Published in final edited form as:
Alcohol Clin Exp Res. 2013 September ; 37(9): 1527–1535. doi:10.1111/acer.12129.

Impact of lifetime alcohol use on liver fibrosis in a population of HIV-infected patients with and without hepatitis C coinfection

Daniel Fuster[1], **Judith I. Tsui**[1], **Debbie M. Cheng**[1,2], **Emily K Quinn**[3], **Carly Bridden**[1], **David Nunes**[4], **Howard Libman**[5], **Richard Saitz**[1,6], and **Jeffrey H. Samet**[1,7]

[1]Clinical Addiction Research and Education (CARE) Unit, Section of General Internal Medicine, Department of Medicine, Boston Medical Center and Boston University School of Medicine, Boston, MA

[2]Department of Biostatistics, Boston University School of Public Health, Boston, MA

[3]Data Coordinating Center, Boston University School of Public Health, Boston, MA

[4]Section of Gastroenterology, Department of Medicine, Boston Medical Center and Boston University School of Medicine, Boston, MA

[5]Divisions of General Medicine and Primary Care and Infectious Diseases, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

[6]Department of Epidemiology, Boston University School of Public Health, Boston, MA

[7]Department of Community Health Sciences, Boston University School of Public Health, Boston, MA

Abstract

Background—The effect of alcohol on liver disease in HIV infection has not been well characterized.

Methods—We performed a cross-sectional multivariable analysis of the association between lifetime alcohol use and liver fibrosis in a longitudinal cohort of HIV-infected patients with alcohol problems. Liver fibrosis was estimated with two non-invasive indices, “FIB-4”, which includes platelets, liver enzymes, and age; and “APRI”, which includes platelets and liver enzymes. FIB-4<1.45 and APRI<0.5 defined absence of liver fibrosis. FIB-4>3.25 and APRI>1.5 defined advanced liver fibrosis. The main independent variable was lifetime alcohol consumption (<150 kg, 150–600kg, >600 kg).

Results—Subjects (n=308) were 73% male, mean age 43 years, 49% with hepatitis C virus (HCV) infection, 60% on antiretroviral therapy, 49% with an HIV RNA load<1000 copies/mL, and 18.7% with a CD4 count<200 cells/mm^3. Forty-five percent had lifetime alcohol consumption >600 kg, 32.7% 150–600 kg, and 22.3% <150 kg; 33% had current heavy alcohol use, and 69% had >9 years of heavy episodic drinking. Sixty-one percent had absence of liver fibrosis and 10% had advanced liver fibrosis based on FIB-4. In logistic regression analyses controlling for age, gender, HCV infection, and CD4 count, no association was detected between lifetime alcohol consumption and absence of liver fibrosis (FIB-4<1.45) [adjusted odds ratio (AOR)=1.12 (95%CI: 0.25–2.52) for 150–600 kg versus <150 kg; AOR=1.11 (95%CI:0.52–2.36) for >600 kg vs. <150 kg; global p=0.95]. Additionally, no association was detected between lifetime alcohol use and

Corresponding author: Daniel Fuster MD PhD. Clinical Addiction Research and Education (CARE) Unit, Section of General Internal Medicine, Department of Medicine, Boston Medical Center and Boston University School of Medicine, 801 Massachusetts Avenue, 2nd floor (Room #2079), Boston, MA, 02118. (Daniel.Fuster@bmc.org).

advanced liver fibrosis (FIB-4>3.25). Results were similar using APRI, and among those with and without HCV infection.

Conclusions—In this cohort of HIV-infected patients with alcohol problems, we found no significant association between lifetime alcohol consumption and absence of liver fibrosis or the presence of advanced liver fibrosis, suggesting that alcohol may be less important than other known factors that promote liver fibrosis in this population.

Keywords

alcohol; HIV; Hepatitis C virus; liver fibrosis

Introduction

Hepatitis C virus (HCV) infection is common in HIV-infected adults; especially in those with past injection-drug use (Alter, 2007). In recent years, non-AIDS-related and liver-related mortality have increased in HIV-infected patients in developed countries (Bica et al., 2001; Obel et al., 2011). Liver fibrosis is the main predictor of progression to hepatic failure in chronic HCV infection and other forms of liver disease (Thomas et al., 2000). Cirrhosis is also a strong predictor of lack of response to HCV antiviral therapy (Ghany et al., 2009; Thomas et al., 2000).

Both alcohol use and HIV infection are known to have an adverse effect on the course of chronic HCV infection, with more rapid progression of liver fibrosis and a faster evolution to end-stage liver disease and liver-related death (Hutchinson et al., 2005; Thein et al., 2008). However, the effect of alcohol on the burden of HCV-related liver disease among HIV-infected persons has received less attention in the literature.

HCV infection prevalence is higher among those with alcohol dependence than in the general population (Peters and Terrault, 2002; Roudot-Thoraval et al., 1997), probably due to increased risk of exposure as heavy alcohol use is frequent in injection-drug users (Campbell et al., 2006) and alcohol use is associated with HCV risky behaviors (Stein et al., 2000). Furthermore, HCV-infected individuals tend to drink more alcohol than the general population (Stoller et al., 2006).

In the setting of HCV monoinfection, heavy alcohol use has a synergistic effect on HCV-related liver injury, with a higher likelihood of persistent infection (Thimme et al., 2002), greater viral replication (McCartney and Beard, 2010), more cytotoxicity, and increased oxidative stress (Bellentani et al., 1997; Castellano-Higuera et al., 2008). Moreover, heavy alcohol use induces an impaired immune response (Szabo et al., 2006) that has been related to a lower likelihood of sustained response to HCV antiviral therapy (Siu et al., 2009).

In studies of HCV/HIV-coinfected patients, alcohol is one of the many factors that increase the likelihood of biopsy-proven liver damage (Benhamou et al., 1999; Tural et al., 2003). In these and other studies of the natural history of HCV infection, alcohol consumption has been assessed as a dichotomous variable (yes vs. no) (Benhamou et al., 1999; Chaudhry et al., 2009; Thomas et al., 2000; Tural et al., 2003). Most studies have focused on current heavy alcohol consumption, using a threshold of 40–50 grams (Benhamou et al., 1999; Tural et al., 2003) of daily alcohol intake or the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) definition for heavy use (the equivalent of 70 grams of alcohol daily for men and 56 grams for women) (Chaudhry et al., 2009). Lifetime alcohol consumption is perhaps the best measure of alcohol use when considering its impact on chronic liver disease. However, the impact of lifetime alcohol consumption, a measure of cumulative alcohol exposure, on the outcome of liver fibrosis in HIV-infected patients, is not known.

Liver biopsy remains the gold standard to assess liver fibrosis, but it is an invasive and costly procedure (Gebo et al., 2002), and less likely to be performed in patients with current alcohol or other substance use disorders (Sanvisens et al., 2011). Several non-invasive indices to estimate liver fibrosis have been described in recent years. Among these, the "FIB-4" (Sterling et al., 2006) and the aspartate aminotransferase/platelet ratio index (APRI) (Wai et al., 2003) have been validated against the gold standard of liver biopsy in HCV-monoinfected patients and HCV/HIV-coinfected patients (Loko et al., 2008; Nunes et al., 2005; Sebastiani et al., 2009; Vallet-Pichard et al., 2007). They are derived from laboratory parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT] levels, and platelet count) that are commonly used in the evaluation of liver disease. Those indices are especially helpful for detecting either absence of liver fibrosis or presence of advanced liver fibrosis (Sterling et al., 2006; Wai et al., 2003). APRI and FIB-4 have not been validated against liver biopsy in HIV-infected patients without HCV, but they have been used by several cohorts to estimate the burden of liver disease in patients who would not undergo a liver biopsy (Blackard et al., 2011; Chaudhry et al., 2009; Mendeni et al., 2011; Price et al., 2012). Recently, studies have found that non-invasive markers of liver fibrosis are predictors of mortality in both HCV-infected patients and HCV/HIV-coinfected patients (Bambha et al., 2012; Nunes et al., 2010; Sanvisens et al., 2011).

In this study, we looked at the relationship between lifetime (total) alcohol consumption, and liver fibrosis using non-invasive measures in a cohort of HIV-infected adults with alcohol problems, half of whom were coinfected with HCV. We additionally evaluated associations between another measure of lifetime alcohol consumption (years of heavy episodic drinking) and current heavy alcohol use and liver fibrosis.

Patients and methods

Design

This is a cross-sectional analysis examining the association between lifetime alcohol use and the absence of liver fibrosis in HIV-infected patients with current or past alcohol problems. Data were obtained from a prospective, observational cohort study (HIV-Longitudinal Interrelationships of Viruses and Ethanol [HIV-LIVE]), in which assessments occurred at 6-month intervals over a maximum of 42 months (Samet et al., 2007).

Subjects

Recruitment for the HIV-LIVE cohort occurred from multiple sources: a previous cohort study; an intake clinic for HIV-infected patients; HIV primary care and specialty clinics at two hospitals; homeless shelters; drug treatment programs; subject referrals; and flyers. Enrollment occurred between August 2001 and July 2003. Eligibility criteria were as follows: 1) documented HIV antibody test by ELISA and confirmed by Western blot; 2) two or more affirmative responses to the CAGE alcohol screening questionnaire (Samet et al., 2004b), or physician investigator diagnosis of alcoholism; and 3) ability to speak English or Spanish. Exclusion criteria were: 1) scoring<21 on the 30-item Mini-Mental State Examination (i.e., cognitive impairment) (Folstein et al., 1975); and 2) inability to provide informed consent (Walley et al., 2008). In addition to the above eligibility criteria, the present analysis included only those HIV-LIVE subjects with laboratory parameters available to calculate the FIB-4 and APRI. The Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess Medical Center approved this study.

Measures

Dependent variable—The primary outcome of this study was the absence of liver fibrosis based on non-invasive indices (FIB-4 and APRI) at study entry or at the earliest possible time point during follow up. Values of non-invasive indices were calculated as follows:

FIB-4 = [age×AST (IU/ L)/ platelet count (10^9/ L)×ALT (IU/ L)$^{1/2}$].

Aspartate aminotransferase/ platelet ratio index (APRI) = (patient AST/ AST upper limit of normal [40 U/L])×100/ platelets (10^9/ L).

The two primary outcomes representing absence of liver fibrosis were defined as FIB-4 <1.45 and APRI <0.5. FIB-4 values <1.45 are consistent with the absence of liver fibrosis with a negative predictive value of 90% and a sensitivity of 70%. FIB-4 values >3.25 are consistent with significant liver fibrosis with a positive predictive value 67% and a specificity of 97%, with an area under the receiver operating curve [AUROC] of 0.765 (Sterling et al., 2006). An APRI score <0.5 predicts absence of liver fibrosis with a sensitivity of 91% and a specificity of 47%, while a score >1.5 is consistent with advanced liver fibrosis with a sensitivity of 41% and a specificity of 95%, with an AUROC of 0.88 (Wai et al., 2003).

Two secondary outcomes representing the presence of advanced liver fibrosis (FIB-4 values >3.25, APRI >1.5) were also examined.

Main independent variables—The main independent variable was total lifetime alcohol intake (measured in kilograms). Lifetime alcohol use was quantified by multiplying the number of lifetime alcohol units×14 grams of alcohol/unit. Number of lifetime alcohol units was captured by Lifetime Drinking History (Skinner and Sheu, 1982), a structured interview where the subject recalls patterns of alcohol consumption from the first year of regular drinking to the present. Subjects were classified into three categories based on two clinically relevant thresholds [<150,000 g (150 kg), 150 kg–600,000 g (600 kg) and >600 kg.] (Hutchinson et al., 2005; Monto et al., 2004; Poynard et al., 1997; Rehm et al., 2010). Two standard drinks per day is the threshold at which risk for alcoholic liver disease increases (Rehm et al., 2010) and 4 standard drinks per day has been established as the threshold for advanced liver fibrosis in HCV infection monoinfection (Monto et al., 2004; Poynard et al., 1997). The thresholds we chose correspond approximately to the following drinking patterns: for <150 kg, <2 standard drinks (28 g)/day for 14 years; for >600 kg, > 4 standard drinks/day for 28 years. We note that the patterns above are simply example patterns that the thresholds could represent. The lifetime alcohol intake variable was defined by duration and quantities of use, such that a variety of drinking patterns could result in the same lifetime intake (e.g., an individual who drank 2 drinks a day for 14 years would be equivalent to an individual who drank 4 drinks a day for 7 years).

Secondary measures of alcohol use were number of years of heavy episodic drinking and current heavy alcohol use (past 30 days). Years of heavy episodic drinking [years when the patient had >1 episode of heavy alcohol use (≥5 drinks on one occasion)] was categorized based on tertiles. Current heavy alcohol use (last 30 days) was defined according to National Institute on Alcohol Abuse and Alcoholism guidelines: >14 drinks/ week or ≥5 drinks on one occasion for men ≤65 years of age, and >7 drinks/ week or ≥4 drinks on one occasion for all women and for men >65 years of age.

Covariates—Potential confounders controlled for in the analyses were age, sex, HCV infection, and CD4 cell count/mm^3 [categorized as <200, 200–500 and >500]. HCV infection was defined as a positive HCV antibody test with confirmatory testing that detected HCV RNA.

Any subject that was missing any covariate, including CD4 and HCV, was excluded from the adjusted models.

Analysis

Descriptive statistics were used to describe the overall study sample. Baseline characteristics were compared across groups using Chi-square/Fisher's exact test for categorical values and ANOVA for continuous variables.

Separate multivariable logistic regression models were fit to evaluate the association between each of the three alcohol use variables and the outcomes absence of liver fibrosis (FIB-4 values <1.45, APRI <0.5) and presence of advanced liver fibrosis (FIB-4 values >3.25, APRI >1.5).

The primary analyses evaluated the associations between total lifetime alcohol intake and each of the two indicators of absence of liver fibrosis, controlling for all covariates listed above. Spearman correlations were used to evaluate potential collinearity between independent variables and covariates. No pair of variables included in the same regression model was highly correlated (r>0.40). Additional exploratory models were also stratified by HCV infection status, as we anticipated that the effect of alcohol use on liver fibrosis might differ according to HCV infection; by the use of antiretroviral therapy and by the presence of active Hepatitis B infection (presence of HBsAg). Adjusted odds ratios (AORs) and 95% confidence intervals are reported for each model. All analyses were conducted using two-sided tests and a significance level of 0.05. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., NC, USA).

Results

Of 400 subjects, 308 had data to calculate FIB-4 and APRI and comprised the sample for the current study. There was no difference according to gender, age and HCV coinfection between the 308 patients included in the study and the 92 patients from the cohort without available FIB-4 and APRI data.

Study subjects were mostly men (73.1%) and had a mean age of 42.8 years (Table 1). Nearly half were HCV-infected, and two-thirds had a body mass index greater than 24, consistent with being overweight. HIV-related characteristics were as follows: 60.4% on antiretroviral therapy; 49.3% with an HIV viral load below 1000 copies/mL; and 18.7% with a CD4 count below 200 cells/mm^3. One hundred and sixty five patients (53.7%) had prior or current injection drug use and the mean duration of injection-drug use was 11.7 years.

Forty-five percent of the study population had lifetime alcohol consumption greater than 600 kg, two-thirds had more than 9 years of heavy episodic drinking and 33% reported current heavy alcohol use. According to the FIB-4, 60.7% of the study population had values consistent with absence of liver fibrosis (FIB-4 <1.45), while 10.1% had values consistent with advanced liver fibrosis (FIB-4 >3.25). According to APRI, 57.8% of the study population had values consistent with absence of liver fibrosis, while 9.1% had values consistent with advanced liver fibrosis.

Of the total study population (n= 308), there was missing information regarding lifetime alcohol intake, years binge drinking and current heavy alcohol use for 17, 7 and 2 subjects respectively. Moreover, 19 subjects had missing CD4 count data and 2 had missing HCV RNA data.

Table 2 shows the results of the unadjusted analyses of the association between alcohol use and the absence of liver fibrosis. Table 2 also shows the three adjusted regression models, one for each measure of alcohol use. In logistic regression analyses controlling for age, gender, HCV infection, and CD4 count, no association was detected for lifetime alcohol consumption and the absence of liver fibrosis (FIB-4 <1.45) [adjusted odds ratio (AOR)=1.12, (95%CI: 0.25, 2.52) for 150–600 kg vs. <150 kg ; AOR=1.11.(95%CI: 0.52, 2.36) for >600 kg vs. <150 kg; global p=0.95]

No significant association was found for lifetime alcohol and the absence of liver fibrosis measured with APRI. Additionally, no significant associations were observed for years of heavy episodic drinking or current heavy alcohol use and absence liver fibrosis using either FIB-4 or APRI. HCV infection, CD4 count and age were significantly and inversely associated with the absence of liver fibrosis as determined by FIB-4.

Table 3 shows the results of the unadjusted bivariable analysis and the multivariable logistic regression models for the association between the three measures of alcohol use (lifetime alcohol consumption, years of heavy episodic drinking and current heavy alcohol use) and the presence of advanced liver fibrosis. No significant association was found between any of the three measures of alcohol use and advanced liver fibrosis as determined by either FIB-4 or APRI.

Analyses stratified by HCV infection status showed that results did not differ substantively by HCV status (Table 4). In addition, we performed two other stratified analysis of the association between lifetime alcohol consumption and the absence of liver fibrosis, the first stratified by antiretroviral therapy and the second stratified by presence of Hepatitis B surface antigen (HBsAg) (Table 5). Results did not differ according to the use of antiretroviral therapy. In those participants who were HBsAg positive (n=24) the point estimate for the adjusted odds of absence of liver fibrosis (FIB-4 <1.45) was 0.04 (0.00, 1.67) for those with a higher lifetime alcohol intake, but this result did not reach statistical significance.

Discussion

Liver disease is a major concern in many HIV-infected patients. In this study, we examined the association between lifetime alcohol use and liver fibrosis determined by FIB-4 and APRI in a cohort of HIV-infected patients with alcohol problems. The main finding is that there was no significant association between lifetime alcohol use and the absence or presence of liver fibrosis.

Additionally, no significant association was detected between years of heavy episodic drinking or current heavy alcohol use and the absence of liver fibrosis or the presence of advanced liver fibrosis.

A small number of studies have evaluated the effects of alcohol on liver fibrosis using noninvasive indices to estimate liver fibrosis in unselected cohorts of HIV-infected patients. One study of an HIV-infected urban cohort found that hazardous/heavy alcohol use (same NIAAA definition as used in this study) over the past 6 months was associated with a high APRI index, reflecting significant fibrosis (Chaudhry et al., 2009). Of note, when the study group was stratified by HCV infection, high APRI score was associated with hazardous alcohol use only among those without HCV infection; however, authors acknowledged the analyses were limited by a low percentage (11%) of hazardous drinkers in the coinfected group (Chaudhry et al., 2009). Blackard et al. (2011) evaluated predictors of FIB-4 in a cohort of women with HIV infection and found that alcohol use (i.e., any use in the prior 6 months) was associated with a higher FIB-4 in HIV monoinfected women but not in HCV/

HIV-coinfected women. In our study, the magnitude of association between heavy alcohol use and absence of liver fibrosis appeared stronger in the HIV monoinfected participants (AOR=0.75) than in the HCV/HIV-coinfected participants (AOR=0.85), although the difference was not statistically significant.

This is the first study of which we are aware that examined the effect of lifetime alcohol use on liver fibrosis using FIB-4 and APRI in HIV infection. We anticipated that lifetime alcohol consumption might better predict liver injury than current heavy alcohol use, as some patients who are currently abstinent might have had substantial alcohol exposure in the past. The method we used to capture lifetime alcohol exposure, Lifetime Drinking History (Skinner and Sheu, 1982), has been validated (Koenig et al., 2009). However, despite employing a methodologically rigorous approach using a more appropriate measure of alcohol use given the outcome being studied, we were unable to detect an impact of lifetime alcohol use on liver fibrosis. Exploratory analyses did not suggest that results differed significantly based on HCV, or on antiretroviral treatment use. Even though we were underpowered to detect any small difference among groups, we also performed an additional stratified analysis by the presence of HBsAg. In those participants who were HBsAg positive, the point estimates suggested that patients with higher amounts of lifetime alcohol intake had lower odds of presenting FIB-4 values consistent with the absence of liver fibrosis, but these results did not reach statistical significance.

The apparent lack of association between lifetime alcohol intake and liver fibrosis in this study of HIV-infected subjects with alcohol problems was unexpected and deserves some discussion. Studies that have used more crude measures of prior alcohol intake have noted associations between alcohol use and fibrosis determined by liver biopsy (Benhamou et al., 1999; Hutchinson et al., 2005; Poynard et al., 1997; Tural et al., 2003). However, as noted, other studies using FIB-4 have failed to show an impact on liver damage of current alcohol use in HCV/HIV-coinfected patients, though associations have been observed in HIV-infected patients without HCV infection (Blackard et al., 2011). One possible explanation is that the synergy between alcohol and HCV described in HIV negative persons might be overshadowed by the deleterious effect that HIV-related immune suppression has on the presence of liver fibrosis, and the synergy between HIV and HCV alone. Alcohol might be a less important promoter of liver damage in this setting, with competing risks such as HCV infection, immune suppression, fatty liver disease and antiretroviral therapy-related liver toxicity (Joshi et al., 2011). In support of this hypothesis, we did observe a significant association between CD4 count and liver fibrosis, as well as a strong effect from HCV. Larger studies are needed to elucidate the differential effects of alcohol based on HCV status in HIV-infected cohorts.

There are a number of limitations to the study. The study was focused on a population with alcohol problems, and therefore the range of cumulative exposure to alcohol may have been narrower than that in the general population. However, we did find a spectrum of self-reported alcohol exposure, as 22.3% of the study population reported a lifetime alcohol intake <150 kg., while 45% reported >600 kg. Even though lifetime drinking history is a reliable measure of alcohol exposure (Koenig et al., 2009; Skinner and Sheu, 1982), it may be subject to recall bias. Furthermore, lifetime drinking collapses a spectrum of drinking patterns into a measure of cumulative use. It may be that patterns of use are more informative. However, we attempted to address this by analyzing years of heavy episodic use and found similar results. Another limitation of our study is the use of non-invasive indices for fibrosis that have not been widely validated for alcoholic liver disease (Lieber et al., 2006; Naveau et al., 2009). If higher liver enzyme levels due to alcohol misuse would have overestimated the amount of patients with advanced liver fibrosis, we would be biased to find an between alcohol intake and liver fibrosis, and we did not find any. Future studies

should explore the use of other non-invasive methods of the extent of liver fibrosis. An additional limitation was the relatively small number of individuals with advanced fibrosis; hence our additional focus on absence of fibrosis as the primary outcome. Nonetheless, non invasive indices as APRI and FIB-4 are clinically useful as they are easily available, can predict clinical events and guide clinical decisions (Nunes et al., 2010; Sanvisens et al., 2011).

Because our main finding was unexpected, because of methodological limitations, and because few if any other studies have examined the association (lifetime use and liver fibrosis among HIV-infected), we would not feel confident concluding that a lifetime of heavy alcohol use has no effect on liver fibrosis in people with HIV infection. But the absence of any clear signal does raise questions about the role of long-term heavy exposure to alcohol in this circumstance, an area of inquiry that will require additional investigation. Furthermore, our findings should not be interpreted to mean that HCV/HIV-coinfected adults could drink alcohol without consequences given the spectrum of known alcohol-related complications (Samet et al., 2004a). Current heavy alcohol use was associated with fibrosis in prior studies. And regardless of its impact on liver fibrosis, alcohol use in this setting is detrimental for a number of reasons. Current heavy alcohol use has been noted as a contraindication to HCV antiviral therapy, (Ghany et al., 2009) and has also been related to decreased adherence to HCV antiviral treatment (Anand et al., 2006) and a lower likelihood of sustained viral response (McCartney et al., 2008). Moreover, heavy alcohol use among HIV-infected patients is associated with lower antiretroviral treatment adherence (Chander et al., 2006) and a faster CD4 decline in those not exposed to antiretroviral therapy (Samet et al., 2007).

In summary, in this first examination of the impact of lifetime alcohol use on liver disease in a cohort of HIV-infected patients with current or past alcohol problems, we found no statistically significant association between lifetime alcohol consumption and liver fibrosis. Our results suggest that lifetime alcohol consumption may be a less important promoter of liver fibrosis than HCV infection or HIV-related immune suppression.

Acknowledgments

Financial Disclosure: This study was supported by funding from the NIAAA R01-AA13216, K24-AA015674 and NIDA R25DA13582.

Dr. Fuster is a postdoctoral grantee from the Spanish Ministry of Education/Fundación Española para la Ciencia y la Tecnología (EDU/3495/2010). Prior to the award of that grant, Dr. Fuster was partially funded by grants from Ministry of Science and Innovation, Spain (grants RD06/001/0021 and RD06/006/1014) and Ministry of Health (grant EC11-042).

References

Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol. 2007; 13:2436–2441. [PubMed: 17552026]

Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, Wright T. VA-HCV-001 Study Group. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. Gastroenterology. 2006; 130:1607–1616. [PubMed: 16697724]

Bambha K, Pierce C, Cox C, French AL, Tien PC, Sharp GB, Augenbraun M, Glesby MJ, Villacres MC, Plankey M, Strickler HD, Gange SJ, Peters MG. Assessing mortality in women with hepatitis C virus and human immunodeficiency virus using indirect markers of fibrosis. AIDS. 2012; 26:599–607. [PubMed: 22156972]

Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, Saveria Croce L, Sasso F, Pozzato G, Cristianini G, Brandi G. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. Gut. 1997; 41:845–850. [PubMed: 9462221]

Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, Vidaud M, Bricaire F, Opolon P, Katlama C, Poynard T. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology. 1999; 30:1054–1058. [PubMed: 10498659]

Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, Snydman DR. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis. 2001; 32:492–497. [PubMed: 11170959]

Blackard JT, Welge JA, Taylor LE, Mayer KH, Klein RS, Celentano DD, Jamieson DJ, Gardner L, Sherman KE. HIV mono-infection is associated with FIB-4 - A noninvasive index of liver fibrosis - in women. Clin Infect Dis. 2011; 52:674–680. [PubMed: 21248367]

Campbell JV, Hagan H, Latka MH, Garfein RS, Golub ET, Coady MH, Thomas DL, Strathdee SA. STRIVE Project. High prevalence of alcohol use among hepatitis C virus antibody positive injection drug users in three US cities. Drug Alcohol Depend. 2006; 81:259–265. [PubMed: 16129567]

Castellano-Higuera A, Gonzalez-Reimers E, Aleman-Valls MR, Abreu-Gonzalez P, Santolaria-Fernandez F, De La Vega-Prieto MJ, Gomez-Sirvent JL, Pelazas-Gonzalez R. Cytokines and lipid peroxidation in alcoholics with chronic hepatitis C virus infection. Alcohol Alcohol. 2008; 43:137–142. [PubMed: 18216180]

Chander G, Lau B, Moore RD. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. J Acquir Immune Defic Syndr. 2006; 43:411–417. [PubMed: 17099312]

Chaudhry AA, Sulkowski MS, Chander G, Moore RD. Hazardous drinking is associated with an elevated aspartate aminotransferase to platelet ratio index in an urban HIV-infected clinical cohort. HIV Med. 2009; 10:133–142. [PubMed: 19207596]

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

Gebo KA, Herlong HF, Torbenson MS, Jenckes MW, Chander G, Ghanem KG, El-Kamary SS, Sulkowski M, Bass EB. Role of liver biopsy in management of chronic hepatitis C: a systematic review. Hepatology. 2002; 36:S161–S172. [PubMed: 12407590]

Ghany MG, Strader DB, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009; 49:1335–1374. [PubMed: 19330875]

Hutchinson SJ, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. Clin Gastroenterol Hepatol. 2005; 3:1150–1159. [PubMed: 16271348]

Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. Lancet. 2011; 377:1198–1209. [PubMed: 21459211]

Koenig LB, Jacob T, Haber JR. Validity of the lifetime drinking history: a comparison of retrospective and prospective quantity-frequency measures. J Stud Alcohol Drugs. 2009; 70:296–303. [PubMed: 19261242]

Lieber CS, Weiss DG, Morgan TR, Paronetto F. Aspartate aminotransferase to platelet ratio index in patients with alcoholic liver fibrosis. Am J Gastroenterol. 2006; 101:1500–1508. [PubMed: 16863553]

Loko MA, Castera L, Dabis F, Le Bail B, Winnock M, Coureau G, Bioulac-Sage P, de Ledinghen V, Neau D. Groupe d'Epidemiologie Clinique du SIDA en Aquitaine (GECSA). Validation and comparison of simple noninvasive indexes for predicting liver fibrosis in HIV-HCV-coinfected patients: ANRS CO3 Aquitaine cohort. Am J Gastroenterol. 2008; 103:1973–1980. [PubMed: 18796094]

McCartney EM, Beard MR. Impact of alcohol on hepatitis C virus replication and interferon signaling. World J Gastroenterol. 2010; 16:1337–1343. [PubMed: 20238400]

McCartney EM, Semendric L, Helbig KJ, Hinze S, Jones B, Weinman SA, Beard MR. Alcohol metabolism increases the replication of hepatitis C virus and attenuates the antiviral action of interferon. J Infect Dis. 2008; 198:1766–1775. [PubMed: 18956976]

Mendeni M, Foca E, Gotti D, Ladisa N, Angarano G, Albini L, Castelnuovo F, Carosi G, Quiros-Roldan E, Torti C. Evaluation of liver fibrosis: concordance analysis between noninvasive scores

(APRI and FIB-4) evolution and predictors in a cohort of HIV-infected patients without hepatitis C and B infection. Clin Infect Dis. 2011; 52:1164–1173. [PubMed: 21467023]

Monto A, Patel K, Bostrom A, Pianko S, Pockros P, McHutchison JG, Wright TL. Risks of a range of alcohol intake on hepatitis C-related fibrosis. Hepatology. 2004; 39:826–834. [PubMed: 14999703]

Naveau S, Gaude G, Asnacios A, Agostini H, Abella A, Barri-Ova N, Dauvois B, Prevot S, Ngo Y, Munteanu M, Balian A, Njike-Nakseu M, Perlemuter G, Poynard T. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. Hepatology. 2009; 49:97–105. [PubMed: 19053048]

Nunes D, Fleming C, Offner G, Craven D, Fix O, Heeren T, Koziel MJ, Graham C, Tumilty S, Skolnik P, Stuver S, Horsburgh CR Jr, Cotton D. Noninvasive markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. Am J Gastroenterol. 2010; 105:1346–1353. [PubMed: 20179698]

Nunes D, Fleming C, Offner G, O'Brien M, Tumilty S, Fix O, Heeren T, Koziel M, Graham C, Craven DE, Stuver S, Horsburgh CR Jr. HIV infection does not affect the performance of noninvasive markers of fibrosis for the diagnosis of hepatitis C virus-related liver disease. J Acquir Immune Defic Syndr. 2005; 40:538–544. [PubMed: 16284529]

Obel N, Omland LH, Kronborg G, Larsen CS, Pedersen C, Pedersen G, Sorensen HT, Gerstoft J. Impact of non-HIV and HIV risk factors on survival in HIV-infected patients on HAART: a population-based nationwide cohort study. PLoS One. 2011; 6:e22698. [PubMed: 21799935]

Peters MG, Terrault NA. Alcohol use and hepatitis C. Hepatology. 2002; 36:S220–S225. [PubMed: 12407597]

Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997; 349:825–832. [PubMed: 9121257]

Price JC, Seaberg EC, Badri S, Witt MD, D'Acunto K, Thio CL. HIV Monoinfection Is Associated With Increased Aspartate Aminotransferase-to-Platelet Ratio Index, a Surrogate Marker for Hepatic Fibrosis. J Infect Dis. 2012; 205:1005–1013. [PubMed: 22291196]

Rehm J, Taylor B, Mohapatra S, Irving H, Baliunas D, Patra J, Roerecke M. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug Alcohol Rev. 2010; 29:437–445. [PubMed: 20636661]

Roudot-Thoraval F, Bastie A, Pawlotsky JM, Dhumeaux D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. The Study Group for the Prevalence and the Epidemiology of Hepatitis C Virus. Hepatology. 1997; 26:485–490. [PubMed: 9252163]

Samet JH, Cheng DM, Libman H, Nunes DP, Alperen JK, Saitz R. Alcohol consumption and HIV disease progression. J Acquir Immune Defic Syndr. 2007; 46:194–199. [PubMed: 17667330]

Samet JH, Horton NJ, Meli S, Freedberg KA, Palepu A. Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. Alcohol Clin Exp Res. 2004a; 28:572–577. [PubMed: 15100608]

Samet JH, Phillips SJ, Horton NJ, Traphagen ET, Freedberg KA. Detecting alcohol problems in HIV-infected patients: use of the CAGE questionnaire. AIDS Res Hum Retroviruses. 2004b; 20:151–155. [PubMed: 15018702]

Sanvisens A, Fuster D, Serra I, Tor J, Tural C, Rey-Joly C, Muga R. Estimated Liver Fibrosis and its Impact on All-Cause Mortality of HCV-Monoinfected and HCV/HIV-Coinfected Drug Users. Curr HIV Res. 2011; 9:256–262. [PubMed: 21675942]

Sebastiani G, Halfon P, Castera L, Pol S, Thomas DL, Mangia A, Di Marco V, Pirisi M, Voiculescu M, Guido M, Bourliere M, Noventa F, Alberti A. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. Hepatology. 2009; 49:1821–1827. [PubMed: 19291784]

Siu L, Foont J, Wands JR. Hepatitis C virus and alcohol. Semin Liver Dis. 2009; 29:188–199. [PubMed: 19387918]

Skinner HA, Sheu WJ. Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. J Stud Alcohol. 1982; 43:1157–1170. [PubMed: 7182675]

Stein MD, Hanna L, Natarajan R, Clarke J, Marisi M, Sobota M, Rich J. Alcohol use patterns predict high-risk HIV behaviors among active injection drug users. J Subst Abuse Treat. 2000; 18:359–363. [PubMed: 10812309]

Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M. APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006; 43:1317–1325. [PubMed: 16729309]

Stoller EP, Hund AJ, Webster NJ, Blixen CE, Perzynski AT, McCormick RA, Kanuch SW, Dawson NV. Alcohol consumption within the context of hepatitis C: a qualitative study of non-problematic drinkers. Alcohol Alcohol. 2006; 41:546–552. [PubMed: 16855001]

Szabo G, Aloman C, Polyak SJ, Weinman SA, Wands J, Zakhari S. Hepatitis C infection and alcohol use: A dangerous mix for the liver and antiviral immunity. Alcohol Clin Exp Res. 2006; 30:709–719. [PubMed: 16573590]

Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS. 2008; 22:1979–1991. [PubMed: 18784461]

Thimme R, Bukh J, Spangenberg HC, Wieland S, Pemberton J, Steiger C, Govindarajan S, Purcell RH, Chisari FV. Viral and immunological determinants of hepatitis C virus clearance, persistence, and disease. Proc Natl Acad Sci U S A. 2002; 99:15661–15668. [PubMed: 12441397]

Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, Nolt K, Nelson KE, Strathdee SA, Johnson L, Laeyendecker O, Boitnott J, Wilson LE, Vlahov D. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. 2000; 284:450–456. [PubMed: 10904508]

Tural C, Fuster D, Tor J, Ojanguren I, Sirera G, Ballesteros A, Lasanta JA, Planas R, Rey-Joly C, Clotet B. Time on antiretroviral therapy is a protective factor for liver fibrosis in HIV and hepatitis C virus (HCV) co-infected patients. J Viral Hepat. 2003; 10:118–125. [PubMed: 12614468]

Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, Fontaine H, Pol S. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology. 2007; 46:32–36. [PubMed: 17567829]

Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003; 38:518–526. [PubMed: 12883497]

Walley AY, Cheng DM, Libman H, Nunes D, Horsburgh CR Jr, Saitz R, Samet JH. Recent drug use, homelessness and increased short-term mortality in HIV-infected persons with alcohol problems. AIDS. 2008; 22:415–420. [PubMed: 18195568]

Table 1

Characteristics of adults with HIV infection and current or past alcohol problems

Characteristic	Total study population [n=308]
Males [n (%)]	225 (73.1)
Age (years) [mean (SD)]	42.8 (7.3)
HCV infection (HCV RNA) [n (%)] (n=307)	150 (48.9)
HBsAg positive [n (%)] (n=298)	26 (8.7)
CD4 count [cells/mm^3] (n=289)	
<200 [n (%)]	54 (18.7)
200–500 [n (%)]	121 (41.9)
>500 [n (%)]	114 (39.4)
HIV RNA viral load [copies/ mL] (n=274)	
<1000 [n (%)]	135 (49.3)
≥1000 [n (%)]	139 (50.7)
Body mass index [kg/ m^2] (n=293)	
<21 [n (%)]	26 (8.9)
21–24 [n (%)]	71 (24.2)
>24 [n (%)]	196 (66.9)
Antiretroviral therapy [n (%)]	186 (60.4)
Lifetime injection drug use [n (%)]	165 (53.7)
Duration of injection-drug use (years) [mean (SD)] (n=307)	11.7 (12.8)
Lifetime alcohol consumption [kg of alcohol] (n=291)	
<150 kg [n (%)]	65 (22.3)
150–600 kg [n (%)]	95 (32.7)
>600 kg [n (%)]	131 (45.0)
Heavy episodic drinking [years] (n=301)	
<9 years [n (%)]	94 (31.2)
9–21 years [n (%)]	117 (38.9)
>21 years [n (%)]	90 (29.9)
Heavy alcohol use [NIAAA definition] (last 30 days) [n (%)] (n=306)	101 (33.0)
FIB-4	
Absence of liver fibrosis (<1.45) [n (%)]	187 (60.7)
Advanced liver fibrosis (>3.25) [n (%)]	31 (10.1)
APRI	

Characteristic	Total study population [n=308]
Absence of liver fibrosis (<0.5) [n (%)]	178 (57.8)
Advanced liver fibrosis (>1. 5) [n (%)]	28 (9.1)

HCV RNA: Hepatitis C virus Ribonucleic acid; HBsAg: Hepatitis B surface antigen.

Table 2

Unadjusted bivariable analysis and multivariable logistic regression models evaluating the association between alcohol use and absence of liver fibrosis [FIB-4 <1.45 and APRI <0.5]

Variable	Unadjusted OR (95% CI) for FIB-4 <1.45	p-value	Adjusted OR (95% CI) for FIB-4 <1.45	p-value	Unadjusted OR (95% CI) for APRI <0.5	p-value	Adjusted OR (95% CI) for APRI <0.5	p-value
Model 1								
Lifetime alcohol consumption [kg of alcohol] (n=272)								
<150 kg	1	0.59	1	0.95	1	0.4	1	0.52
150–600 kg	0.77 (0.40, 1.48)		1.12 (0.52, 2.52)		1.30 (0.68, 2.47)		1.36 (0.64, 2.90)	
>600 kg	0.73 (0.39, 1.36)		1.11 (0.52, 2.36)		0.90 (0.49, 1.63)		0.96 (0.47, 1.93)	
Sex:								
Female			1.02 (0.52, 2.02)	0.95			0.94 (0.50, 1.77)	0.85
Male			1				1	
HCV infection (HCV RNA)			0.29 (0.16, 0.52)	<0.01			0.16 (0.09, 0.28)	<0.01
CD4 count [cells/mm^3]				*				
<200			0.30 (0.14, 0.67)	<0.01			0.56 (0.26, 1.20)	0.26
200–500			0.44 (0.23, 0.82)	<0.01			0.69 (0.38, 1.26)	
>500			1				1	
Age [per additional year]			0.89 (0.85, 0.93)	<0.01			1.00 (0.96, 1.04)	0.98
Model 2								
Heavy episodic drinking (n=282)								
<9 years	1	0.21	1	0.42	1	0.52	1	0.99
9–21 years	1.55 (0.88, 2.71)		1.37 (0.70, 2.68)		1.29 (0.74, 2.24)		0.99 (0.52, 1.87)	
>21 years	1.01 (0.56, 1.81)		1.58 (0.78, 3.71)		0.97 (0.54, 1.73)		1.02 (0.52, 2.00)	
Sex								

Variable	Unadjusted OR (95% CI) for FIB-4 <1.45	p-value	Adjusted OR (95% CI) for FIB-4 <1.45	p-value	Unadjusted OR (95% CI) for APRI <0.5	p-value	Adjusted OR (95% CI) for APRI <0.5	p-value
Female			0.94 (0.49, 1.80)	0.85			0.98 (0.53, 1.82)	0.95
Male			1				1	
HCV infection (HCV RNA)			0.33 (0.19, 0.58)	<0.01			0.17 (0.10, 0.28)	<0.01
CD4 count [cells/mm^3]				*				
<200			0.32 (0.15, 0.70)	<0.01			0.57 (0.27, 1.21)	0.25
200–500			0.40 (0.22, 0.74)	<0.01			0.67 (0.38, 1.21)	
>500			1				1	
Age [per additional year]			0.89 (0.85, 0.93)	<0.01			0.99 (0.96, 1.03)	0.75
Model 3								
Heavy alcohol use [NIAAA definition] (last 30 days) (n=286)	0.99 (0.61, 1.61)	0.96	0.89 (0.50, 1.58)	0.69	0.82 (0.51, 1.33)	0.43	0.86 (0.49, 1.50)	0.59
Sex:								
Female			0.99 (0.52, 1.89)	0.97			1.02 (0.55, 1.88)	0.95
Male			1				1	
HCV infection (HCV RNA)			0.31 (0.18, 0.54)	<0.01			0.16 (0.09, 0.27)	<0.01
CD4 count [cells/mm^3]				*				
<200			0.31 (0.14, 0.67)	<0.01			0.55 (0.26, 1.16)	0.23
200–500			0.40 (0.22, 0.74)	<0.01			0.68 (0.38, 1.22)	
>500			1				1	
Age [per additional year]			0.89 (0.86, 0.93)	<0.01			0.99 (0.96, 1.03)	0.68

HCV RNA: Hepatitis C virus Ribonucleic acid;

*global p-value <0.05; OR (95% CI): Odds ratio (95% Confidence interval).

Table 3

Unadjusted bivariable analysis and multivariable logistic regression models evaluating the association between alcohol use and advanced liver fibrosis [FIB-4 >3.25 and APRI >1.5].

Variable	Unadjusted OR (95% CI) for FIB-4 >3.25	p-value	Adjusted OR (95% CI) for FIB-4 >3.25	p-value	Unadjusted OR (95% CI) for APRI >1.5	p-value	Adjusted OR (95% CI) for APRI >1.5	p-value
Model 1								
Lifetime alcohol consumption [kg of alcohol] (n=272)								
<150 kg	1	0.41	1	0.11	1	0.57	1	0.39
150–600 kg	0.49 (0.17, 1.40)		0.27 (0.07, 0.98)		0.56 (0.18, 1.75)		0.42 (0.12, 1.53)	
>600 kg	0.69 (0.28, 1.70)		0.64 (0.23, 1.81)		0.84 (0.31, 2.23)		0.76 (0.26, 2.19)	
Sex:								
Female			2.38 (0.91, 6.19)	0.08			0.54 (0.17,1.75)	0.31
Male			1				1	
HCV infection (HCV RNA)			3.39 (1.17, 9.78)	0.02			5.16 (1.66, 16.06)	<0.01
CD4 count [cells/mm^3]				*				*
<200			12.75 (2.45, 66.38)	<0.01			6.65 (1.61, 27.45)	<0.01
200–500			7.54 (1.62, 35.04)	<0.01			3.55 (0.95, 13.30)	0.06
>500			1				1	
Age [per additional year]			1.08 (1.01, 1.15)	0.02			1.04 (0.98, 1.11)	0.24
Model 2								
Heavy episodic drinking (n=282)								
<9 years	1	0.66	1	0.39	1	0.89	1	0.61
9–21 years	0.86 (0.36, 2.05)		1.28 (0.46, 3.51)		0.98 (0.39, 2.47)		1.25 (0.45, 3.47)	
>21 years	0.64 (0.24, 1.72)		0.61 (0.21, 1.81)		0.80 (0.28, 2.24)		0.72 (0.24, 2.17)	
Sex								

Variable	Unadjusted OR (95% CI) for FIB-4 >3.25	p-value	Adjusted OR (95% CI) for FIB-4 >3.25	p-value	Unadjusted OR (95% CI) for APRI >1.5	p-value	Adjusted OR (95% CI) for APRI >1.5	p-value
Female			1.98 (0.79, 4.69)	0.14			0.45 (0.14, 1.43)	0.18
Male			1				1	
HCV infection (HCV RNA)			4.18 (1.46, 11.92)	<0.01			6.41 (2.07, 19.80)	<0.01
CD4 count [cells/mm^3]				*				*
<200			10.20 (1.99, 52.24)	<0.01			6.00 (1.47, 24.48)	0.01
200–500			8.27 (1.81, 37.92)	<0.01			4.07 (1.11, 14.94)	0.03
>500			1				1	
Age [per additional year]			1.07 (1.01, 1.14)	0.02			1.04 (0.98, 1.10)	0.24
Model 3								
Heavy alcohol use [NIAAA definition] (last 30 days) (n=286)	0.97 (0.44, 2.14)	0.94	1.10 (0.45, 2.65)	0.84	1.15 (0.51, 2.59)	0.74	1.14 (0.47, 2.77)	0.77
Sex:								
Female			1.85 (0.75, 4.55)	0.18			0.44 (0.14, 1.37)	0.15
Male			1				1	
HCV infection (HCV RNA)			4.35 (1.55, 12.19)	<0.01			6.55 (2.15, 19.97)	<0.01
CD4 count [cells/mm^3]				*				*
<200			10.95 (2.20, 54.41)	<0.01			6.61 (1.65, 26.49)	0.03
200–500			7.90 (1.73, 35.95)	<0.01			4.07 (1.11, 14.93)	<0.01
>500			1				1	
Age [per additional year]			1.06 (1.00, 1.13)	<0.05			1.03 (0.97, 1.10)	0.33

HCV RNA: Hepatitis C virus Ribonucleic acid;

*global p-value <0.05; OR (95% CI): Odds ratio (95% Confidence interval).

Table 4

Multivariable logistic regression models evaluating the association between alcohol use and absence of liver fibrosis (FIB-4 <1.45) stratified by HCV infection status

Variable	Adjusted odds ratio (95% IC) for absence of liver fibrosis	p-value
HCV negative		
Lifetime alcohol consumption [kg. of alcohol] (n=139)		
<150 kg.	1	0.52
150–600 kg.	1.61 (0.47, 5.53)	
>600 kg.	0.95 (0.29, 3.10)	
Heavy episodic drinking (n=144)		
<9 years	1	0.37
9–21 years	1.68 (0.63, 4.47)	
>21 years	2.17 (0.70, 6.73)	
Heavy alcohol use [NIAAA definition] (last 30 days) (n=148)	0.75 (0.32, 1.76)	0.51
HCV positive		
Lifetime alcohol consumption [kg. of alcohol] (n=133)		
<150 kg.	1	0.76
150–600 kg.	0.84 (0.27, 2.61)	
>600 kg.	1.18 (0.43, 3.26)	
Heavy episodic drinking (n=138)		
<9 years	1	0.97
9–21 years	1.07 (0.41, 2.80)	
>21 years	1.11 (0.44, 2.81)	
Heavy alcohol use [NIAAA definition] (last 30 days) (n=138)	0.85 (0.38, 1.92)	0.7

Table 5

Multivariable logistic regression models evaluating the association between alcohol use and absence of liver fibrosis (FIB-4 <1.45) stratified by antiretroviral therapy use and by presence of Hepatitis B surface antigen (HBsAg) status

Variable	Adjusted odds ratio (95% IC) for absence of liver fibrosis	p-value
Antiretoviral therapy.		
Lifetime alcohol consumption [kg. of alcohol] (n=175)		
<150 kg.	1	0.70
150–600 kg.	1.17 (0.43, 3.17)	
>600 kg.	1.45 (0.48, 2.24)	
No antiretoviral therapy.		
Lifetime alcohol consumption [kg. of alcohol] (n=116)		
<150 kg.	1	0.86
150–600 kg.	1.25 (0.27, 5.85)	
>600 kg.	0.93 (0.21, 4.04)	
HBsAg positive		
Lifetime alcohol consumption [kg. of alcohol] (n=24)		
<150 kg.	1	0.14
150–600 kg.	0.27 (0.01, 6.62)	
>600 kg.	0.04 (0.00, 1.67)	
HBsAg negative		
Lifetime alcohol consumption [kg. of alcohol] (n=259)		
<150 kg.	1	0.87
150–600 kg.	1.26 (0.50, 3.17)	
>600 kg.	1.22 (0.53, 2.85)	