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Alcohol Consumption and HIV Disease Progression

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Abstract

Objective—To assess the relation between alcohol consumption and laboratory markers of HIV disease progression.

Methods—We prospectively assessed CD4 cell counts, HIV RNA levels, and alcohol consumption for up to 7 years in 595 HIV-infected persons with alcohol problems recruited between 1997 and 2003. We investigated the relation of these markers of HIV disease progression to alcohol consumption using longitudinal regression models controlling for known prognostic factors, including adherence and depressive symptoms, and stratified by antiretroviral therapy (ART) use.

Results—Among subjects who were not on ART, heavy alcohol consumption was associated with a lower CD4 cell count (adjusted mean decrease of 48.6 cells/μL compared with abstinence; $P = 0.03$) but not with higher $\log_{10}$ HIV RNA. Among subjects who were on ART, heavy alcohol consumption was not associated with a lower CD4 cell count or higher $\log_{10}$ HIV RNA.

Conclusions—Heavy alcohol consumption has a negative impact on the CD4 cell count in HIV-infected persons not receiving ART. In addition to the known deleterious effects of alcohol on ART adherence, these findings suggest that avoiding heavy alcohol consumption in patients not on ART may have a beneficial effect on HIV disease progression.

Keywords

alcohol; CD4; HIV disease progression; HIV viral load

Identifying modifiable factors that affect HIV disease progression provides opportunities to improve HIV treatment. Several such factors have been identified, including medication adherence, depressive symptoms, and hepatitis C coinfection.[1–3] Because antiretroviral therapy (ART) is a key determinant of the clinical course of HIV disease, understanding the impact of modifiable factors in its presence and absence is important.[4]

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Alcohol use is common among HIV-infected persons,[5–7] and its impact on HIV disease progression has been examined in in vitro, animal, and human studies. Alcohol can adversely affect immunologic function in HIV-infected persons by various mechanisms,[8] including increased HIV replication in lymphocytes.[9,10] Research on the impact of alcohol on simian immunodeficiency virus (SIV) demonstrates increased viral loads in infected rhesus monkeys given intoxicating levels of alcohol at the time of viral inoculation compared with controls that received no alcohol.[11–16] These data indicate that the viral set point is increased and clinical deterioration is more rapid in alcohol-exposed monkeys.

In humans, the literature shows mixed effects of alcohol. Evidence from a large observational cohort of homosexual men, the Multicenter AIDS Cohort Study (MACS), before the advent of highly active ART, found no association between alcohol use and HIV disease progression.[17] We previously published cross-sectional data suggesting a negative impact of alcohol use on HIV disease progression in the era of highly active ART.[18] Alcohol consumption was associated with lower CD4 cell counts and higher HIV viral loads among those receiving ART. No comparable association was found for similar patients not on ART, however.

In this study, we report on the impact of alcohol use among HIV-infected persons with current or past alcohol problems prospectively assessed for up to 7 years to test the following hypothesis: alcohol consumption is independently associated with more rapid HIV disease progression as measured by the CD4 cell count and HIV viral load (HIV RNA).

METHODS

Study Design

We analyzed the effect of alcohol consumption on CD4 cell counts and HIV RNA levels in 2 prospective cohorts of HIV-infected patients with alcohol problems.

Subject Recruitment

Subjects recruited between 1997 and 2003 were participants in the HIV Alcohol Longitudinal Cohort (ALC) or HIV Longitudinal Interrelationships of Viruses and Ethanol (LIVE) study. Both were prospective observational cohort studies of HIV-infected persons with current or past alcohol problems. Data were collected at study enrollment and then every 6 months from 1997 to 2001 for the HIV-ALC study and from 2001 to 2006 for the HIV-LIVE study.

The recruitment sites of the HIV-ALC (n = 349) have been previously reported[18] and were comparable to those in the HIV-LIVE study. HIV-LIVE subjects (n = 400) were recruited from the HIV-ALC study (n = 154, 38%) and the following sites: (1) the Diagnostic Evaluation Unit,[19] an intake clinic for HIV-infected patients at Boston Medical Center (BMC) (n = 88, 22%); (2) HIV Primary Care and Specialty Clinics at Beth Israel Deaconess Medical Center (BIDMC), Boston, MA (n = 31, 8%); and (3) other sites (n = 127, 32%), including a respite facility for homeless persons, a methadone clinic, BMC's primary care practices, referrals by friends, newspaper advertisements, and posted flyers at homeless shelters and HIV/AIDS social service agencies in the Boston area.

Eligibility criteria included (1) documented HIV antibody test by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot (medical record or tested at enrollment), (2) affirmative responses to 2 or more CAGE alcohol screening questions[7] or physician investigator diagnosis of alcohol abuse or dependence, (3) ability to speak English or Spanish, and (4) at least 1 contact person to assist with follow-up. Exclusion criteria included (1) score <21 on the 30-item Mini-Mental State Examination,[20,21] (2) inability to provide informed consent or answer the interview questions, and (3) plans to move from the Boston area in the subsequent 12 months.

All subjects provided written informed consent before enrollment. The Institutional Review Boards of the BMC and BIDMC approved this study.

Subject Assessment

Subjects received an interviewer-administered baseline assessment in English or Spanish. For the Spanish interview, standardized scales were used when available; the remainder of the questionnaire was translated from English into Spanish and back-translated. The CD4 cell count and HIV viral load were obtained at the study visit if not available by review of medical records within the past 4 months.

Outcomes

The primary outcomes were CD4 cell count per microliter and $\log_{10}$ HIV RNA copies per milliliter, which are 2 laboratory markers of HIV disease progression. Measurement of HIV RNA (viral load) was performed using a branched-chain DNA (bDNA) assay or polymerase chain reaction (PCR).[22] The lower threshold of detection varied between 50 and 500 copies/mL over the course of the study. In analyses, undetectable HIV RNA levels were assigned half the value of the lower limit of detection. One secondary outcome, the CD4% (CD4 count/total lymphocyte count), was examined as a complementary measure of immune status that may better reflect one's risk for opportunistic infection in the setting of hypersplenism or postsplenectomy status.[23,24]

Primary Independent Variable

The main independent variable, alcohol consumption in the past 30 days, which was categorized as heavy, moderate, or abstinent, was assessed using a validated calendar method.[25] The "heavy" category was derived from the National Institute on Alcohol Abuse and Alcoholism definition of amounts that risk consequences (> 14 drinks per week or ≥5 drinks on a single occasion for men <66 years old and >7 drinks per week or ≥4 drinks on a single occasion for men ≥66 years old and all women).[26] "Moderate" alcohol use was defined as any drinking less than heavy amounts.

Potential Confounders

Other variables included in regression analyses were gender; age; race (black, white, or other); HIV risk behavior (injection drug use, men having sex with men [MSM], or heterosexual sex); homelessness; 3-day adherence to ART; depressive symptoms; time since study enrollment; year of study entry; and participation in the HIV-ALC study, HIV-LIVE study, or both. Homelessness was defined as at least 1 night in a shelter or on the street in the past 6 months.[27] Current ART use was assessed with the question, "Are you currently taking antiretroviral medications for HIV?" Three-day adherence to antiretroviral medications was determined with the AIDS Clinical Trials Group Questionnaire for Adherence to Antiretroviral Medications.[28] Adherence was a dichotomous variable, where patients <100% adherent during the previous 3 days were considered not adherent. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression (CES-D) scale.[29]

Additional information collected to characterize subjects more completely included current and lifetime alcohol dependence (Composite International Diagnostic Interview [CIDI] Lifetime and 12 Month),[30] current drug dependence (CIDI 12 Month), and use of ART before study entry.

Statistical Analysis

Descriptive baseline statistics (proportions, means, and standard deviations) were used to characterize the study sample overall and by alcohol consumption status. Continuous variables

were compared between alcohol consumption groups using analysis of variance for normally distributed variables and, otherwise, by the Kruskal-Wallis test. χ^2 tests were used to compare categoric variables based on alcohol consumption level. We examined the relation between alcohol consumption and HIV disease progression outcomes by fitting 2 separate multivariable longitudinal regression models (on and not on ART) for each of 3 outcomes (CD4 cell count, CD4%, and $\log_{10}$ HIV RNA).Generalized linear mixed effcts models were used to account for the correlation from repeated observations on the same subject. Models were stratified based on ART status, a factor previously shown to modify the effect of alcohol consumption level on HIV progression.[18] Subjects consistently on or not on ART contributed to that ART status, respectively. For subjects who went on or off ART during the study, we took an approach to avoid potential carryover effects from ART. If a subject went from on to off, the on observations were included but the off observations were not. If a subject went from off to on, both observations were included. Observations from subjects who changed multiple times were only counted the first time a change was made.

Potential confounding factors were included in all regression models. Baseline CD4 cell count was a covariate in analyses of the CD4 outcome. Baseline CD4% was handled in a similar manner. Analyses of HIV viral load did not adjust for baseline $\log_{10}$ HIV RNA, because subjects with established infection had likely achieved their viral set points; thus, HIV RNA level would be expected to remain fairly constant over time. To minimize the potential for colinearity, we verified that no pair of variables included in the same regression model was highly correlated ($r > 0.40$). All analyses were conducted using 2-sided tests and a significance level of 0.05. Analyses were performed with the use of SAS software (version 9.1.3; SAS Institute, Cary, NC).

RESULTS

Characteristics for the cohort (n = 595) at study entry and stratified by level of alcohol consumption are listed in Table 1. The cohort included 25% women, 66% nonwhites, and 27% homeless persons, with a mean age of 41 years. Injection drug use was the HIV risk behavior in more than half of the subjects; for the remainder, the risk behavior was divided between MSM and heterosexual sex. Assessment of alcohol use in the past 30 days revealed heavy consumption in 30% of subjects and moderate consumption in 10%; 59% of subjects were abstinent. One quarter (128 of 595) of all subjects used alcohol and illicit drugs (heroin or cocaine), 19% used alcohol alone, and 15% used heroin or cocaine alone. The average daily alcohol consumption of subjects drinking in the past 30 days was 5.4 drinks. Of subjects with a history of injection drug use, 32% (114 of 354) had injected drugs in the previous 6 months.

The median number of assessment time points per subject was 9, and the maximum was 15. The number of observations included in the analyses for CD4 cell count was 1475 for the on ART group and 384 for the not-on-ART group (1273 and 350 respectively for the CD4% secondary outcome). The number of observations included in the analyses for HIV RNA was 1808 and 603 for the on ART group and for the not-on-ART group, respectively. The number of outcomes in the CD4 analyses was less than that in the HIV RNA analyses, because the former adjusted for baseline CD4 cell count. Thus, CD4 analyses only included outcome data from follow-up assessments. Seventy-three percent (1360 of 1859) of the CD4 test results and 71% (1710 of 2411) of the HIV RNA test results were collected within 1 month of the interview.

The results of the 6 regression analyses are presented in Table 2. Among those subjects not on ART, CD4 cell counts averaged 48.6 cells/μL lower for those with heavy alcohol use compared with abstinence ($P = 0.03$). Note that this difference does not represent change over time within individual subjects but, instead, the average difference between subjects with heavy alcohol use compared with abstinence across all time points, adjusting for baseline CD4 cell count

among other covariates. There was not a significant association, however, between heavy alcohol consumption and viral load for subjects not on ART. No association was observed for moderate drinking and any of the outcomes in the not-on-ART group. For subjects on ART, no significant association was found for the primary outcomes at any level of alcohol consumption. Because depressive symptoms have been shown to be associated with HIV disease progression, we controlled for the CES-D score in our main analyses as a potential confounder. Because depression may be in the causal pathway between alcohol and HIV disease progression, however, we fit additional models without the CES-D score. In these analyses, among subjects not on ART, similar results were found (CD4 cell counts were an average of 58.4 cells/μL lower for those with heavy alcohol use compared with abstinence; $P = 0.02$). Among subjects on ART, nonsignificantly higher $\log_{10}$ HIV RNA was found in those with heavy alcohol consumption compared with those who abstained (adjusted mean increase = 0.13; $P = 0.09$). The secondary outcome, CD4%, did not show any significant relation with alcohol consumption in either group (in the analyses adjusted for depressive symptoms; see Table 2).

DISCUSSION

The findings demonstrate a clinically and statistically significant effect of heavy alcohol consumption on the CD4 cell count among persons not on ART. Controlling for medication adherence, this effect was not observed in those receiving ART.

Previous efforts to examine this relation in HIV-infected persons have been limited by the study design (eg, cross-sectional)[18] or timing (eg, before the advent of highly active ART).[17,31] The current study prospectively examined alcohol consumption at 6-month intervals among HIV-infected persons selected on the basis of alcohol use. Use of a cohort with past or current alcohol problems was chosen, because a hypothesized modest effect of alcohol on HIV disease progression would require a relatively large study population, careful alcohol measurement, and subjects with heavier levels of alcohol consumption. Other factors, including psychosocial issues, known to be associated with HIV disease progression were measured and controlled for in the multivariable analyses to assess the independent effect of heavy or moderate alcohol consumption on markers of HIV disease progression. This study comprehensively assessed alcohol consumption using validated self-report instruments;[25] extended follow-up; and inclusion of multiple time-varying covariates in the regression analyses, including measures of ART adherence and depressive symptoms.

The finding of an impact on the CD4 cell count in subjects not on ART supports the study hypothesis that alcohol consumption has a direct effect on HIV disease progression. The impact seems to be relatively modest, however, and was not observed for moderate drinking or among persons on ART after controlling for adherence and other known associations with HIV disease progression. It may be difficult to detect a modest effect of heavy drinking on CD4 cell count among those on ART, because the large beneficial effect of ART on CD4 cell count may overcome any deleterious effect of alcohol. Only 10% of the cohort reported moderate levels of alcohol consumption. Such a low prevalence of moderate alcohol use is not surprising, given the fact that most of the subjects in this cohort met criteria for lifetime alcohol dependence. Individuals with current or past alcohol dependence are likely to abstain or drink heavily.[32] The modest number of moderate drinkers in the cohort limited our ability to assess the impact of moderate alcohol consumption on HIV disease progression, however. In particular, among subjects not on ART, we are unable to conclude that there is no effect of moderate drinking because it is likely that the study was underpowered to detect effects of the observed magnitude. Nevertheless, it is noteworthy that the magnitude and direction of the CD4 cell count change among those on ART with moderate drinking suggest that a larger study would be unlikely to find a detrimental effect.

The mechanism of alcohol's impact on the CD4 cell count is unclear. Attributing it to decreased medication adherence or to likelihood of receiving ART would not explain the finding of lower CD4 cell counts in persons not on ART. Attributing lower CD4 cell counts to a decreased likelihood of receiving ART should be adequately addressed by controlling for baseline CD4 cell count. Evidence from Bagby et al[16] in macaque monkeys demonstrating clinical deterioration of immune function in SIV-infected animals with chronic alcohol exposure suggests a more direct effect on immune function. The absence of a correlation of heavy alcohol use with HIV viral load in our study contrasts with the findings of an increased viral set point associated with heavy drinking in these animal studies. This difference may be attributable to the fact that under experimental conditions, the monkeys were all intoxicated at the time of SIV inoculation, a scenario that was not likely the case for all subjects in this observational cohort of persons with chronic HIV infection. The absence of impact on HIV viral load among those not on ART also suggests that the decrement in CD4 cell count is not mediated by an increased viral load, which is an important determinant of the trajectory of CD4 cell count decline. Findings from this cohort raise the possibility that the effect of alcohol on the CD4 cell count is CD4 cell specific or related to the nonspecific lymphopenia associated with alcohol use.[33] The absence of a significant association of alcohol consumption on CD4% suggests that the alcohol effect observed may relate to a decrease of lymphocytes overall as opposed to a selective decrement of cells.

The observation that heavy alcohol consumption has an effect on the CD4 cell count in HIV-infected patients not receiving ART is in contrast to that previously described in the medical literature. One of the earliest reports on this subject was by Kaslow et al,[17] in which MACS participants were examined every 6 months to assess the relation between alcohol and AIDS-defining illnesses. No effect was found among the 1706 HIV-infected men; however, the level of alcohol exposure was unclear. The highest alcohol consumption considered was 2 or more drinks per day, and mean consumption was not described. This level of consumption contrasts with an average of 7 drinks per day in the current study's heavy drinkers.

In the analyses excluding depressive symptoms, the finding of an association of borderline significance between heavy drinking and a modest increase of HIV viral load among subjects on ART is consistent with the findings of Chander et al,[34] in which heavy alcohol consumption correlated with significantly less viral suppression in cross-sectional analyses. These authors attributed this finding to the poorer adherence expected among heavy drinkers on ART. This is a possibility, and such an association in the current study may have been attenuated by the inclusion of ART adherence as a covariate in the regression analysis.

One limitation of this study was that we did not enroll HIV-infected persons in a cohort at the time of seroconversion (ie, an inception cohort) and follow their alcohol use, CD4 cell counts, and viral loads over time. To address this limitation, analyses controlled for baseline CD4 cell count. Lack of an inception cohort also allows the possibility that participants in the not-on-ART group may have been exposed to ART in the past but were no longer receiving it at the time of study enrollment. It is unclear how such exposure would alter the current findings. As in any observational study, the effects of heavy alcohol use could be confounded. It is possible that we did not adequately control for all potential contributing factors to HIV disease progression. Multiple characteristics known to be associated with HIV disease progression were included as covariates in the multivariable analyses, however. Another limitation is the fact that alcohol use was assessed 30 days before the interview and CD4 cell counts and HIV RNA levels, by study design, could have been obtained up to 4 months before the interview. Most of these outcomes were within 1 month of the subject interview, however.

Although alcohol consumption in HIV-infected persons is common,[5,7,35] heavy consumption in US cohorts is less frequent than in countries in which HIV infection and high per capita

alcohol consumption coexist (eg, Russia, South Africa).[36,37] A modest impact of a common problem (heavy alcohol use) in patients with a prevalent disease (HIV infection) can have major public health consequences. Heavy alcohol use s a potentially modifiable factor that seems to have a modest impact on HIV disease progression. Based on our findings, we believe that HIV-infected persons who drink alcohol heavily and are not on ART might decrease their risk of disease progression if they abstain from alcohol use. There is extensive evidence of the efficacy of a brief intervention for unhealthy alcohol use in nondependent drinkers in medical settings and of the efficacy of psychosocial and pharmacologic treatments for alcohol dependence.[38,39] Although limited evidence demonstrates that intervention for alcohol problems in people with HIV is effective, its implementation among HIV-infected populations seems to be a worthwhile goal.[40] In addition to the known deleterious effects of alcohol on ART adherence, these findings suggest that avoiding heavy alcohol consumption in patients not on ART may have a beneficial effect on HIV disease progression.

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TABLE 1

Baseline Characteristics of 595 Adults With HIV Infection and Current or Past Alcohol Problems, Overall and by Alcohol Consumption Status

	Total Sample 595	None 353 (59%)	Abstinent 61 (10%)	Heavy 180 (30%)	*P*
Age [y], mean (SD)	41 (7.4)	41 (7.3)	41 (8.2)	41 (7.4)	0.54
Male, No. (%)	446 (75)	252 (71)	53 (87)	141 (78)	0.02
Race, No. (%)					
Black	245 (41)	141 (40)	24 (39)	80 (44)	
White	202 (34)	115 (33)	21 (34)	66 (37)	0.30
Other	147 (25)	97 (27)	16 (26)	34 (19)	
Homeless, No. (%)	163 (27)	92 (26)	12 (20)	59 (33)	0.09
CD4 count [cells/μL], median (IQR)*	372 (209, 565.5)	378.5 (209, 564)	408.5 (268, 624)	337 (184, 539)	0.15
CD4%, median (IQR)†	22 (14, 30)	22 (14, 30)	25 (17, 32)	21 (14, 30)	0.42
Log_{10} HIV RNA, mean (SD)‡	3.3 (1.2)	3.2 (1.2)	3.0 (1.2)	3.5 (1.2)	0.02
HIV viral load [copies/mL], median (IQR)‡	1400 (0, 19,662)	963 (0, 17,988)	976 (0, 9554)	3031 (94, 31,490)	0.96
HIV risk group, No. (%)					
Heterosexual/blood	140 (24)	76 (22)	12 (20)	52 (30)	
Injection drug use	313 (54)	207 (61)	28 (46)	78 (45)	0.001
MSM	123 (21)	59 (17)	21 (34)	43 (25)	
CES-D, mean (SD)	22 (13)	22 (13)	20 (14)	23 (13)	0.28
Current alcohol dependence, No. (%)§	29 (12)	14 (9)	0 (0)	15 (22)	0.005
Lifetime alcohol dependence, No. (%)§	222 (91)	135 (89)	23 (96)	64 (93)	0.42
Current drug dependence, No. (%)§	103 (42)	65 (43)	6 (25)	32 (46)	0.18
Drinks per day, median (IQR)	0 (0, 0.7)	0 (0, 0)	0.17 (0.07, 0.40)	2.6 (0.8, 6.8)	<0.0001
Drinks per day, mean (SD)	2.2 (8.2)	0 (0)	0.4 (0.5)	7.2 (13.7)	<0.0001
Currently receiving ART, No. (%)	355 (60)	218 (62)	37 (61)	100 (56)	0.38
100% adherent, past 3 days, No. (%)	249 (70)	170 (78)	20 (54)	59 (59)	0.0002
ART adherence status, No. (%)					
Not on medications	239 (40)	135 (38)	24 (39)	80 (44)	
On medications, not adherent	105 (18)	47 (13)	17 (28)	41 (23)	0.0007
On medications, adherent	249 (42)	170 (48)	20 (33)	59 (33)	
ART ever, No. (%)‖	467 (81)	283 (83)	47 (77)	137 (79)	0.39
Study cohort, No. (%)					
HIV-LIVE only	245 (41)	152 (43)	24 (39)	69 (38)	
HIV-ALC only	195 (33)	125 (35)	17 (28)	53 (29)	
Both	154 (26)	76 (22)	20 (33)	58 (32)	0.06

*n = 572 (Total), n = 338 (Abstinent), n = 58 (Moderate), n = 175 (Heavy).

†n = 568 (Total), n = 336 (Abstinent), n = 58 (Moderate), n = 173 (Heavy).

‡n = 557 (Total), n = 330 (Abstinent), n = 55 (Moderate), n = 171 (Heavy).

§n = 245 (Total), n = 152 (Abstinent), n = 24 (Moderate), n = 69 (Heavy).

‖n = 577 (Total), n = 342 (Abstinent), n = 61 (Moderate), n = 174 (Heavy).

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TABLE 2

Adjusted Mean Differences in CD4% Cell Count and Log_{10} HIV RNA for Subjects With Moderate and Heavy Alcohol Consumption Compared With Abstinent in the Past Month, Stratified by Receipt of ART

ART Status	Alcohol Consumption Status	CD4 Cell Count*† Adjusted Mean Difference (vs. Abstinent)* (SE)	CD4 Cell Count*† *P*	CD4%Cell Count*† Adjusted Mean Difference (vs. Abstinent) (SE)	CD4%Cell Count*† *P*	Log_{10} HIV RNA*‡ Adjusted Mean Difference (vs. Abstinent) (SE)	Log_{10} HIV RNA*‡ *P*
On ART‡	Abstinent	—	—	—	—	—	—
	Moderate	11.5 (13.8)	0.40	0.35 (0.35)	0.29	0.032 (0.08)	0.67
	Heavy	−1.2 (11.0)	0.92	0.35 (0.33)	0.32	0.12 (0.07)	0.10
Not on ART	Abstinent	—	—	—	—	—	—
	Moderate	−25.8 (17.7)	0.15	−0.80 (0.83)	0.35	−0.113 (0.08)	0.16
	Heavy	−48.6 (21.9)	0.03	−1.0 (5.1)	0.23	0.007 (0.08)	0.92

*Adjusts for gender; age; race; HIV risk behavior; homelessness; depressive symptoms; time since study enrollment; year of study entry; and participation in the HIV-ALC study, HIV-LIVE study, or both.

†Also adjusts for baseline value of the outcome.

‡Also adjusts for 3-day self-reported adherence.