohol categories: 0, no alcohol consumption; 1, no more than 14 drinks per week and no more than 4 drinks per occasion for men or no more than 7 drinks per week and no more than 3 drinks per occasion for women; 2, more than 14 drinks per week or more than 4 drinks per occasion for men or more than 7 drinks per week or more than 3 drinks per occasion for women.

Table 3

Results of multivariate multinomial logistic regression (RRR with 95%CI). Correlates of increased APRI in a cohort of HIV/HCV coinfected individuals, adjusted for age and self-reported race. Reference category is APRI<0.4. n=662.

Participant Characteristic	Unadjusted RRR for RRR for 0.4<APRI<1.5	Adjusted RRR for 0.4<APRI<1.5	Unadjusted RRR for APRI>1.5	Adjusted RRR for APRI>1.5
Gender				
Female	1.00	1.00	1.00	1.00
Male	1.66 (1.16-2.38)	1.78 (1.20-2.65)	1.59 (0.99-2.54)	1.56 (0.93-2.61)
HIV transmission category IDU?				
No	1.00	1.00	1.00	1.00
Yes	1.66 (1.09-2.54)	1.56 (1.00-2.43)	1.91 (1.06-3.45)	1.85 (0.77-4.27)
HbSAg +				
No	1.00	1.00	1.00	1.00
Yes	1.34 (0.66-2.74)	1.11 (0.53-2.33)	2.00 (0.88-4.55)	1.81 (0.77-4.27)
CD4 nadir				
≤50	1.00	1.00	1.00	1.00
51-200	0.91 (0.58-1.42)	0.91 (0.61-1.54)	1.18 (0.68-2.07)	1.26 (0.71-2.25)
201-350	0.56 (0.34-0.92)	0.63 (0.38-1.05)	0.73 (0.39-1.37)	0.78 (0.40-1.49)
>350	0.48 (0.29-0.81)	0.48 (0.27-0.84)	0.34 (0.15-0.75)	0.31 (0.13-0.72)
HIV RNA <400				
No	1.00	1.00	1.00	1.00
Yes	0.74 (0.52-1.05)	0.72 (0.49-1.05)	0.66 (0.41-1.05)	0.64 (0.39-1.05)
Alcohol category				
0 (no consumption)	1.00	1.00	1.00	1.00
1 (non-hazardous)	0.87 (0.55-1.36)	0.79 (0.49-1.27)	1.21 (0.69-2.11)	1.11 (0.61-2.01)
2 (hazardous)	1.70 (0.93-3.14)	1.89 (0.98-3.66)	1.95 (0.93-4.10)	2.05 (0.91-4.62)

Abbreviations: IDU, injection drug use; HBSAg, hepatitis B surface antigen.

Alcohol categories: 0, no alcohol consumption; 1, no more than 14 drinks per week and no more than 4 drinks per occasion for men or no more than 7 drinks per week and no more than 3 drinks per occasion for women; 2, more than 14 drinks per week or more than 4 drinks per occasion for men or more than 7 drinks per week or more than 3 drinks per occasion for women.

Table 4

Results of multivariate multinomial logistic regression (RRR with 95%CI). Correlates of increased APRI in HIV-infected patients without HCV infection, adjusted for age and self-reported race. Reference category is APRI<0.4. n=697.

Participant Characteristic	Unadjusted RRR for RRR for 0.4<APRI<1.5	Adjusted RRR for 0.4<APRI<1.5	Unadjusted RRR for APRI>1.5	Adjusted RRR for APRI>1.5
Gender				
Female	1.00	1.00	1.00	1.00
Male	1.61 (1.09-2.36)	1.45 (0.95-2.21)	1.22 (0.60-2.49)	1.48 (0.66-3.30)
HIV transmission category IDU?				
No	1.00	1.00	1.00	1.00
Yes	1.67 (0.98-2.85)	1.92 (1.10-3.35)	2.85 (1.23-6.62)	3.85 (1.49-9.97)
HbSAg +				
No	1.00	1.00	1.00	1.00
Yes	2.35 (1.32-4.17)	2.06 (1.13-3.75)	4.20 (1.77-9.99)	3.57 (1.36-9.33)
CD4 nadir				
≤50	1.00	1.00	1.00	1.00
51-200	0.68 (0.44-1.04)	0.67 (0.43-1.06)	0.66 (0.29-1.49)	0.79 (0.32-1.91)
201-350	0.68 (0.42-1.09)	0.63 (0.38-1.04)	0.83 (0.36-1.92)	0.89 (0.35-2.25)
>350	0.51 (0.28-0.92)	0.43 (0.23-0.80)	0.13 (0.02-1.03)	0.13 (0.02-1.00)
HIV RNA <400				
No	1.00	1.00	1.00	1.00
Yes	0.64 (0.45-0.91)	0.61 (0.42-0.89)	0.17 (0.07-0.41)	0.17 (0.07-0.44)
Alcohol category				
0 (no consumption)	1.00	1.00	1.00	1.00
1 (non-hazardous)	1.30 (0.88-1.93)	1.21 (0.80-1.85)	0.54 (0.20-1.45)	0.53 (0.18-1.49)
2 (hazardous)	1.50 (0.83-2.71)	1.69 (0.91-3.14)	2.69 (1.13-6.39)	3.72 (1.40-9.87)

Abbreviations: RRR, relative risk ratio; 95%CI, 95% confidence interval; APRI, aspartate aminotransferase to platelet ratio index; IDU, injection drug use..

Alcohol categories: 0, no alcohol consumption; 1, no more than 14 drinks per week and no more than 4 drinks per occasion for men or no more than 7 drinks per week and no more than 3 drinks per occasion for women; 2, more than 14 drinks per week or more than 4 drinks per occasion for men or more than 7 drinks per week or more than 3 drinks per occasion for women.