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The impact of alcohol use on depressive symptoms in HIV-infected patients

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Abstract

Aims—To examine the impact of alcohol use on depressive symptoms in HIV-infected patients.

Design—Data were collected at 6-month intervals and analyzed to evaluate the association between alcohol dependence and consumption on depressive symptoms using longitudinal mixed effects regression models controlling for specified covariates.

Measurements—The two independent variables were current alcohol dependence assessed using the Composite International Diagnostic Interview (CIDI) and past month consumption (heavy versus not heavy drinking) using a validated calendar-based method. The primary outcome was depressive symptoms as measured by the Center for Epidemiologic Studies Depression Scale (CES-D).

Participants—HIV-infected adults with current or past alcohol problems.

Findings—Alcohol dependence and heavy alcohol use were significantly associated with higher CES-D scores in unadjusted models. In adjusted analyses, the association of current alcohol dependence persisted (mean difference in CES-D was 3.49 for dependence vs. non-dependence; 95% CI: 1.76–5.22), however the effect of heavy drinking was no longer statistically significant (mean difference in CES-D was 1.04 for heavy vs. not heavy drinking; 95% CI: -0.24–2.32).

Conclusions—Alcohol use is associated with more depressive symptoms in HIV-infected patients with alcohol problems. This association remains significant after adjusting for potential confounders only when alcohol use meets criteria for alcohol dependence.

Keywords

Alcohol drinking; Alcoholism; Depression; Depressive disorder; HIV; Acquired Immunodeficiency Syndrome

INTRODUCTION

The lifetime prevalence of an alcohol use disorder is higher in people living with HIV/AIDS (26% to 60%) than it is in the general population (14-24%).¹⁻⁹ In a national sample of HIV-infected patients, 8% to 12% were heavy drinkers, a proportion approximately twice that of the U.S. national average.^{10, 11} Depressive symptoms are also more common in HIV-infected patients with studies reporting a lifetime prevalence of depression ranging from 22% to 45% compared to 4% in the general population.¹²⁻¹⁷

Alcohol use and depressive symptoms significantly impact on the course of each other.¹⁸⁻²⁰ Given the high prevalence of these conditions in HIV-infected patients, they are likely to co-occur more frequently in this patient population.

Both alcohol use and depressive symptoms have a substantial impact on HIV-related behaviors and disease outcomes. Alcohol use has been associated with suboptimal utilization of medical services. For example, patients with alcohol use disorders delay seeking treatment for HIV infection.²¹ Alcohol problems in HIV-infected patients are associated with poor adherence to antiretroviral therapy (ART),^{8, 11, 22-25} worse treatment response, and more rapid HIV disease progression as evidenced by lower CD4 lymphocyte counts and higher HIV RNA,^{23, 24} and an increase in high-risk sexual behaviors.²⁶⁻³⁰ Similarly, depressive symptoms have a multifaceted effect on HIV-infected persons, including increased immune dysfunction, biochemical alterations, and adverse effects on medication adherence.³¹⁻³³ In addition, depressive symptoms in HIV-infected patients have been associated with increased deaths with one study revealing a mortality rate in HIV-infected women with depressive symptoms of twice that found in those without depressive symptoms.³⁴

In sum, both alcohol and depressive symptoms co-occur in adults and more often in those with HIV infection; both can impact HIV behaviors and outcomes. While these findings are compelling, research to date has not examined the impact of alcohol use on depressive symptoms in HIV-infected patients. Knowledge regarding how these factors relate to each other, particularly how alcohol consumption can affect depressive symptoms, is important because, if strongly associated, addressing alcohol use could have substantial impact on both depressive symptoms and HIV behaviors and outcomes. Therefore, the purpose of this study was to determine if current alcohol dependence and alcohol consumption affect depressive symptoms in people with HIV infection. We studied this association in a prospective cohort of HIV-infected patients with past or current alcohol problems.

METHODS

Study Design

We conducted an analysis of data from a prospectively followed cohort of HIV-infected subjects enrolled in the HIV-LIVE (HIV-Longitudinal Interrelationships of Viruses and Ethanol) Study between August 2001 and July 2003. Data on alcohol use behaviors and depressive symptoms were collected prospectively every six months by trained interviewers using standardized instruments. In-person assessment interviews and laboratory tests were scheduled every six months for a total of 36 months of follow-up. We examined the association

between alcohol dependence and consumption with depressive symptoms in this cohort of HIV-infected adults with current or past alcohol problems.

Eligibility criteria included the following: HIV infection documented by HIV antibody test by enzyme-linked immunosorbent assay (ELISA) with Western Blot confirmation; current or past alcohol problems supported either by two or more positive responses to the CAGE alcohol screening questionnaire^{35, 36} or by a study physician investigator's clinical determination of alcohol abuse or dependence; the ability to speak English or Spanish; identification of a contact person who knew the subject's whereabouts; a score of greater than 20 on the Folstein Mini-Mental State Examination;^{37,38} and a trained interviewer assessment that the subject was capable of giving informed consent and answering the interview questions. Subjects were recruited from several different sources including: 1) a previous cohort study of people with HIV and alcohol problems (n=154, 38%)²⁵; 2) the Diagnostic Evaluation Unit (DEU), an intake clinic for HIV-infected patients at Boston Medical Center (BMC) (n=87, 22%)³⁹; 3) the HIV Primary Care and Specialty Clinics at Beth Israel Deaconess Medical Center (BIDMC) (n=31, 8%); and 4) additional health care centers, homeless shelters, drug treatment programs, subject referrals and flyers (n=128, 32%). The Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess Medical Center approved this study. Additional privacy protection was secured by the issuance of a Certificate of Confidentiality by the Department of Health and Human Services to protect subjects from release of their research data even under a court order or subpoena.

Measurements

The primary outcome variable was the Center for Epidemiologic Studies, Depression Scale (CES-D)⁴⁰ score. The CES-D is a 20-item self-report questionnaire used to assess the presence and severity of depressive symptoms with scores ranging from 0 to 60.

One of the two independent variables of interest was current alcohol dependence, defined as a diagnosis of alcohol dependence by meeting diagnostic criteria in the past six months and assessed using the reference standard Composite International Diagnostic Interview (CIDI).⁴¹ The second independent variable was past-month alcohol consumption (heavy drinking [>4 drinks on one day or >14 drinks per week on average for men; >3 or >7 , respectively, for women] versus not heavy drinking [none or moderate] amounts) as assessed using a validated calendar-based method.⁴² We further stratified the cohort into abstinent (no alcohol consumption), moderate (any alcohol consumption but not heavy drinking), heavy drinking and very heavy drinking (>4 separate days of >4 drinks on one day for men; >4 separate days of >3 drinks on one day for women).

Other specific subject characteristics assessed included age, sex, race/ethnicity, homelessness (defined as having spent at least one night either on the street or in a shelter in the six months before the interview),⁴³ and hepatitis C (HCV) antibody status. We also assessed for the presence of other medical comorbidities (using the Katz comorbidity scale).⁴⁴ Medical diagnoses were read to the participants, and they indicated whether they had been hospitalized for these reasons in the previous six months. Data were collected on antiretroviral medication use and adherence, past month heroin and cocaine use, CD4 cell counts, and HIV log RNA measurements as measured using branched-chain DNA techniques.⁴⁵ Adherence to ART was determined using the AIDS Clinical Trials Group Questionnaire for Adherence to Anti-Retroviral Medications.⁴⁶ Subjects who reported being less than 100% adherent during the previous three days were considered not adherent.

Participants

The baseline characteristics of the 400 subjects enrolled in the HIV-LIVE Study included a mean age of 43 years (SD=7.4, range=21-71), 75% were men, 41% were black, 33% were white, 19% were Hispanic and 7% were other races/ethnicities. Twenty-five percent of the sample were homeless, 59% (232/396) were hepatitis C antibody positive, 64% reported current illicit drug use. Ten percent met criteria for alcohol dependence, 31% reported heavy drinking, 11% reported moderate drinking, and 58% reported no alcohol consumption. The mean CES-D score was 22 (SD=12.9, range=0-56). 46% reported adherence to antiretroviral medication, 16% reported non-adherence, and 38% reported not being on any antiretroviral medications. The mean CD4 count was 455 cells/mm³ (SD=299, range=8-1809) and the mean HIV log RNA was 2.98 copies/mL (SD=1.35, range=1.5-5.88). The median number of study visits per subject was 4 (interquartile range 3-6 visits) and the median time between baseline and last follow-up visit (in months) was 23.6 months (interquartile range 16.7-30.3 months).

Data Analyses

Analyses of demographic and clinical characteristics at baseline included descriptive statistics. Separate linear mixed effects multiple regression models⁴⁷ were used to examine the association between both alcohol dependence and current alcohol consumption and depressive symptoms. Alcohol dependence and consumption were modeled as time-varying variables. The models controlled for the following covariates: gender, age, race/ethnicity (black vs. non-black), homelessness (yes vs. no), HCV antibody status (positive vs. negative), the Katz comorbidity scale, any past month illicit drug use (yes vs. no), antiretroviral medication use and adherence (3 category variable: not on ART, on ART but not adherent, adherent ART), CD4 cell counts, HIV log RNA measurements and time since study enrollment (months). Age, Katz comorbidity scale, CD4 cell count, and HIV log RNA were included in regression models as continuous variables. All other covariates were included as categorical variables using dummy variables. ART medication status, illicit drug use, CD4 cell count, HIV log RNA, and time since study enrollment were included as time-varying covariates. All other covariates were taken from the baseline assessment. The linear mixed models included a random intercept and random slope for each subject to account for the correlation from including multiple observations from the same subject. Models were fit using an unstructured variance covariance matrix and empirical standard errors were reported for all analyses. Subjects who completed at least one follow-up were included in the analyses, thus subjects with missing data at one or more time-points were not excluded from analyses. To minimize the potential for co-linearity, we assessed correlation between each pair of independent variables and verified that no pair of variables included in the same regression model was highly correlated (i.e. >0.40). All analyses used 2-tailed tests of significance and were performed using SAS software (version 8.2; SAS Institute, Cary, NC). P-values <0.05 were considered statistically significant.

RESULTS

Using longitudinal regression models, we found that current alcohol dependence was associated with higher CES-D scores in unadjusted models (24 vs. 21; $p<.0001$) and that the association persisted in adjusted analyses (24 vs. 21; $p<.0001$) (Table 1). The impact of alcohol dependence and the specified covariates on depressive symptoms are displayed in Table 2. Subjects with alcohol dependence, who were HCV antibody-positive, or currently using illicit drugs exhibited significantly higher CES-D scores (all p -values <.01). Subjects who were black or who were adherent to their ART exhibited significantly lower CES-D scores (all p -values <.05). We conducted an additional analysis with data on relationship status (marital/partner status) in order to assess potential mediating effects, but found that after adjusting for marital/partner status, the results for alcohol dependence and heavy drinking were unchanged (data not shown).

In contrast, while the unadjusted mean CES-D scores were significantly higher for heavy drinkers compared with those who were not (23 vs. 21; $p=.005$) (Table 3), in the adjusted analysis controlling for the specified covariates, the difference in the mean CESD scores was attenuated and no longer significant (22 vs. 21; $p=.11$).

When this relationship was further assessed using the four drinking categories (Figure 1), depressive symptoms appeared to increase as drinking levels increase (adjusted mean CES-D scores [SD]: non-drinkers 21 [0.81]; moderate drinkers 21 [1.01]; heavy drinkers 22 [0.93]; very heavy drinkers 23 [1.15]), however the differences were not statistically significant.

DISCUSSION

As both unhealthy alcohol use and depressive symptoms are common among HIV-infected persons, understanding the relationship between these two comorbidities has significance for optimal patient care. Our study found that current alcohol dependence was independently associated with more depressive symptoms in HIV-infected patients with current or past alcohol problems. We did not detect a statistically significant association between heavy drinking and depressive symptoms. Exploratory analyses suggest a potential “dose-related” effect of drinking level on depressive symptoms although the results did not reach statistical significance. Finally, our results substantiate previous work that demonstrated additional factors such as being HCV antibody positive or currently using illicit drugs being associated with depressive symptoms among HIV-infected patients with alcohol problems.⁴⁸ Our study also found that those who were black or adherent to their antiretroviral medications had significantly lower CES-D scores. This relationship between race and depression in patients with alcohol dependence has also been found in a large national sample⁴⁹. Similarly, the relationship we found between adherence to antiretroviral medications and depression has been demonstrated by a number of studies though the directionality of the relationship (i.e. change in adherence leading to change in depressive symptoms versus change in depressive symptoms leading to change in adherence) is not clear^{25, 50, 51}.

The relationship between substance abuse and mental health was highlighted recently by the Institute of Medicine (IOM) in its report entitled “Improving the Quality of Health Care for Mental and Substance-Use Conditions: Quality Chasm Series.”⁵² This report has as a fundamental principle that the physical health of the patient is tightly linked to his/her substance use status and mental health. The current results demonstrate that, in addition, these important mental health and substance use factors not only relate to physical health, such as HIV disease, but also relate to each other. Depressive symptoms are not independent of the use and consequences of one’s alcohol use. Our study highlights the important relationship between alcohol use and depressive symptoms in patients with HIV disease. The importance of depressive symptoms among HIV-infected persons has been previously noted, perhaps most impressively in a prior study in HIV-infected women in which depressive symptoms, as measured by the CES-D scale, were associated with HIV disease progression and death.³⁴ Therefore, any worsening of depressive symptoms is of major concern and any factor that might ameliorate depressive symptoms is of great interest.

A recent systematic review of the literature specifically focusing on the impact of alcohol problems in individuals with major depression found that alcohol problems are common in persons with depression and that they are associated with a number of adverse clinical and health care outcomes.¹⁸ While the majority of these data focused on the effect of alcohol dependence on depression outcomes and revealed findings similar to our study, they did not provide data on the impact of lower levels of alcohol consumption such as heavy or problem drinking, on depressive symptoms. A subsequent study by Alati et al did find a linear relationship between alcohol consumption and depressive and anxiety symptoms at certain

stages in the lives of their subjects but also concluded that this relationship was dependent upon the gender and age of the subjects.⁵³ Of note, we are unaware of any similar studies that have examined the impact of alcohol dependence or use on depression outcomes specifically in HIV-infected patients.

Our study has several limitations. Although we did not detect an association between current heavy drinking and depressive symptoms in this cohort, it is important to note that our study cohort had a significant burden of depressive symptoms at baseline and therefore may be masking some of the impact varying levels of alcohol had on these symptoms. Furthermore, while the CES-D is recognized as a well-validated scale that has been extensively used in medically ill patient populations to measure depressive symptoms, it is not a diagnostic instrument for depression. A recent study examining the association between alcohol and depression highlighted that there are certain factors such as gender and methods of measuring these two conditions that one must take into consideration when examining the alcohol-depression relationship.⁵⁴ Also, the current study does not provide information on the use of antidepressant therapy in these patients which, if present, may have mitigated the impact of alcohol use. Finally, this study was potentially underpowered to detect effects of the observed magnitude for heavy drinking. Although the observed one unit increase in depressive symptoms in subjects with heavy alcohol use compared to those without heavy alcohol use may be clinically important, it was not statistically significant and the resulting confidence intervals were wide. Thus we are also unable to conclude that no association exists. A larger cohort may be necessary to provide definitive conclusions on the effect of heavy drinking.

In summary, we found in our study that HIV-infected patients with alcohol dependence had significantly more depressive symptoms. These findings highlight the impact on depressive symptoms of the severe end of the spectrum of alcohol use disorders, alcohol dependence. Although an increase in depressive symptoms was noted among those with heavy drinking, it was small and not statistically significant. However, our findings support a potential dose-response relationship between increasing levels of alcohol use and more depressive symptoms and the lack of statistical significance may have been due to inadequate sample size. In addition, there are specific potentially modifiable factors including current illicit drug use and antiretroviral medication adherence, associated with this relationship.

The findings of our study are important as they provide information about an HIV-infected population per se and present data regarding the impact of both alcohol dependence and lower levels of alcohol use on depressive symptoms. Future investigations should systematically evaluate the effect that varying levels of alcohol use have on depressive symptoms in a larger cohort of HIV-infected patients. In addition, they should explore the impact of alcohol use on the effectiveness of pharmacologic and/or psychotherapeutic treatment for depression in this population. Finally, future work should focus on the how different interventions treating alcohol problems ultimately affect various aspects of HIV disease.

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Figure 1.
Association of Varying Levels of Alcohol with Depressive Symptoms

Table 1

The Association Between Current Alcohol Dependence and Depressive Symptoms

	Currently Alcohol Dependent	Not Alcohol Dependent	Mean Difference (95% CI)	P-value
Unadjusted Mean Depressive Symptoms (SE)[*]	24 (0.93)	21 (0.57)	3.54 (1.89,5.19)	<0.0001
Adjusted [^] Mean Depressive Symptoms (SE)^{**}	24 (1.05)	21 (0.77)	3.49 (1.76,5.22)	<0.0001

* Analyses based on 400 subjects contributing 1721 observations

** Analyses based on 391 subjects contributing 1509 observations

[^] The adjusted mean scores control for gender, age, race/ethnicity (black vs. non-black), homelessness, HCV antibody status, the Katz comorbidity scale, past month illicit drug use, ART medication use and adherence, CD4 cell counts, HIV log RNA measurements, and time in months since study enrollment

Table 2

Multivariable Analysis of the Association Between Current Alcohol Dependence and Covariates with Depressive Symptoms

Characteristic	Adjusted Mean Difference in Depressive Symptoms (SE)	95% Confidence Interval	P-value
Currently Alcohol Dependent	3.49 (0.88)	1.76, 5.22	<0.0001
Female	2.36 (1.34)	-0.28, 5.00	0.08
Age	-0.03 (0.08)	-0.18, 0.13	0.73
Black Race	-2.52 (1.14)	-4.76, -0.27	0.03
Homelessness	1.43 (1.29)	-1.10, 3.96	0.27
HCV Antibody Positive	4.60 (1.17)	2.31, 6.89	<0.0001
Katz Medical Comorbidity	0.05 (0.18)	-0.30, 0.40	0.78
Current Illicit Drug Use	1.71 (0.63)	0.48, 2.94	0.006
HIV Log RNA	0.41 (0.28)	-0.15, 0.96	0.15
CD4 Cell Count	-0.002 (0.001)	-0.0046, 0.0006	0.13
Adherent to Highly Active Antiretroviral Therapy vs. not on meds	-1.76 (0.88)	-3.48, -0.04	0.04
Not Adherent to Highly Active Antiretroviral Therapy vs. not on meds	-1.22 (0.91)	-3.00, 0.56	0.18

Table 3

The Association Between Current Heavy Drinking and Depressive Symptoms

	Current Heavy Drinking	Not Heavy Drinking	Mean Difference (95% CI)	P-value
Unadjusted Mean Depressive Symptoms (SE)*	23 (0.75)	21 (0.58)	1.76 (0.53, 2.98)	0.005
Adjusted [^] Mean Depressive Symptoms (SE)**	22 (0.90)	21 (0.77)	1.04 (-0.24, 2.32)	0.11

* Analyses based on 400 subjects contributing to 1726 observations

** Analyses based on 391 subjects contributing to 1514 observations

[^] The adjusted mean scores control for gender, age, race/ethnicity (black vs. non-black), homelessness, HCV antibody status, the Katz comorbidity scale, past month illicit drug use, ART medication use and adherence, CD4 cell counts, HIV log RNA measurements, and time in months since study enrollment