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Pain and Mortality Risk in a Cohort of HIV-Infected Persons with Alcohol Use Disorders

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Abstract

Pain has been associated with increased risk for mortality in some studies. We analyzed data from a cohort study [HIV-longitudinal interrelationships of viruses and ethanol (HIV-LIVE)] of HIV-infected persons with alcohol use disorders enrolled 2001–2003 to explore whether reporting moderate or greater pain interference was associated with mortality. The main independent variable was pain that at least moderately interfered with work based on a single question from the SF-12. Primary analyses dichotomized at “moderately” or above. Cox proportional hazards models assessed the association between pain interference and death adjusting for demographics, substance use, CD4 count, HIV viral load and co-morbidities. Although significant in unadjusted models (HR = 1.58 (95 % CI 1.03–2.41; *p* value = 0.04)), after adjusting for confounders, ≥moderate pain interference was not associated with an increased risk of death [aHR = 1.30 (95 % CI 0.81–2.11, *p* value = 0.28)]. Among HIV-infected persons with alcohol use disorders, we did not detect a statistically significant independent association between pain interference and risk of death after adjustment for potential confounders.

Keywords

HIV; Pain; Mortality; Symptoms

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Introduction

Chronic pain, commonly defined as pain lasting for more than 3 months without evidence of ongoing tissue injury [1], is a major clinical problem among persons living with human immunodeficiency virus (HIV) with the prevalence of pain in clinical samples of HIV-infected persons ranging from 30 to 90 % [2–11]. Chronic pain has a major impact on society, contributing to substantial individual functional impairment, healthcare utilization, and costs [12].

Some population based studies have demonstrated associations between chronic or widespread pain and mortality [13–15]. Some explanations for this association are that pain may be a marker of underlying undiagnosed co-morbidities or it may signal a more rapid trajectory of aging. Alternatively, pain itself may be a physiologic stress which could lead to epigenetic changes and accelerated cell death [16]. This hypothesis is supported by research demonstrating associations between shortened telomere length (i.e., a marker for cellular aging) and chronic pain [17]. Finally, pain may be associated with psychological distress which may predispose to death from substance use, trauma or suicide. To our knowledge there are no studies evaluating whether pain is associated with mortality in HIV-infected populations. However, the relationship between chronic pain and mortality may be of particular significance in individuals with HIV as they are prone to premature aging and associated co-morbidities due to chronic inflammation [18, 19].

Our overall objective was to determine whether chronic pain was associated with increased risk of death in a cohort of HIV-infected persons. We pursued this by investigating whether reporting moderate or greater pain interference with work (both outside and inside the home) was independently associated with all-cause mortality. Additionally, we explored associations between multiple levels of pain interference and mortality risk.

Methods

Design

This study utilized data from the HIV-LIVE (HIV-longitudinal interrelationships of viruses and ethanol [HIV-LIVE]) study, a prospective, observational cohort study of individuals living with HIV who had alcohol use disorders in which assessments occurred at 6-month intervals over a maximum of 48 months. Recruitment for the HIV-LIVE study took place between August 2001 and July 2003, and subjects were followed until March 2006.

Subjects

Subjects were recruited 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. The previous cohort study (HIV-ALC) was also a prospective observational cohort study of HIV-in-fected persons with current or past alcohol use disorders. The recruitment sites of the HIV-ALC (n = 349) have been previously reported [20] and were similar 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 for the study were as follows: (1) documented HIV antibody test by ELISA and confirmed by Western blot; (2) two or more affirmative responses to the CAGE alcohol screening questionnaire [21], or physician investigator diagnosis of current or past alcoholism based on a clinical interview; and (3) ability to speak English or Spanish. The majority screened eligible with CAGE, 24/399 (6 %) were deemed eligible based on clinical interview only. Exclusion criteria were: (1) evidence of cognitive impairment (scoring <21 on the 30-item Folstein mini-mental state examination [22]); and (2) inability to provide informed consent. The Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess Medical Center approved this study.

Dependent Variable

The dependent variable was all-cause mortality. Deaths were ascertained through the National Death Index (NDI) from 2001 to the end of 2009. Methods for establishing a match can be found on the NDI website (http://www.csc.gov/nchs/ndi.htm). In brief, each record is matched by first and last name, date of birth, sex, social security number and state of birth. A censor date of 12/31/2009 was used for participants who were still alive at the end of the period in which NDI data was available.

Independent Variables

The main predictor of interest was pain that at least moderately interfered with work during the past month, assessed at baseline and each 6 month follow-up visit and modeled as a time-varying covariate. This was based on responses to a single question from the Short Form-12 (SF-12) [23] which asks, “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?” with possible responses being “not at all/a little bit/moderately/quite a bit/extremely”. For the primary analyses, we dichotomized at the threshold of “moderately” or above. Secondary analyses were also performed examining all categories, with referent being “not at all”. We used this variable as a proxy for chronic pain: prior research has demonstrated that even current (past week) moderate or greater pain assessed at a single point in time has reasonable sensitivity and specificity (82 and 84 %, respectively) for detecting chronic pain [24].

Additional Covariates

Additional covariates included in the analysis as potential confounders were age, sex, black race (non-black being referent), low CD4 cell count (<200 cells/μL), current use of antiretroviral therapy (ART), HCV co-infection (defined as HCV antibody positive result by ELISA confirmed with the presence of detectable HCV RNA), smoking, current (past month) hazardous drinking, recent (past 6 month) any cocaine or heroin use, depressive symptoms, and co-morbidities. Hazardous alcohol use was defined according to National Institute on Alcohol Abuse and Alcoholism guidelines for “at-risk” drinking: >14 drinks/

week or ≥5 drinks on one occasion for men ≤65 years of age, and >7 drinks/week or ≥4 drinks on one occasion for all women and for men >65 years of age and was assessed using a validated calendar method [25]. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) [26, 27], and a threshold of ≥21 was used to define substantial depressive symptoms. Burden of co-morbidities was measured with a modified Charlson–Katz co-morbidity score [28] which included all items except for heart failure as this was not assessed in the study questionnaire. All covariates were selected a priori based on their potential to be confounders and included in the adjusted models. Time-varying covariates included CD4 cell count, ART use, smoking, hazardous drinking, heroin or cocaine use, and depressive symptoms. Information on painful symptoms as reported on the HIV symptom inventory [29] was included for descriptive purposes only.

Statistical Analyses

Baseline characteristics were compared across groups (i.e., those with moderate or greater pain interference and those with less than moderate pain interference) using χ^2 or Fisher's exact test for categorical values and *t* tests or Wilcoxon Rank sum test for continuous variables, as appropriate (i.e. if the distribution appeared skewed based on descriptive statistics the non-parametric test was used). Mortality rates were calculated using person-years (p-y) of observation for descriptive purposes. Person-year rates were obtained by dividing the number of deaths observed during the study period by the total time of follow-up.

Cox proportional hazard models were fit to evaluate the associations between pain interference and overall mortality adjusting for potential confounders (age, sex, race, low CD4 cell count, current use of antiretroviral therapy, HCV co-infection, smoking, current hazardous drinking, recent cocaine/heroin use, depressive symptoms, and co-morbidities). Time varying covariates were recorded during the course of the HIV-LIVE study period, up to 2006. The following were modeled as time-varying in the regression models: pain interference, CD4 cell count, ART use, smoking, hazardous drinking, any heroin or cocaine use, and depressive symptoms. Data on time-varying covariates was collected at each 6 month assessment visit during the study period. Regression parameters were estimated based on a partial likelihood function [30] where, at each observed death time, the values of pain interference (and other time-varying covariates) at that time point were used for subjects in the risk set at that time. Adjusted hazard ratios (HR) and 95 % confidence intervals (CI) are reported for each model using those with less than moderate pain interference as the reference category (or no pain interference for secondary analyses). Schoenfeld residuals [31] were used to identify violations in the proportional hazards assumption of the Cox model. For each model, covariate-wise residuals were plotted against time to identify trends, which would indicate poor model fit. Residuals did not show patterns over time, suggesting acceptable model fit. Spearman correlations were used to evaluate correlations between independent variables and covariates and no pair of variables included in the same regression model was highly correlated ($r > 0.40$). Analyses were conducted using two-sided tests and a significance level of 0.05. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., NC, USA).

Results

Of the 400 HIV-infected participants, at baseline 158 (39.5 %) reported pain that interfered with work at a moderate or greater level; 109 (27 %) had no pain interference at all visits, 72 (18 %) had pain interference at all visits, 219 changed pain interference status at least once (55 %). At baseline, those with moderate or greater pain interference appeared to be more likely to be older, have more depressive symptoms and a greater burden of co-morbidities compared to individuals with less than moderate pain interference (Table 1). In contrast, among patients who did and did not report moderate or greater pain interference, there were no significant differences in the proportions who reported being on ART or who had a low CD4 cell count. Experiencing painful symptoms over the past month was frequently reported by participants (Table 1). At baseline, 71.3 % of the overall sample reported muscle or joint pain, 57.8 % reported headache and 62.2 % reported peripheral neuropathy (pain, numbness or tingling in the hands or feet).

In total, there were 2387 study visits for 400 participants. The mean number of assessments for participants in the study was 6 (±SD 2); median number of assessments 7 (IQR: 5, 8); 32 % of subjects completed all 8 possible assessments as of December 31st, 2009, 85 participants had died; median follow-up for death data was 6.7 years and included 2688 person-years of observation. The mortality rate was estimated as 3.72 versus 2.81 per 100 PY for those with moderate or greater pain interference compared to those without. In the unadjusted Cox model, moderate or greater pain interference was significantly associated with a higher relative hazard for death [HR = 1.58 (95 % CI 1.03–2.41; p value = 0.04)] (Table 2).

After adjustment for all covariates (age, sex, race, low CD4 cell count, current use of ART, HCV co-infection, smoking, current hazardous drinking, recent any cocaine or heroin use, depressive symptoms, and co-morbidity index), the hazard ratio was attenuated and non-significant (aHR = 1.30 (95 % CI 0.81–2.11, p value = 0.28)). Notably, the two covariates that were significantly associated with mortality were low CD4 cell count and co-infection with hepatitis C virus infection. Covariates that were of borderline significance ($p < 0.1$) were age, use of ART and recent any cocaine or heroin use. Secondary analyses using multiple categories of the pain interference variable similarly found significant associations (global p value = 0.01) in the unadjusted model, with the two highest levels of pain interference being associated with an increased hazards for death (HR = 2.64 (95 % CI 1.35–5.15) for “quite a bit” and HR = 3.04 (95 % CI 1.42–6.50) for “extremely”); however, no association across the pain interference categories was observed in the adjusted model (aHR = 1.84 (95 % CI 0.90–3.80) for “quite a bit” and aHR = 1.64 (95 % CI 0.72–3.76) for “extremely”; global $p = 0.39$) (Table 3).

Discussion

Among HIV-infected persons with alcohol use disorders, we observed higher rates of death among individuals who reported moderate or greater pain interference in unadjusted analyses. However after adjustment for potential confounders (demographics, HIV disease status, co-morbidities and substance use), we did not detect a statistically significant

association between pain interference and mortality. Secondary analyses suggested that participants who reported the most extreme levels of pain interference may be at the highest risk for death over time; however, results were based on a modest number of outcomes and did not meet thresholds for statistical significance.

Among patients with HIV, chronic pain is associated with worse quality of life [32, 33] and increased psychological distress [11, 34] as well as increased healthcare utilization [35] and among some, suboptimal adherence [36]. We are unaware of any prior studies that have examined associations between pain interference and mortality in people with HIV infection. However, studies have been conducted in the general population that have reported mixed results. A recently published systematic review [37] on the topic of chronic pain and mortality identified ten studies which were considered of adequate quality. The authors found statistically significant heterogeneity of results from studies, and a modest but non-significant pooled estimate (mortality rate ratio = 1.14; 95 % CI 0.95–1.37) for the relationship between chronic pain and all-cause mortality. Our study, which is based on a smaller sample size than most other studies, similarly found a non-significant association of modest magnitude after adjustment for other factors such as age, CD4 cell count, co-morbidities and substance use, factors that are known to contribute to both pain [8, 38] and mortality [39]. Post hoc power calculations indicate that the study would have 80 % power to detect a hazard ratio as small as 1.9. Thus the study was likely underpowered to detect the hazard ratio of 1.3 that was observed. It is unclear from this study whether there is an independent mechanism through which pain interference modestly contributes to mortality.

This study also provides descriptive information about factors that may differ among HIV-infected persons with and without pain interference (Table 1). Unlike as in some prior studies that reported associations between pain and adherence to HIV medications [36, 40], pain was not associated with ART use or HIV control. In the fully adjusted models, the only factors that were independently associated with mortality were HCV co-infection and low CD4 cell count, which are established risk factors for mortality among persons with HIV and alcohol use disorders [41].

There were limitations to this study. The study sample size was modest: although we did not detect a significant association between moderate or greater pain interference and mortality, we were underpowered to detect effect sizes less than 1.9. The relatively small number of death outcomes did not allow us to examine associations between pain interference and specific causes of mortality (e.g., cancer, trauma). Although we collected data on the death outcome up through 2009, we did not have continuous information on the independent variable, pain interference, during the entire period that we searched for deaths, as study assessments ended in 2006. We did not have detailed information on pain severity or specific pain diagnoses, however, we did have information of the prevalence of certain painful symptoms as reported in Table 1. We did not have information on use of specific pain medications such as opioids which could also impact mortality. If persons with pain interference were more likely to use opioids and overdose then this could underlie an association between pain interference and mortality. Alternatively, it is possible that use of opioids would reduce likelihood of reporting pain that interferes with daily living and bias toward the null. Research with larger clinical samples should be undertaken to examine

relationships between pain, opioid use and specific causes of mortality (e.g. opioid overdose, trauma, cardiovascular causes) among persons with HIV, and our effect sizes may be useful in designing future studies. Furthermore, care should be taken to distinguish more extreme from less extreme levels of pain interference as our findings suggest differences in risk for mortality.

In summary, this study observed that among HIV-in-fected persons with alcohol use disorders, reporting moderate or greater pain interference was not independently associated with increased mortality. However, caution should be taken interpreting results, as our study was likely underpowered to detect a modest effect size such as the one we observed (HR = 1.3). Pain is an important patient-centered outcome that should be addressed among persons with HIV. It may perhaps be reassuring to providers and patients that it does not appear to independently predict risk of death. Future research with larger samples would be helpful to clarify relationships between pain and mortality in HIV.

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Table 1

Baseline characteristics of HIV-LIVE cohort participants, overall and stratified by pain interference

	Overall (n = 400)	≥Moderate pain interference (n = 158)	<Moderate pain interference (n = 242)	Test statistic	*p* value
Age (mean ± SD)	42.5 (7.4)	43.5 (7.3)	41.9 (7.5)	t = −2.08	$p = 0.04$
Female	101 (25.3 %)	42 (26.6 %)	59 (24.4 %)	$X^2 = 0.25$	$p = 0.62$
Race					
Black	166 (41.5 %)	62 (39.2 %)	104 (43.0 %)	$X^2 = 1.35$	$p = 0.72$
White	131 (32.8 %)	57 (36.1 %)	74 (30.6 %)		
Hispanic	75 (18.8 %)	28 (17.7 %)	47 (19.4 %)		
Other	28 (7.0 %)	11 (7.0 %)	17 (7.0 %)		
HIV viral load >500 (n = 362)	194 (53.6 %)	78 (54.9 %)	116 (52.7 %)	$X^2 = 0.17$	$p = 0.68$
CD4 \200 cells/μL (n = 378)	75 (19.8 %)	28 (18.8 %)	47 (20.5 %)	$X^2 = 0.17$	$p = 0.68$
Current ART use	248 (62.0 %)	105 (66.5 %)	143 (59.1 %)	$X^2 = 2.20$	$p = 0.14$
HCV seropositive (n = 397)	200 (50.4 %)	83 (53.2 %)	117 (48.5 %)	$X^2 = 0.82$	$p = 0.36$
Current smoking	306 (76.5 %)	125 (79.1 %)	181 (74.8 %)	$X^2 = 0.99$	$p = 0.32$
Past month hazardous drinking[a] (n = 399)	125 (31.3 %)	45 (28.7 %)	80 (33.1 %)	$X^2 = 0.86$	$p = 0.36$
Past 6 month heroin/cocaine use	199 (49.8 %)	70 (44.3 %)	129 (53.3 %)	$X^2 = 3.10$	$p = 0.08$
Moderate depressive symptoms[b]	212 (53.0 %)	106 (67.1 %)	106 (43.8 %)	$X^2 = 20.81$	$p < 0.01$
Co-morbidity index[c]	3.5 (3.5)	4.1 (3.8)	3.2 (3.3)	z = 2.89	$p < 0.01$
Muscle or joint pain	285 (71.3 %)	138 (87.3 %)	147 (60.7 %)	$X^2 = 33.01$	$p < 0.01$
Headache	231 (57.8 %)	109 (69.0 %)	122 (50.4 %)	$X^2 = 13.52$	$p < 0.01$
Peripheral neuropathy	248 (62.2 %)	123 (77.9 %)	125 (51.9 %)	$X^2 = 27.39$	$p < 0.01$

[a] Based on National Institute on Alcohol Abuse and Alcoholism guidelines for “at-risk” drinking: >14 drinks/week or ≥5 drinks on one occasion for men ≤65 years of age, and >7 drinks/week or ≥4 drinks on one occasion for all women and for men >65 years of age

[b] CES-D score ≥21

[c] Charlson–Katz based co-morbidity index, maximum score 36

Table 2

Relative hazards for death associated with moderate or greater pain interference (dichotomous variable), results from Cox proportional hazards models

	Unadjusted HR (95 % CI)	*p* value	Fully adjusted HR (95 % CI)	*p* value
Moderate or greater interference	1.58 (1.03–2.41)	0.04	1.30 (0.81–2.11)	0.28
Age (years)			1.03 (1.00–1.06)	0.09
Female			1.09 (0.66–1.81)	0.73
Black			1.18 (0.75–1.86)	0.47
CD4 <200 cells/μL			3.12 (1.98–4.91)	<0.01
Current ART use			0.65 (0.41–1.03)	0.07
HCV seropositive			2.26 (1.36–3.77)	0.002
Current smoking			0.93 (0.55–1.57)	0.79
Past month hazardous drinking			0.82 (0.46–1.46)	0.50
Past 6 month heroin/cocaine use			1.57 (0.98–2.52)	0.06
Moderate depressive symptoms[a]			0.97 (0.59–1.59)	0.89
Co-morbidity Index[b]			1.04 (0.98–1.11)	0.18

[a] CES-D score ≥21

[b] Charlson–Katz based co-morbidity index, maximum score 36

Table 3

Relative hazards for death associated with levels of pain interference, results from Cox proportional hazards models

	Unadjusted HR (95 % CI)	*p* value	Fully adjusted HR (95 % CI)	*p* value
Pain interference:				
Not at all	Ref	0.01[a]	Ref	0.39[a]
A little bit	1.69 (0.89–3.21)		1.19 (0.61–2.31)	
Moderately	1.34 (0.64–2.82)		1.03 (0.47–2.27)	
Quite a bit	2.64 (1.35–5.15)		1.84 (0.90–3.80)	
Extremely	3.04 (1.42–6.50)		1.64 (0.72–3.76)	
Age (years)			1.03 (1.00–1.06)	0.09
Female			1.13 (0.68–1.88)	0.64
Black			1.13 (0.72–1.78)	0.60
CD4 <200 cells/μL			3.02 (1.91–4.78)	<0.01
Current ART use			0.67 (0.42–1.08)	0.10
HCV seropositive			2.26 (1.36–3.77)	<0.01
Current smoking			0.90 (0.53–1.52)	0.68
Past month hazardous drinking			0.86 (0.48–1.53)	0.60
Past 6 month heroin/cocaine use			1.53 (0.95–2.46)	0.08
Moderate depressive symptoms[b]			0.93 (0.56–1.55)	0.79
Co-morbidity index[c]			1.04 (0.98–1.11)	0.22

[a] Global *p* value

[b] CES-D score ≥21

[c] Charlson–Katz based co-morbidity index, maximum score 36