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Recent drug use, homelessness and increased short-term mortality in HIV-infected persons with alcohol problems

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Abstract

Objective—To assess the impact of recent heavy alcohol use, heroin/cocaine use, and homelessness on short-term mortality in HIV-infected persons.

Methods—Survival in a longitudinal cohort of 595 HIV-infected persons with alcohol problems was assessed at 6-month intervals in 1996–2005. The time-varying main independent variables were heavy alcohol use (past 30 days), heroin/cocaine use (past 6 months), and homelessness (past 6 months). Date of death was determined using the Social Security Death Index. Outcomes were limited to deaths occurring within 6 months of last assessment to ensure recent assessments of the main independent variables. Cox proportional hazards models were fit to the data.

Results—Death within 6 months of their last assessment occurred in 31 subjects (5.2%). Characteristics at study entry included mean age 41 years, 25% female, 41% African-American, 24% with CD4 cell count <200 cells/μl; 41% taking antiretroviral therapy, 30% heavy alcohol use, 57% heroin or cocaine use, and 28% homelessness. Heroin or cocaine use [hazard ratio (HR), 2.43; 95% confidence interval (CI), 1.12–5.30] and homelessness (HR, 2.92; 95% CI, 1.32–6.44), but not heavy alcohol use (HR, 0.57; 95% CI, 0.23–1.44), were associated with increased mortality in analyses adjusted for age, injection drug use ever, CD4 cell count, and current antiretroviral therapy.

Conclusions—Recent heroin or cocaine use and homelessness are associated with increased short-term mortality in HIV-infected patients with alcohol problems. Optimal management of HIV-infected patients requires regular assessments for drug use and homelessness and improved access to drug treatment and housing.

Keywords

alcohol; cocaine; heroin; HIV; homeless persons; mortality

Introduction

Since the advent of combination active antiretroviral therapy (ART) in 1996, mortality in HIV-infected patients with access to these drugs has decreased substantially [1-7]. However several studies have noted smaller mortality improvements in patients infected with HIV from injection drug use compared with other transmission routes [1,6,8-11]. Recent drug use [12,13], alcohol use [14,15], and homelessness [16-19] are common modifiable conditions in HIV-infected patients. The impact of recent homelessness, alcohol use, or illicit drug use on survival among HIV-infected patients is not clear.

Some cohort studies have found no increased mortality from recent homelessness, alcohol, or drug use [20,21]. While two studies showed increased mortality among subjects using drugs at every follow-up assessment compared with those using drugs at no follow-up assessments [22,23], these studies categorized subjects based on their pattern of use over the cohort, rather than using time-varying analyses allowing subjects' status to change during follow-up time. One study of HIV-infected women found an increased risk of non-AIDS-related mortality with recent injection drug use [11]. None of these studies focused on short-term mortality by restricting the outcome to those deaths occurring within 6 months of the last study assessment.

Because substance use and homelessness are dynamic conditions that change over time, focusing on deaths occurring within a shorter period of time, such as 6 months after they are measured ('short-term mortality'), increases the likelihood of measuring a mortality impact from these conditions when they are active. To address the issue of whether substance use and homelessness, as modifiable characteristics, are associated with mortality, we studied the impact of recent heavy alcohol use, recent heroin or cocaine use, and recent homelessness as time-dependent variables on short-term mortality in HIV-infected patients with current or past alcohol problems.

Methods

Population

A survival analysis was performed using data collected from two prospective cohorts, the HIV-Alcohol Longitudinal Cohort (HIV-ALC) and the HIV-Longitudinal Interrelationships of Viruses and Ethanol (HIV-LIVE) cohort, which have been described in prior publications [24,25]. Both cohorts used identical recruitment sites in Boston, Massachusetts. Entry criteria included confirmed HIV positive antibody test, two or more affirmative answers on the CAGE alcohol screening questionnaire [15,26,27] or diagnosis by a study coinvestigator physician of current or past alcohol abuse or dependence, English or Spanish speaking, and at least one contact person available to assist with follow-up. Between July 1997 and July 2001, HIV-ALC enrolled and followed 349 patients. Between September 2001 and November 2005, the HIV-LIVE study enrolled and followed 400 subjects, 154 of whom had also participated in HIV-ALC. The combined HIV-ALC and HIV-LIVE cohort analyzed in this study included 595 subjects.

Data collection and independent variables

Laboratory and interview data were collected by trained research associates every 6 months. The 30-day timeline followback method was used at each interview to measure alcoholic intake

[28-30]. Recent heavy alcohol use was defined according to National Institute on Alcohol Abuse and Alcoholism guidelines: >14 drinks/week or >4 drinks on one occasion for men <65 years of age, and >7 drinks/week or >3 drinks on one occasion for all women and men ≥65 years of age. Recent heroin or cocaine use was defined as any use over the last 12 months at study entry and over the last 6 months at follow-up assessments via the Composite International Diagnostic Interview - Short Form: Drug Dependence (CIDI-SF DD) [31]. Recent homelessness was defined as having spent a night in the past 6 months in an overnight shelter or on the street.

Potential confounders defined at study entry included age, sex, race/ethnicity, prior injection drug use, prior suicide attempt, CD4 cell count (<200 cells/μl versus ≥200 cells/μl), log of HIV viral load, and time of study entry (prior to August 2001 versus after August 2001). Because of the limited number of outcomes, for multivariable analyses, race/ethnicity was dichotomized as black versus nonblack. Time of study entry was considered as a covariate in order to control for potential improvement in HIV care and access between the study entry period for HIV-ALC and HIV-LIVE.

Potential confounders modeled as time-varying covariates included ART status and adherence over 3 days [32], physical and mental health status using the 12-item Short Form Health Survey [33,34], and depressive symptoms using the Center for Epidemiologic Studies Depression (CES-D) scale [35,36]. ART status was examined using the following categories: not on ART, on ART but not adherent, and on ART and adherent. Adherence was defined as 100% adherence over the 3 previous days. Because of the limited number of outcomes, ART status was dichotomized for the multivariable analyses: on ART versus not on ART. Depressive symptoms were dichotomized using a cut-off of ≥23 or greater in the CES-D indicating substantial depressive symptoms.

Assessment of date and cause of death

The primary outcome for this study was time from study enrollment to death. Events were restricted to those deaths that occurred within 6 months after the subjects' last study interview ('short-term' mortality) in order to ensure the availability of recent assessments of substance use and homelessness. The observation time for all other subjects was defined as the time from study enrollment until 6 months following their last study visit.

Dates of death were determined by searching the Social Security Death Index from 1997 to 2005. Causes of death were obtained for subjects who died prior to 2004 via the National Death Index Plus and for subjects who died between 1 January 2004 and 15 November 2005 from the Massachusetts Registry of Vital Records using copies of death certificates. Three of the study physicians (AW, HL, and DN) independently allocated each death into the following categories: HIV related, liver related, overdose, non-HIV/nonliver-related cancer, other infection related, trauma, cardiovascular, and other (deaths for which there was not enough information or death that did not fit into one of the categories above). After independent categorization, the three authors resolved discrepancies through consensus.

Analysis

Time-varying Cox proportional hazards models were used to examine the association of the main independent variables with short-term mortality. Preliminary unadjusted models were fit for each independent variable. It was not possible to fit a multivariable model that included all the main independent variables and potential confounders because of the modest number of deaths occurring within 6 months of the final study visit. A multivariable model was fitted that included the three main independent variables and covariates that have been demonstrated to be important mortality predictors in HIV-infected patients: age, CD4 cell count <200 cells/μl,

prior injection drug use, and ART use [37]. Hepatitis C infection was not included because of substantial correlation ($r = 0.76$) between this infection and past intravenous drug use among the 399 subjects in the HIV-LIVE cohort for whom HCV infection status was available. The remaining covariates were added one at a time to assess whether any one was a confounder. A change in the parameter estimate of $\geq 10\%$ was used to identify confounding. All analyses were performed using SAS 9.1.3 (SAS Institute, Cary, North Carolina, USA).

Results

Of the 595 study subjects, 31 subjects (5.2%) died within 6 months of their last study interview, and 99 subjects (16.6%) died overall. The mean follow-up time was 2.7 years. Characteristics of all 595 subjects at study entry are shown in Table 1. Across the study follow-up, heavy alcohol use was reported in no assessments, at least one assessment, and at all assessments by 52%, 37%, and 11% of subjects, respectively. The respective proportions for heroin/cocaine use were 49%, 35%, and 16%, respectively; for homelessness they were 62%, 26%, and 11%, respectively.

Unadjusted Cox proportional hazards models for each of the main independent variables and potential confounders are also presented in Table 1. Recent heroin or cocaine use [hazard ratio (HR), 2.39; 95% confidence interval (CI), 1.18-4.85] and recent homelessness (HR, 2.85; 95% CI, 1.34-6.07) were both associated with increased mortality. Recent heavy alcohol use was not significantly associated with mortality (HR, 0.61; 95% CI, 0.25-1.49).

In the multivariable Cox proportional hazards model controlling for age, prior injection drug use, CD4 cell count, and ART use, recent heroin or cocaine use (HR, 2.43; 95% CI, 1.12-5.30) and recent homelessness (HR, 2.92; 95% CI, 1.32-6.44), but not recent heavy alcohol use (HR, 0.57; 95% CI, 0.23-1.44), were associated with a higher risk of mortality (Table 1). Further adjustment for health status, depressive symptoms, gender, race, prior suicide attempt, and time of study entry did not reveal confounding of the association between the main independent variables and mortality.

Overdose, liver-related conditions, and HIV-related conditions were the three most common categories for the 31 deaths occurring within 6 months of an assessment and for the 99 deaths overall (Table 2).

Discussion

In this longitudinal cohort of HIV-infected patients with current or past alcohol problems, recent heroin or cocaine use and homelessness were associated with an increased risk of short-term mortality. The major strength of this study is the use of regular reassessments of substance use and homelessness states as time-varying covariates. Substance use and homelessness are often conditions that occur together, with presumably similar causes and effects. Yet we were able to disentangle their impacts by including them, along with known important covariates, such as CD4 cell count and prior injection drug use, in multivariable Cox proportional hazards models.

We did not find a similar impact on mortality risk from recent heavy alcohol use. It may be that heavy alcohol use affects only long-term, not short-term, mortality, acting via chronic liver disease. Alternatively, the short-term mortality risk from heavy alcohol use may be mitigated by a 'sick quitter' phenomenon, where sicker subjects are less likely to be drinkers [38,39].

There are several limitations to our study. First, we had a modest number of deaths occurring within 6 months of last interview, limiting our power and ability to control for all potential confounders in the same model. Nonetheless, this definition of the outcome enabled us to focus

on the short-term effects of recent conditions. Second, the generalizability of our findings may be limited because we studied HIV-infected subjects with current or past alcohol problems recruited from one urban area. Third, loss to follow-up may have introduced a bias. For example, subjects who missed study visits may have been more likely to be drinking heavily, using drugs, or homeless. However, this bias would likely have biased results towards the null hypothesis.

Many of the deaths in this cohort, such as those caused by overdose, trauma, and infection, were likely acute, preventable, and directly related to recent drug use and homelessness. Integration of effective substance abuse treatment with HIV care has been demonstrated to be effective [40-43]. Successful housing programs with integrated services for homeless people with mental health or substance abuse problems have been described [44-46]. In addition to providing standard medical treatment, optimal management of HIV-infected patients requires regular assessments for drug use and homelessness and improved access to substance abuse treatment and housing.

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Characteristics and relative hazards of short-term mortality among 595 HIV-infected patients with alcohol problems

Table 1

	All subjects at study entry	Crude HR (95% CI) ^a	Adjusted HR (95% CI) ^{a,b}
Mean age [years (SD)]	41 (7.43)	1.04 (1.00-1.09)	1.06 (1.01-1.13)
Female [No. (%)]	148 (25)	1.38 (0.61-3.10)	
Race/ethnicity [No. (%)]			
African-American	246 (41)	1.05 (0.43-2.55)	
White	202 (34)	Ref	
Other	147 (25)	1.73 (0.68-4.38)	
African-American versus other		0.80 (0.39-1.65)	
Prior injection drug use [No. (%)]	354 (60)	2.81 (1.15-6.87)	1.75 (0.69-4.43)
Prior suicide attempt [No. (%)]	119 (20)	0.54 (0.19-1.55)	
Depressive symptoms ^c [No. (%)]	291 (49)	1.41 (0.70-2.86)	
Study entry pre-August 2001 [No. (%)]	349 (59)	1.31 (0.52-3.31)	
Mean SF-12 score (SD)			
PCS [*]	44 (11.2)	0.96 (0.93-1.00)	
MCS [*]	39 (14.1)	0.98 (0.95-1.00)	
Mean HIV RNA [log copies/ml (SD)]	2.71 (1.98)	1.20 (0.98-1.46)	
CD4 cell count <200 cells/ μ l [No. (%)]	136 (24)	2.43 (1.14-5.15)	3.58 (1.59-8.06)
Medication status [No. (%)]			
Not on ART [*]	240 (40)	1.88 (0.89-3.99)	
On ART, not adherent [*]	105 (18)	1.02 (0.28-3.62)	
On ART, adherent [*]	249 (42)	Ref	
Off ART versus on ART [*]		1.88 (0.93-3.80)	2.92 (1.33-6.40)
Heavy alcohol use in prior 30 days [*] [No. (%)]	180 (30)	0.61 (0.25-1.49)	0.57 (0.23-1.44)
Heroin/cocaine use ^{c, *} [No. (%)]	218 (37)	2.39 (1.18-4.85)	2.43 (1.12-5.30)
Homeless in prior 6 months [*] [No. (%)]	164 (28)	2.85 (1.34-6.07)	2.92 (1.32-6.44)

HR, hazard ratio; CI, confidence interval; SF-12, 12-item Short-Form Health Survey; PCS, physical component summary; MCS, mental component summary; ART, antiretroviral therapy.

^aFor crude and adjusted hazard models, variables were measured at study entry, except for those marked with *, which were analyzed as time-varying variables.

^bThe adjusted Cox proportional hazards model included age, prior injection drug use, CD4 cell count, off ART versus on ART, heavy alcohol use, heroin or cocaine use, and homelessness.

^cHeroin or cocaine use in the last 12 months for study entry, heroin or cocaine use in the last 6 months for follow-up visits.

Table 2

Causes of death

Cause of death category	Short-term mortality (<i>n</i> = 31) ^{<i>a</i>}	Overall mortality (<i>n</i> = 99) ^{<i>b</i>}
HIV-related, No. (%)	5 (16)	15 (15)
Liver-related	6 (19)	19 (19)
Overdose	7 (23)	14 (14)
Infection-related	3 (10)	10 (10)
Non-HIV/Nonliver-related cancer	2 (6)	8 (8)
Trauma	2 (6)	4 (4)
Cardiovascular	1 (3)	1 (1)
Other	5 (16)	28 (28)

^{*a*}Deaths occurring within 6 months of subjects' last study interview.

^{*b*}All deaths identified anytime during the study period.