Risky Alcohol Use and Serum Aminotransferase Levels in HIV-Infected Adults With and Without Hepatitis C

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ABSTRACT. Objective: The purpose of this study was to examine the association between risky drinking amounts and serum aminotransferase levels in HIV-infected adults with and without hepatitis C virus (HCV) infection. **Method:** In a prospective cohort of HIV-infected adults with current or past alcohol problems, we assessed whether drinking risky amounts (as defined by the National Institute on Alcohol Abuse and Alcoholism) was associated with higher levels of serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) over time, stratifying analyses by HCV status. Generalized linear mixed effects regression models were used to examine the association between risky drinking and natural log-transformed AST and ALT over time. **Results:** Among HIV/HCV–coinfected persons (n = 200), risky drinking was associated with a higher adjusted mean AST (62.2 vs. 51.4 U/L; adjusted ratio of means 1.2, 95% CI [1.07, 1.37], p = .003) and ALT (51.3 vs. 41.6 U/L; adjusted ratio of means 1.2, 95% CI [1.07, 1.42], p = .004) compared with non–risky drinking. In contrast, among HIV-infected adults without HCV infection (n = 197), there were no significant differences between those who did and did not drink risky amounts in AST (34.7 vs. 33.3 U/L; adjusted ratio of means = 1.0, 95% CI [0.95, 1.14], p = .36) or ALT (29.1 vs. 28.7 U/L; adjusted ratio of means = 1.0, 95% CI [0.91, 1.13], p = .78). **Conclusions:** Among HIV-infected adults with HCV, those who drink risky amounts have higher serum aminotransferase levels than those who do not drink risky amounts. These results suggest that drinking risky amounts may be particularly harmful in HIV/HCV-coinfected adults and supports recommendations that providers pay special attention to drinking in this population. (*J. Stud. Alcohol Drugs, 74,* 266–270, 2013)

ALCOHOL USE CONTRIBUTES TO adverse health outcomes (e.g., cirrhosis and liver cancer) among people with hepatitis C virus (HCV) infection (Peters and Terrault, 2002; Schiff and Ozden, 2003), and those with HIV/HCV coinfection have accelerated progression of HCV-related liver disease (Sulkowski, 2008). Since the advent of potent combination antiretroviral therapy, chronic HCV infection has emerged as a major cause of morbidity and mortality among HIV-infected persons (Weber et al., 2006). Despite these risks, about half of HIV-infected persons in the U.S. drink alcohol, and both HIV- and HCV-infected persons have been observed to drink greater amounts than the general population (Armstrong et al., 2006; Galvan et al., 2002).

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Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are biomarkers that are commonly measured in healthcare settings. Although not entirely specific to the liver (in particular AST), elevated serum aminotransferase levels may suggest hepatic injury from various mechanisms, including viral hepatitis, alcoholic liver disease, or drug-related toxicity. Increased aminotransferases are often signals that prompt further clinical evaluation and, on occasion, changes in medication dose or selection. Furthermore, elevated serum aminotransferase levels have been associated with mortality in national and community-based samples (Kim et al., 2004; Lee et al., 2008). Risky drinking amounts have been found to be associated with AST in a national sample of male adults that excluded individuals with known HCV (Tsai et al., 2012). Studies of serum aminotransferases and drinking in populations with HIV and HCV infection are lacking. The effects of risky drinking amounts on the liver appear to be greater among persons with HCV infection, suggesting a synergistic effect of alcohol and the viral infection (Corrao and Arico, 1998; Donato et al., 2002). It is important to understand the effects of risky drinking on these commonly used liver tests among HIV-infected patients with and without HCV in order to interpret these results

clinically and to counsel patients appropriately on the effects of alcohol use.

Thresholds of consumption that define risky amounts are established by public health agencies around the world based on associations between alcohol consumption amounts and health harms. Yet there is little research linking these thresholds to common clinical consequences in HIV-infected adults with and without HCV. The aim of this study was to assess the association between risky drinking amounts as defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (NIAAA, 1995) and serum aminotransferase levels among HIV-infected adults with and without HCV coinfection. We hypothesized that risky drinking amounts would be associated with higher AST and ALT levels in both HIV/HCV-coinfected persons as well as those infected with HIV alone and, secondarily, that the association would be stronger among individuals who were coinfected with HCV.

Method

Design

Data were obtained from a prospective, observational cohort study (HIV-Longitudinal Interrelationships of Viruses and Ethanol [HIV-LIVE]; Samet et al., 2007), in which study visits occurred at 6-month intervals across a maximum of 48 months.

Subjects

Recruitment for the HIV-LIVE study 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 (a) documented HIV antibody test by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot, (b) two or more affirmative responses to the CAGE alcoholism screening questionnaire (Mayfield et al., 1974; Samet et al., 2004) or physician-investigator diagnosis of alcoholism, and (c) ability to speak English or Spanish. Exclusion criteria were (a) scoring less than 21 on the 30-item Folstein Mini-Mental State Examination (Folstein et al., 1975) (indicating cognitive impairment) and (b) an inability to provide informed consent. The institutional review boards of Boston Medical Center and Beth Israel Deaconess Medical Center approved this study.

Dependent variables

The two primary outcomes were AST and ALT levels. AST and ALT measurements were recorded at baseline and every 12 months. If available, results were recorded from the medical record, and, if data were not available, testing was performed at the study visit. Testing occurred at clinical laboratories at Boston Medical Center and Beth Israel Deaconess Medical Center, which are Clinical Laboratory Improvement Amendments–certified laboratories. The upper limit of normal for testing was 40 U/L for AST and 31 U/L for ALT. For primary analyses, AST and ALT were natural log-transformed because of skewness in their distributions, and final results were back-transformed to facilitate interpretation. In addition, as a secondary analysis we examined the dichotomous outcome of having either AST or ALT elevated to greater than twice the normal limit, a threshold with clinical significance.

Independent variables

The main independent variable was risky alcohol use in the past 30 days (yes vs. no) as defined by NIAAA (1995) guidelines. Alcohol use was assessed using the Timeline Followback calendar-based method (Sobell and Sobell, 1992). Risky alcohol use was defined as (a) drinking greater than 14 standard drinks per week or greater than 4 drinks in a day for men or (b) drinking greater than 7 drinks per week or greater than 3 drinks in a day for women using NIAAA definitions for a standard drink. Analyses compared adults with risky drinking to those without (individuals who either abstained or drank less than risky amounts). Potential confounders controlled for in the multivariable analysis were age, sex, race, marital status, diabetes mellitus, cirrhosis, body mass index (BMI), cluster of differentiation 4 (CD4) cell count, current antiretroviral medication use and lifetime alcohol use (grams of alcohol consumed). Diabetes mellitus and cirrhosis were based on patient self-report. Lifetime alcohol use was quantified by multiplying the number of lifetime alcohol units × 14 g of alcohol/unit. Chronic HCV infection was considered an effect modifier, and therefore the primary analyses were stratified based on this factor. HCV antibody testing was performed for all subjects, and positive HCV antibody results were confirmed with HCV RNA testing.

Statistical analyses

Descriptive statistics were used to characterize the study sample at baseline by chronic HCV infection. Chi-square and Student's *t* tests were used to compare variables between the HCV-infected and uninfected subgroups, as appropriate. We examined the relationship between risky drinking and natural log-transformed AST and ALT levels over time by fitting separate multivariable longitudinal regression models for each outcome, adjusting for potential confounders (age, sex, race, cirrhosis, diabetes mellitus, BMI, CD4 cell count, use of antiretroviral medications, and lifetime alcohol use). Generalized linear mixed-effects models that included subject-specific random intercepts and slopes were used to

account for the correlation from using repeated observations on the same subject. Group differences and corresponding confidence intervals (CIs) were back-transformed from the natural log scale to calculate the ratio of results for risky drinkers relative to non–risky drinkers. Risky alcohol use, CD4 count, BMI, and antiretroviral medications were included in regression analyses as time-dependent variables. Additional longitudinal regression models were used to model the effect of risky drinking on the relative odds of having AST or ALT levels twice the normal threshold value. Because the effect of risky drinking on serum aminotransferase levels was expected to differ based on chronic HCV infection status, analyses were stratified by HCV status, and the estimated effect of risky drinking is reported separately for those groups. Although stratified analyses were planned a priori, tests of interaction between risky drinking and HCV infection status were also performed on the entire cohort; however, we did not expect to be adequately powered to detect interactions. Before performing regression modeling, we calculated the correlations between independent variables to assess potential collinearity, and no pair of variables had a Spearman correlation greater than .40. All analyses were conducted using two-sided tests and a significance level of 0.05. The statistical analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

Results

Of the 400 participants in the HIV-LIVE cohort, 397 had been tested for HCV infection and were included in the current analysis. Of these 397 HIV-infected subjects, 200 (50.4%) were found to have detectable HCV RNA and were considered to be HIV/HCV-coinfected. At baseline, HIV/HCV-coinfected participants were more likely to be older (*M* [*SD*] = 44 [7] vs. 41 [8] years, $p < .01$), have a lower BMI (26 [4] vs 27 [6] kg/m^2, $p < .01$), and have a lower CD4 count (413 [264] vs. 495 [325] cells/μL), and they were more likely to have cirrhosis (19% vs. 6%, $p < .01$) and diabetes mellitus (10% vs. 4%, $p < .01$). HCV-positive participants reported greater lifetime alcohol use compared with those without HCV (*Mdn* = 42.8 vs. 27.6 kg, $p < .01$). There was no difference between HIV/HCV-coinfected and HIV-infected participants in the percentage that was female (27% vs. 23%, $p = .4$), White (34% vs. 32%, $p = .43$) or on antiretroviral therapy (65% vs. 60%, $p = .35$). At baseline, participants who were HIV/HCV-coinfected were more likely to have AST or ALT increased to at least twice the upper limit of normal compared with HIV-infected patients (34% vs. 10%, $p < .01$). There were no differences in the percentage who were drinking risky amounts between HCV-infected and uninfected participants (29% vs. 34%, $p = .32$).

The median follow-up for the study sample was 23.7 months (interquartile range [IQR]: 12.2–31.7 months), the median number of follow-up assessments was 6 (IQR: 4–7), and the median number of AST and ALT measurements was 3 (IQR: 2–4). Analyses of longitudinal data included 1,258 observations from 397 subjects. Adjusted mean AST and ALT levels over time for participants with and without risky drinking and the ratio of group means are presented in Table 1 by HCV infection status. These results were calculated from longitudinal regression models adjusted for time, age, sex, race, marital status, diabetes mellitus, cirrhosis, BMI, CD4 count, antiretroviral treatment, and lifetime alcohol use. Among coinfected individuals, risky drinking was associated with a higher mean AST (adjusted means = 62.2 vs. 51.4 U/L; adjusted ratio of means = 1.2, 95% CI [1.07, 1.37], $p = .003$) and ALT (adjusted means = 51.3 vs. 41.6 U/L; adjusted ratio of means = 1.2, 95% CI [1.07, 1.42], $p = .004$) compared with those who did not drink risky amounts. Thus mean AST and ALT levels were approximately 20% higher in those who drank risky amounts compared with those who did not. In contrast, among HIV-infected adults without HCV, there were no significant differences in AST or ALT between those who did and did not drink risky amounts (AST adjusted ratio of means = 1.0, $p = .36$; ALT adjusted ratio of means = 1.0, $p = .78$, respectively). The *p* value for the test of interaction between risky drinking and HCV infection was .18 for the AST model and .06 for the ALT model. Using the dichotomous outcome, we found that risky drinking was associated with a significantly higher odds of having AST or ALT elevated more than twice normal in the HIV/HCV-coinfected group (odds ratio = 2.18, 95% CI [1.26, 3.76], $p = .005$) but not among those without HCV (odds ratio = 1.84, 95% CI [0.86, 3.94], $p = .12$).

Table 1. Differences in adjusted[a] mean AST and ALT levels over time between HIV-infected adults with and without risky drinking, stratified by HCV infection ($N = 397$)[b]

Variable	Adjusted mean (U/L)		Adjusted ratio of means for risky vs. no risky drinking [95% CI]	*p*
	Risky drinking	No risky drinking		
HCV positive ($n = 200$)				
AST	62.2	51.4	1.2 [1.07, 1.37]	.003
ALT	51.3	41.6	1.2 [1.07, 1.42]	.004
HCV negative ($n = 197$)				
AST	34.7	33.3	1.0 [0.95, 1.14]	.36
ALT	29.1	28.7	1.0 [0.91, 1.13]	.78

Notes: AST = aspartate aminotransferase; ALT = alanine aminotransferase; HCV = hepatitis C virus; U/L = units per liter. [a]Adjusted for age, sex, race, cirrhosis, diabetes mellitus, body mass index, cluster of differentiation 4 (CD4) count, use of antiretroviral treatment, and lifetime alcohol use; [b]analyses of 1,258 observations.

Discussion

This study found a significant association between current risky drinking amounts as defined by the NIAAA and increased serum aminotransferase levels among HIV/

HCV-coinfected adults with current or past alcohol problems. However, the association was not significant among individuals with HIV monoinfection. The observed estimates suggest that alcohol may have a differential effect on AST and ALT depending on HCV status, reinforcing the message that drinking risky amounts of alcohol may be particularly harmful among HIV-infected patients who are also infected with HCV.

This study contributes to the relatively small body of literature that examines the effects of risky drinking amounts on AST and ALT among HIV-infected persons with and without HCV. A study of 2,365 HIV-infected adults without hepatitis B or C virus infection found that heavy alcohol use (defined as >40 g/day for women, >60 g/day for men—a threshold higher than that used in this study) was significantly associated with persistently elevated ALT levels (Kovari et al., 2010). Another study of 1,358 HIV-infected adults that examined risky drinking defined by NIAAA guidelines found that drinking risky amounts was associated with a noninvasive marker for liver fibrosis based on AST (aspartate aminotransferase to platelet ratio) (Chaudhry et al., 2009). Interestingly, that study found the magnitude of association to be somewhat stronger among HIV-infected participants without HCV compared with those with HCV. However, the authors noted that relatively small numbers of HIV/HCV-coinfected participants (11%) were drinking risky amounts, and the outcome of interest was a ratio of AST/platelets rather than AST alone. In contrast, a study of 318 injection drug users found that changes in AST and ALT correlated with changes in drinking only among persons who were HCV RNA positive, supporting a greater effect of alcohol on AST and ALT among individuals with chronic HCV infection (Drumright et al., 2011). Thus, the findings in this study are consistent with some, but not all, past reports and add support to the plausible viewpoint that risky alcohol use places the HIV/HCV-coinfected individual at the greatest risk of harm with respect to liver damage.

The study results provide some evidence to support Medicare quality performance measures which include physician counseling on alcohol risk among patients with HCV (Centers for Medicare & Medicare Services, 2011). Despite these measures and guidelines that recommend counseling patients to abstain or moderate alcohol use in the context of HCV, patients may still receive conflicting messages, perhaps in part because of physicians' awareness of evidence gaps (Blixen et al., 2008). Yet even when patients with HCV are counseled appropriately, numerous psychosocial factors may interfere with their ability to comply with recommendations to limit drinking (Perzynski et al., 2011). This study reinforces the need to target HCV-infected patients as a riskier subgroup for alcohol-related risks among HIV-infected populations, and supports research to develop tailored interventions to reduce drinking.

There are a number of study limitations. The sample size limited our ability to detect small differences in effect, which may have played a role with our nonsignificant findings among the HIV-monoinfected group. Likewise, it would have been of interest to have compared differences in AST and ALT between participants who drank non–risky versus risky amounts or non–risky amounts versus none. However, the small numbers of participants in the sample who drank non–risky amounts did not allow for such analyses. Transaminases are a reflection of hepatic injury but may not accurately reflect liver fibrosis or clinically manifest disease (Haber et al., 1995; Healey et al., 1995; Wilson et al., 2006). However, patients with persistently normal liver enzyme levels tend to have milder forms of histological damage (Sanchez-Conde et al., 2006), AST and ALT are components of several noninvasive indices to predict liver fibrosis (Martinez et al., 2011), and increased transaminase levels can prompt medication changes and additional testing. Moreover, elevated liver enzyme levels are associated with a higher risk of mortality in HIV/HCV-coinfected patients (Lewden et al., 2002) and in the general population (Kim, et al., 2004; Lee, et al., 2008). Finally, the study cohort comprised HIV-infected adults with current or past alcohol problems (as defined by the CAGE questionnaire); therefore, the results may not be broadly representative. However, alcohol problems are common (Saitz, 2005), and HIV-infected adults are more likely to drink heavily than the general population (Galvan, et al., 2002). Key strengths of the study are the use of valid interview methods to determine alcohol consumption amounts, the confirmation of HCV antibody tests with HCV RNA tests, and the use of AST and ALT measurements over time. Serum aminotransferases have high variability in individual patients, and a single determination should not be used to screen for hepatic injury (Lazo et al., 2008).

In summary, this study of HIV-infected persons found that risky drinking as defined by NIAAA was associated with significantly higher AST and ALT levels among persons who were coinfected with HCV. This study provides further evidence for the harmful effect of alcohol and HCV on liver health, and it reinforces the need to screen and counsel for hazardous alcohol use among HIV-infected populations, particularly those who are HCV-coinfected. These findings provide quantifiable estimates of the effects of risky drinking on common liver tests among HIV-infected patients and can enable health care providers to give patients more effective counseling about alcohol use.

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