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Longitudinal association of alcohol use with HIV disease progression and psychological health of women with HIV

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Abstract

We evaluated the association of alcohol consumption and depression, and their effects on HIV disease progression among women with HIV. The study included 871 women with HIV who were recruited from 1993–1995 in four US cities. The participants had physical examination, medical record extraction, and venipuncture, CD4+ T-cell counts determination, measurement of depression symptoms (using the self-report Center for Epidemiological Studies-Depression Scale), and alcohol use assessment at enrollment, and semiannually until March 2000. Multilevel random coefficient ordinal models as well as multilevel models with joint responses were used in the analysis. There was no significant association between level of alcohol use and CD4+ T-cell counts. When participants were stratified by antiretroviral therapy (ART) use, the association between alcohol and CD4+ T-cell did not reach statistical significance. The association between alcohol consumption and depression was significant ($p < 0.001$). Depression had a significant negative effect on CD4+ T-cell counts over time regardless of ART use. Our findings suggest that alcohol consumption has a direct association with depression. Moreover, depression is associated with HIV disease progression. Our findings have implications for the provision of alcohol use interventions and psychological resources to improve the health of women with HIV.

Keywords

alcohol use; HIV/AIDS; multilevel longitudinal models; CD4+T-cells; depression

Introduction

Alcohol consumption and abuse are common among persons with HIV (Avins et al., 1994); alcohol consumption rates of 22–60% (Cook et al., 2001; Petry, 1999) and rates of alcohol abuse or dependence of 12–41% (Lefevre et al., 1995). Alcohol abuse rate in HIV-infected individuals is at least twice that found in HIV-seronegative individuals in the USA (Bagby, Marshall, & Georgiades, 2005). There are limited and conflicting data on the role of alcohol use on HIV transmission, disease progression and treatment (Samet, Horton, Traphagen, Lyon, & Freedberg, 2003; Wee, Barrett, Lian, Jayabaskar, & Chan, 2004).

The prevalence of psychiatric disorders including depression in individuals with HIV ranges from 22 to 32% (Bing et al., 2001), which is 2–3 times higher than in HIV-seronegative individuals (Blazer, Kessler, McGonagle, & Swartz, 1994; Kessler et al., 1994). Depression has been linked to CD4+ T-cell decline in several studies (Ickovics et al., 2001; Leserman et al., 1999), but unrelated in others (Lyketsos et al., 1993). CD4+ T-cells play a pivotal role in the body's defense against disease-causing microorganisms, and are the primary target cells of HIV (Meyerhoff, 2001). Several studies suggest that alcohol can adversely affect the CD4+ T-cell population by altering their functional capacity and reducing their numbers, as well as an inhibitory effect on cytotoxic T-lymphocytes (Barve, Kelkar, Gobejishvilli, Joshi-Barve, & McClain, 2002; Peterson, Herzenberg, Vasquez, & Waltenbaugh, 1998; Pol, Artru, Thepot, Berthelot, & Nalpas, 1996). While animal and in vitro studies supports the fact that alcohol has detrimental effects on HIV disease progression (Kumar et al., 2005; Liu, Zha, Nishitani, Chen, & Zack, 2003), clinical studies have been inconclusive (Chandiwana et al., 1999; Kaslow et al., 1989; Lucas, Gebo, Chaisson, & Moore, 2002; Mocroft et al., 1999; Palepu et al., 2003; Samet et al., 2003). A recent study found that heavy alcohol consumption has negative impact on the CD4+ T-cell count in HIV-infected individuals not receiving highly active antiretroviral therapy (HAART) (Samet et al., 2007). Both alcohol and depression may have effect on HIV disease progression (using CD4+ T-cell decline). However, the association between alcohol and depression, and their effects on HIV disease progression are not well characterized.

The primary objective of this study was to evaluate the association of alcohol consumption and depression, and their effects on HIV disease progression among women with HIV using the HIV Epidemiologic Research Study (HERS) cohort (Smith et al., 1997).

Methods

Study population

The rationale and organization of the HERS cohort have been described in detail elsewhere (Ickovics et al., 2006; Smith et al., 1997). The HERS cohort included 871 women with HIV who were recruited from 1993–1995 in four centers: Johns Hopkins School of Public Health, Montefiore Medical School, Brown University, and Wayne State University School of Medicine. Eligibility criteria for enrollment in the study included documented HIV status within the previous 60 days or consenting to HIV testing as part of eligibility screening, fluency in either English or Spanish, age between 16 and 55 years, and reporting one or more HIV-risk behaviors. Women with AIDS diagnosis or opportunistic infections (1987 Centers for Disease Control surveillance definition) were ineligible; these diagnoses were associated with high mortality and concomitant high attrition rate for a longitudinal study. The procedures were approved by institutional review boards at each site and the Centers for Disease Control and Prevention.

Measures

Predictor variables—Baseline demographic characteristics were assessed via structured interview: age, race, marital status, education, employment status, income, and receipt of public assistance. Participants were classified based on drug use status: (1) non-users; (2) Intravenous Drug Users (IDU) or crack/cocaine users; and (3) IDU and crack/cocaine users. HIV RNA viral load quantification was done using branched-DNA signal amplification assay (Chiron, Emeryville, CA). Time of visit was coded as 1 for baseline, 2 for the first visit post baseline, 3 for the second visit post baseline and so on. Participants were classified into two categories based on their use of HAART during the study period (Ickovics et al., 2006).

Outcome variables—CD4+ T-cell counts, depression symptoms and alcohol use were assessed at enrollment, and measured semiannually until March 2000. Flow cytometry of whole blood was used to determine CD4+ T-cell count at each assessment. Decline in CD4+ T-cell count from the base-line value was used as a marker of disease progression. The Center for Epidemiological Studies-Depression (CES-D) was used as a measure of depression (Radloff & Rae, 1979). At baseline, respondents rate 20 symptoms (e.g. appetite change, hopelessness) over last seven days, with responses from zero (*rarely/none of the time*) to three (*most of the time*). A score of 16 or greater is considered the clinical cutoff score for depression. CES-D has been used extensively in studies of the population, clinical cohorts and persons with HIV (Burack et al., 1993; Myers & Weissman, 1980; Roberts & Vernon, 1983). At each visit, participants were asked if they had used any alcohol in the last six months; the drinking frequency and number of drinks per occasion were used to determine the level of alcohol use: non-drinkers, moderate drinkers (≤ 7 drinks per week), and heavy drinkers (> 7 drinks per week) according to the National Institute on Alcohol Abuse and Alcoholism definition of amounts that risk consequences.

Statistical analysis

The HERS data were collected at six-month intervals; hence, it generated repeated measurement data with time being nested within each individual participant. Analysis of repeated measures, using generalized linear mixed models, was conducted to identify the predictors of alcohol use and examine the time-varying effect of alcohol use in HIV-infected patients. Several two-level mixed effects models were utilized; where the level one units were measurement occasions and the level two units were the study participants. The analysis was conducted using a generalized linear latent and mixed models (GLLMM) procedure in STATA (version 9.0) (Rabe-Hesketh & Skrondal, 2001). The advantages of this modeling approach are that it allows for incomplete data across time, time-invariant and time-varying covariates, and can estimate individual changes across time. The GLLMM algorithm analysis treats the variables of a multivariate response as level one unit. This allows the model to use all the data collected for each participant at each time point.

Participants were classified according to their level of alcohol use at each time point, namely: non-drinkers, moderate drinkers (≤ 7 drinks per week), and heavy drinkers (> 7 drinks per week). A two-level ordinal random coefficient (random intercept and slope) model was used to determine the effect of the observed covariates on level of alcohol use. The effects of the observed covariates were allowed to vary across the three levels of alcohol use. Thus, observed covariates can have different or heterogeneous effects on none, moderate, and heavy users of alcohol. Random intercepts were included in the model to model the combined effect of all unobserved participant-specific covariates that cause some participants to be more prone to alcohol use than others, whereas random slopes were included to allow the over time change in alcohol use to vary by participants.

We used a joint response model with depression and CD4+ T-cell counts as responses to investigate the effect of alcohol use on depression severity and CD4+ T-cell counts. The joint modeling of the two outcome variables allowed us to assess not only the marginal effects of alcohol use on CD4+ T-cell counts and depression but also the effects of depression on CD4+ T-cell counts. The correlations between the two outcomes, for the same participant, were incorporated into the joint model using a shared random intercept. A path diagram for the joint response model is shown in Figure 1.

Results

Baseline demographics and characteristics of study participants

The baseline characteristics of participants stratified by alcohol use are shown in Tables 1 and 2. Fifty-nine percent ($N=516$) reported any use of alcohol at baseline. The mean age of the participants was 35.4 years with a standard deviation of 6.8 years. Of the 871 participants who completed baseline assessments, 58.5% ($N=510$) were Blacks, 20.2% ($N=176$) were Whites, 16.4% ($N=143$) were Latinos, and 4.8% ($N=42$) were of other races or ethnicities. There was a significant association between alcohol use and race/ethnicity ($p<0.01$) with Blacks and Whites more likely to be alcohol users. Majority of the participants had at least a high school degree, had a monthly income less than \$1000, and received public assistance. Sixty-three percent of the participants reported no illicit drug use. Those who used alcohol were more likely to use drugs ($p<0.01$). CD4+ T-cell counts were on average 430.89 (SD=270.82), and 79.2% of the participants had viral loads <10,000 copies/ml. Most of the participants had good virologic and immunologic control of their HIV disease. Depression was high among the participants with a mean of 21.64 (SD=13.36). Furthermore, the prevalence of depression was higher in those with any alcohol use compared to non-users ($p=0.01$). Sixty-two percent of participants ($N=539$) had scores >16, the *a priori* clinical cutoff score for depressive symptoms.

Predictors of alcohol use

We determined the predictors of alcohol use among the participants. We first fitted an ordinal random coefficient model under the proportional odds assumption where the effect of the covariates was assumed to be homogeneous across the levels of alcohol use (Table 3). Patient's visit time, HIV viral load, and drug use were found to be significant predictors for the level of alcohol use. We then relaxed the proportional odds assumption for the three significant predictors and re-fitted the ordinal random coefficient model. The parameter estimates from this model indicated that the effect of the three covariates were homogenous across the levels of alcohol use indicating that the proportionality assumption were reasonable with these three predictors. Thus, we retained the ordinal model which assumes homogenous effect of all the covariates across the three levels of alcohol. The parameter estimates (Table 3) for this model indicated that the level of alcohol use increased overtime (OR=1.22; 95% CI: 1.16–1.28), and drug use was associated with the level of alcohol use. Women who used Crack/Cocaine or IDU were more likely to use alcohol (OR=2.98; 95% CI: 1.71–5.20) compared with women who did not use any drug. Moreover, women who used both Crack/Cocaine and intravenous drugs were more likely to use alcohol (OR=4.35; 95% CI: 1.75–10.79) compared with women who did not use any drug. Interestingly, participants with high HIV viral load were less likely to be frequent users of alcohol (OR=0.28; 95% CI: 0.14–0.57). The random intercept and slope variances were estimated as 27.92 (SE=2.28) and 0.27 (SE=0.02), respectively. The relatively small standard errors for these estimates suggest that the women statistically differ in their average alcohol use as well as their over time change in the level of alcohol use.

Association of alcohol use with depression and CD4+ T-cell count

The longitudinal association of the level of alcohol use with depression and CD4+ T-cell counts was estimated by a joint response model (Table 4). Logarithmic transformation of the CD4+ T-cell counts was performed to facilitate normalization of the data distribution. There was no significant association between level of alcohol use and CD4+ T-cell counts. However, level of alcohol use was associated with depression ($p<0.01$). Depression scores were on average of 4.0 and 2.0 units higher for heavy ($p<0.01$) and moderate drinkers ($p<0.01$) when compared with non-drinkers. Depression had a significant negative impact on CD4+ T-cell counts ($p<0.01$). The variance of the shared random intercept was statistically significant ($p<0.01$).

There have been conflicting reports on the effect of alcohol use on CD4+ T-cells in both pre-HAART and HAART eras. We determined whether the use of HAART will affect the results of the joint response model (data not shown). Participants were stratified into two groups; no-HAART and HAART-use. Of the 266 participants who were never on HAART; 82% had CD4+ cell counts of >200 and viral load $<10,000$ throughout the study, so there was likely no clinical indication for treatment. Two hundred and eighty-two participants continued on >2 antiretrovirals after widespread availability (June–September 1999). The effect of alcohol on depression remained statistically significant for both no-HAART and HAART-use groups ($p<0.01$). Furthermore, depression had statistically significant negative effect ($p<0.01$) on CD4+ T-cell count in both treatment groups. The association between alcohol and CD4+ T-cell did not reach statistical significance in both groups. The association of alcohol use with depression and CD4+ T-cells was independent of the treatment status of participant.

Discussion

We found among the HERS participants, a statistically significant association between the level of alcohol use and depression. Furthermore, there was a significant association between depression and CD4+ T-cell decline. However, there was no association between the level of alcohol use and CD4+ T-cell decline.

Our finding of a significant association between the level of alcohol use and depression confirms previous reports where the rate of concurrence of alcohol abuse and depression exceeded the rate expected by chance in the general population (Dixit & Crum, 2000; Grant & Harford, 1995; Kessler et al., 1997). The temporal nature of this association is still debatable; there are reports that depression predates alcohol problems, especially in women (Hesselbrock, Meyer, & Keener, 1985; Wilsnack, Klassen, Schur, & Wilsnack, 1991). Theories to account for the risk of alcoholism among those with depression often focus on the use of alcohol as self-medicating for underlying depression. In the HERS cohort, most of the participants were clinically stable. This argues against possible ill health that will lead to depression among participants and subsequent use of alcohol. Furthermore, the use of alcohol and depression were prevalent at the onset of the study. However, the level of alcohol use was significantly associated with depression severity ($p<0.01$). Dixit and Crum found that risk for heavy drinking was higher among women with a history of depression (Dixit & Crum, 2000). Sullivan et al. found that current alcohol dependence was associated independently with more depressive symptoms in HIV-infected patients with current or past alcohol problems (Sullivan et al., 2008). In a prospective longitudinal study of affective disorders, the Collaborative Depression Study, depression symptoms improved among depressed alcoholics with the improvement of their alcoholism (Mueller et al., 1994). One could speculate from our finding that the level of alcohol was significantly associated with depression severity that alcohol consumption and depression may become a vicious cycle; heavy alcohol consumption may aggravate depression for the drinker and may intensify

depression (Dixit & Crum, 2000). The prevalence of alcohol use and depression is increasing among HIV-infected individuals; further studies to inform on the temporal relationship between the two comorbidities will impact on the optimal care of HIV-infected individuals.

We found that depression had a negative impact on HIV disease progression (i.e. CD4+ cell decline). This is consistent with earlier reports linking psychosocial factors to immune suppression and HIV disease progression (Antelman et al., 2007; Glaser, Rabin, Chesney, Cohen, & Natelson, 1999; Ickovics et al., 2001; Leserman, 2003). Depression may affect the function of the hypothalamic-pituitary-adrenal axis and the central nervous system leading to impairment of cellular immunity, and HIV disease progression (Evans et al., 2002; Gorman et al., 1991; Leserman, 2003). Furthermore, depression may be associated with HIV disease progression through behavioral mechanisms, i.e. non-adherence to medical recommendations (Ickovics & Meade, 2002) and poor nutrition intake (Coodley, Loveless, Nelson, & Coodley, 1994). Further research is needed to investigate how depression impacts HIV disease progression and appropriate interventions to optimize the care of HIV-infected individuals with depression.

There are reports that alcohol consumption has direct impact on HIV disease progression. To our surprise, we did not find significant association between alcohol consumption and CD4+ T-cell count. This contradicts recent reports; in a cross-sectional study, Samet et al. reported a negative impact of alcohol use on HIV disease progression in the era of HAART (Samet et al., 2003). In HIV-infected individuals with current or past alcohol problems followed prospectively for seven years, heavy alcohol consumption was associated with a lower CD4+ T-cell count in persons not receiving antiretroviral therapy (ART) (Samet et al., 2007). In the AIDS Link to Intravenous Experiences (ALIVE) Study, mortality was inversely associated with the use of alcohol; this effect was also reversed in the HAART era (Vlahov et al., 2005). The inconsistencies in these studies (including ours) may be partly due to: (a) methodological differences; (b) the fact that none of these studies enrolled participants at the time of HIV seroconversion, and followed their alcohol use and CD4+ T-cell count over time; and (c) a rather complex interaction among alcohol, depression and CD4+ T-cell counts. There is a need for further investigations into the interplay between alcohol consumption, depression, and CD4+ T-cell decline.

The study HERS data are unusually rich in terms of the variety of biological, psychological, socioeconomic outcomes measured. Thus, the study is unique in allowing multivariate analysis of the interactions of substance use behaviors, demographic characteristics and psychological factors with medical factors and their relation to HIV progression among women with HIV. The data analysis was designed to overcome certain methodological deficiencies of the earlier studies. However, our study has some inherent limitations that should be considered when interpreting the results. Alcohol use and depressive symptoms in the previous six months were measured by self-report, which may have introduced respondent and recall biases. There were factors not measured that may affect depression and HIV-related mortality (health care utilization, substance abuse, psychiatric treatments received, etc.).

In conclusion, our findings suggest that alcohol use has a direct association with depression. Depression is associated with HIV disease progression. Our findings have implications for the provision of alcohol use interventions and psychological resources to improve the health of women with HIV.

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Figure 1.

Path diagram for the two-level joint response model for the i th patient at the j th visit. Where i and j represents participant and visit numbers, respectively. β [Time $\rightarrow$ Depression]; α_1 [Alcohol $\rightarrow$ Depression]; γ [Time $\rightarrow$ CD4+ T-cell counts]; α_2 [Alcohol $\rightarrow$ CD4+ T-cell Count]; α_3 [Depression $\rightarrow$ CD4+ T-cell Count]. The circles represent the shared random intercept; rectangles represent observed variables, and arrows represent linear relations with the indicated coefficients.

Table 1

Descriptive statistics for the HERS Study, USA, at baseline (1993/1995).

Variable	Non-drinkers N=355 (40.8%)			Drinkers N=516 (59.2%)		
	N	Mean	SD	N	Mean	SD
Age (years)	354	35.5	6.4	516	35.3	7.0
Depression ^b	353	20.3	12.6	516	22.6	13.8
CD4+ Tcell count ^c	346	433	285	504	429	261

^a A two-sided *p*-value from a two sample *t*-test.

^b Center for Epidemiological Studies-Depression (CES-D) symptom score was used. Participants rated 20 symptoms (e.g., appetite change, hopelessness), considered to be major components of depression, over the last seven days, with responses from 0 (*rarely/none of the time*) to 3 (*most of the time*). A score of 16 is considered the clinical cutoff score for depression.

^c Number of cells per μ l of whole blood.

Table 2

Descriptive statistics for the HERS study, USA, at baseline (1993/95).

Variable	Non-drinkers		Drinkers		P-value ^a
	N	Percentage (%)	N	Percentage (%)	
Race/ethnicity					<0.01
Black	189	53	321	62	
Latino	78	22	65	13	
White	66	19	110	21	
Other	22	6	20	4	
Income					0.56
<\$500/month	130	37	201	40	
\$500–1000/month	133	38	175	34	
>\$1000/month	86	25	131	26	
Education					0.25
≤High School	171	48	227	44	
>High School	184	52	289	56	
Public assistance					0.59
No	121	34	186	36	
Yes	233	66	328	64	
HAART use					0.71
No	108	34	158	33	
Yes	209	66	324	67	
Drug use					<0.01
None	277	78	269	52	
<i>b</i> IDU or Crack/Cocaine	60	17	195	38	
Both	18	5	52	10	
Viral load copies/ml					0.94
<500	84	24	125	25	
500–9999	192	55	270	54	
>10,000	72	21	104	21	

^aTwo-sided *p*-value from a two sample *t*-test.

^bIDU, intravenous drug use.

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Table 3

Predictors of alcohol use among HERS study participants, USA, 1993/1995–2000.

Predictors	Adjusted odds ratios	
	Odds ratio (95% CI)	P-value
^a Time	1.22 (1.16–1.28)	<0.01
Age	0.99(0.96–1.03)	0.74
Income		
<\$500/month	1.00	
\$500–1000/month	0.92(0.53–1.60)	0.77
>\$1000/month	1.31(0.71–2.44)	0.39
Viral load copies/ml		
<500	1.00	
500–9999	0.63(0.36–1.11)	0.11
>10,000	0.28(0.14–0.57)	<0.01
Drug use		
None	1.00	
^b IDU or Crack/Cocaine	2.98(1.71–5.20)	<0.01
Both	4.35(1.75–10.79)	<0.01
Education		
≤High school	1.00	
>High school	1.53(0.94–2.48)	0.09
Public assistance		
No	1.00	
Yes	0.97(0.58–1.63)	0.92

^aTime of visit coded as; 1 for baseline visit, and 2, 3, 4 etc., for subsequent visits.^bIDU, intravenous drug use.

Table 4

Impact of alcohol use among HERS study participants, USA, 1993/1995–2000.

	Estimate	SE	P-Value
β [Time ^a → Depression ^b]	0.02	0.04	0.56
α_1 [Alcohol → Depression ^b]			
Moderate	1.93	0.26	<0.01
Heavy	3.94	0.47	<0.01
γ [Time ^a → CD4+ T-cell counts]	0.03	0.04	0.45
α_2 [Alcohol → CD4+ T-cell Count]			
Moderate	0.49	0.26	0.10
Heavy	0.75	0.48	0.12
α_3 [Depression ^b → CD4+ T-cell Count]	−0.34	0.01	<0.01

Note: Arrows represent linear relations with the indicated variables.

^aTime of visit coded as; 1 for baseline visit, and 2, 3, 4 etc., for subsequent visits.^bDepression and depression severity were used interchangeably.