Pain Medicine

Pain Medicine 2015; 16: 1870–1881
Wiley Periodicals, Inc.

Chronic Pain in HIV-Infected Patients: Relationship to Depression, Substance Use, and Mental Health and Pain Treatment

Lisa A. Uebelacker, PhD,[*,†] Risa B. Weisberg, PhD,[†,‡] Debra S. Herman, PhD,[*,†] Genie L. Bailey, MD,[†,§] Megan M. Pinkston-Camp, PhD,[†,¶] and Michael D. Stein, MD[*,†,¶]

*Butler Hospital, Providence, Rhode Island; [†]Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, Rhode Island; [‡]Boston VA Healthcare System, Boston, Massachusetts; [§]Stanley Street Treatment and Resources, Fall River, Massachusetts; [¶]The Immunology Center, The Miriam Hospital, Providence, Rhode Island, USA

Reprint requests to: Lisa A. Uebelacker, Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906, USA. Tel: 401-455-6381; Fax: 401-455-6235; E-mail: luebelacker@butler.org.

Disclosure: Dr. Bailey's institution has received grant support from NIDA, Titan Pharmaceuticals, Inc., Alkermes, Inc., BioDelivery Sciences International, Inc., and Orexo. She has received travel support from Titan Pharmaceuticals, Inc. and is on the advisory boards of Braeburn Pharmaceuticals, BioDelivery Sciences International, Inc. and Camurus AB. The other authors have no conflicts of interest to report.

Funding sources: This study was supported by grant NR013438 (MPIs: Uebelacker, Stein) from the National Institute of Nursing Research and the Lifespan/Tufts/Brown Center for AIDS Research (CFAR) grant 2P30AI042853 (PI: Carpenter).

Abstract

Objective. As the advent of highly active antiretroviral therapy, HIV has become a chronic disease for most individuals in developed countries. Chronic pain is a common occurrence for HIV—infected patients and has an impact on quality of life and antiretroviral adherence. The objective of this study was to examine relationships between chronic pain and depression, substance use, mental health treatment, and pain treatment in HIV-infected patients.

Design. Cross-sectional study.

Setting. Three primary care sites where HIV+ patients receive treatment.

Subjects. Two hundred and thirty eight HIV-infected primary care patients.

Methods. We collected self-report and chart-review information on demographics, HIV clinical status, chronic pain, depression, substance use, mental health treatment, and pain treatment. We collected data between October 2012 and November 2013.

Results. Of the patients enrolled in this study, 107 reported no chronic pain, 24 reported mild chronic pain, and 107 reported moderate-severe chronic pain. Participants in the moderate-severe pain group were more likely to have high levels of depressive symptoms than those in the no chronic pain group. Similarly, there was a significant relationship between chronic pain status and interference with life activities due to pain. Participants with moderate-severe chronic pain were more likely to be taking an antidepressant medication than those with mild chronic pain, and more likely to be taking a prescription opioid than the other two groups. We did not find a significant relationship between problematic substance use and chronic pain status.

Conclusions. Despite pharmacologic treatment, moderate-severe chronic pain and elevated depression symptoms are common among HIV-infected patients and frequently co-occur.

Key Words. HIV; Chronic Pain; Depression

Introduction

As the advent of highly active antiretroviral therapy (HAART), HIV has become a chronic disease for most infected individuals in developed countries. As patients living with HIV age, chronic pain can have a major impact on quality of life [1]. Chronic pain in HIV-infected patients can have diverse etiologies, including non-HIV-related conditions such as musculoskeletal low back pain or headache, as well as pain due to the impact of HIV-related conditions such as neuropathy or osteonecrosis [2]. Further, some types of HAART, (i.e., dideoxynucleoside reverse transcription inhibitors) may contribute to neuropathic pain that is difficult to treat [3]. Having pain [4], and particularly untreated pain [5], may be associated with lower rates of HAART adherence with attendant concerns about disease progression. Thus, understanding and managing pain in HIV-infected patients is of critical importance.

Most previous studies of pain in HIV-infected patients in the HAART era have reported correlates of the presence or severity of *current* (i.e., past week) pain rather than chronic pain (i.e., pain lasting 3–6 months or more). Assessing only pain severity in the past week may miss up to one-third of clinically significant pain [6]. Thus, although there is overlap between groups with chronic pain and those with pain in the past week, they are not the same. No previous studies have specifically examined correlates of *chronic* pain in an HIV-infected population. Further, results from research in non-HIV—infected samples suggest the importance of differentiating between mild chronic pain and moderate-severe chronic pain, as the more severe chronic pain likely has a greater impact on quality of life [7,8].

In their biopsychosocial model of chronic pain in HIV, Merlin et al. [2] discuss potential biological mechanisms of chronic pain, including pain relating to aspects of HIV and its treatment as well as psychiatric illness and substance abuse. Certainly, the presence of chronic pain in the general population is associated with increased levels of depression [9,10], and within samples of people with chronic pain, pain severity, and depression symptom severity are correlated [11]. In fact, as severity of pain fluctuates in individuals over time, so does level of depressive symptoms [12]. Previous research specifically in HIV-infected populations has documented that the presence of pain in the past week is associated with more anxiety and depression symptoms [13], having a psychiatric illness [14], and generally poorer mental and physical health [15]. Increasing severity of current pain has also been associated with increasing severity of depression in HIV-infected patients [16,17].

Substance abuse is often associated with chronic pain in the general population [18]. Substance abuse may contribute to causes of chronic pain (i.e., injuries or illnesses) or may be a consequence of chronic pain, as individuals turn to binge drinking or illicit substances as a way to escape pain [18]. Lifetime substance abuse rates are elevated in HIV-infected individuals [19], and HIV-infected patients may be at particularly increased risk for substance use or abuse in the presence of chronic pain. Some previous research on current pain in HIV-infected patients has shown that pain severity is associated with current use of "hard" drugs (i.e., crack, cocaine, or heroin), as well as marijuana, but that pain severity is more closely associated with depressive symptoms than with drug use [17]. Other research has failed to find an association between pain severity level and current daily drinking or current use of other illicit substances [16].

The goal of this study was to examine the relationship between *chronic* pain and depression, substance use, and treatment for depression and pain specifically in HIV-infected patients. We divided our sample into three clinically relevant groups: those with no chronic pain, those with mild chronic pain, and those with moderate-severe chronic pain. This allows us to examine whether having any chronic pain at all is associated with increased levels of other problems, as well as whether having moderate-severe chronic pain is associated with more severe problems than mild chronic pain. We hypothesized that there would be an association between having chronic pain and: 1) depression; 2) binge drinking and substance use; and 3) increased use of antidepressant medication and counseling. Further, we hypothesized that people with moderate-severe chronic pain would show higher rates of depression, substance use, and treatment than those with mild chronic pain. We planned to examine bivariate associations as well as a multivariate model so that we could understand which of our measured variables would account for unique variance in chronic pain status while also controlling for demographics and HIV illness variables. Based on previous research, we hypothesized that depression would be associated with pain status even when accounting for treatment and substance use variables.

Methods

Participants

Between October 2012 and December 2013, we interviewed English-speaking HIV-infected patients (age 18 and older) receiving treatment at three practice sites in southeastern New England. These sites were: a private internal medicine office with an internist and nurse practitioner who provide primary care for 125 HIV+ patients (site 1; $n = 67$); a federally qualified community health center that provides care for 175 HIV+ patients and is staffed by two infectious-disease trained internists and one general internist (site 2; $n = 99$); and an academic hospital-based HIV clinic that provides care for over 1,700 patients and is staffed by six infectious-disease trained internists and two general internists (site 3; $n = 72$). These clinicians serve as primary care providers to patients in this study; none of the providers were serving in a consultative or specialty role. Physicians at

all three sites provided opioid and nonopioid pain medication prescriptions; patients were referred out for other types of pain treatment. Sites 2 and 3 had limited psychotherapy available at the primary care site. Site 3 was at a hospital which did have other types of pain treatment (e.g., physical therapy) and psychiatry available at other locations but not at the HIV clinic.

Procedures

This study was approved by the relevant Institutional Review Boards. Given that it was a brief, one-time survey study, participants verbally consented to answer questions described in this article. Our only inclusion/exclusion criteria were laboratory confirmed HIV positivity, aged 18 or older, and ability to speak English. Participants were not reimbursed for their participation. Procedures were identical at site 1 and site 2. On days when research staff was assigned to the primary care clinic, staff approached consecutive HIV-infected patients and asked whether they would be willing to complete a brief interview for research purposes. We did this as part of screening for a clinical trial addressing pain and depression in HIV-infected patients. (Those who screened positive for depression and chronic pain, and who met other inclusion criteria, were then invited to participate in a study of psychosocial treatment for chronic pain and depression.) There were no other inclusion criteria. All participants at site 1 who were approached agreed to complete the questionnaire. At site 2, five patients who were approached did not complete the questionnaire because they did not speak English, and two refused to complete it.

Procedures differed somewhat at site 3. On days when research staff members were recruiting, they approached consecutive patients and asked if they wanted to participate in a single study visit in which they would be asked questions about HIV, pain, depression, sleep, and substance use. Additionally, at this site, staff posted fliers advertising a study about factors that impact sleep in HIV-infected patients. Thirty-three participants were recruited via approaching consecutive patients, and 39 of the 72 participants recruited at this site had responded to the flier. As noted below, there were a few variables that were not assessed at this clinic; some others (treatment-related variables) were assessed via chart review rather than via self-report.

Assessments

Unless specifically noted, assessments were the same across all three sites. All measures were administered by an interviewer in a private room in the primary care clinic. Interviewers read the questions verbatim to the participants.

Demographic and HIV Variables

We assessed demographics by asking participants to self-report on age, relationship status, race, ethnicity, education, and work status. In the work status variable, "other" includes (but was not limited to) people with disability pending and people who were retired. We assessed four aspects of HIV history via patient interview: date of diagnosis, whether the patient was currently taking HIV medications, whether he/she had ever had an AIDS-related infection, and whether he/she had ever taken a neurotoxic medication such as ziduvudine, zalcitabine, stavudine, or didanosine. The latter two variables were not assessed at site 3.

Pain

To assess current pain severity, we asked participants the following question: "On a 1-00 scale, where 0 = no pain and 100 = pain as bad as you can imagine, what has your average pain been in the past week?" [20]. To define chronic pain, we asked participants: "have you had chronic pain for at least the past 6 months?" (The choice of a 6-month period for chronic pain was based on expert recommendations [21]). We asked participants to self-report on the *primary* bodily location of pain (i.e., "in the last week, where has your pain been primarily?" with options for various areas of the body, such as "back pain" or "neck pain"). To assess interference due to pain, we used the Brief Pain Inventory [22] interference scale (BPI-I). This scale asks about the degree to which pain interferes with important aspects of life, including general activity, mood, walking ability, normal work (including home and housework), relations with others, sleep, and enjoyment of life. In this study, many participants were receiving disability payments, and found the "normal work" question difficult to answer, as level of interference was different for work outside the home when compared to housework. Therefore, we decided not to include this question in the total score. Individuals who reported no pain in the past week were assigned a 0 on the BPI-I. Total BPI-I scores range from 0 to 10, with higher scores representing more pain interference. In this sample, Cronbach's alpha = 0.93 for the BPI-I, indicating good internal consistency.

Depression and Substance Abuse

To assess depression symptoms, we used the Center for Epidemiologic Studies Depression scale (CESD), 10-item version [23]. Scores can range from 0 to 30, a score greater than or equal to 10 is considered to be a positive screen for depression. In this sample, Cronbach's alpha = 0.86 for the 10 items of the CESD, indicating good internal consistency. We also assessed whether participants screened positive for depression using a standard cutoff of the 2-item Patient Health Questionnaire (PHQ-2; ≥ 3 is a positive screen) [24]. To assess alcohol use, we asked about the average number of drinks consumed on those days that the person drank alcohol in the past month. We categorized

individuals as binge drinkers if they consumed 5 or more drinks (for men) or 4 or more drinks (for women) [25] on days when they drank in the past month. We also asked about number of days in the past month that the participant used cocaine, crack, or methamphetamine; we categorized participants dichotomously by whether they had used these drugs in the past month or not. Other researchers have documented the validity of a very similar single item as a screener for hazardous alcohol use [26] and a brief drug use frequency questionnaire [27].

Treatment

We assessed treatment for mental health problems via patient interview. We asked: "do you currently receive any mental health counseling?" and "are you currently taking an antidepressant medication?" At sites 1 and 2, participants also provided information on current pain treatment: counseling specifically regarding pain in the past 6 months, current nonopioid pain medication use (e.g., nonsteroidal anti-inflammatory medications, anticonvulsants specifically for pain), and current opioid pain treatment. To assess current pain medications, we asked: "are you currently taking any medications for pain?" and if patients answered in the affirmative, we asked for and recorded the names of the pain medications. We could then code whether or not they were opioids or other pain medications. At site 3, we did not collect data about counseling specifically regarding pain, and current nonopioid and opioid pain medication were assessed via chart review. (We did not assess or include use of opioids prescribed for opioid use disorder.)

Data Analysis

We divided our sample into three groups: those with no chronic pain (some of whom had acute pain), those with mild chronic pain (i.e., pain severity between 0 and 39 in the past week, and pain for at least 6 months) and those with moderate/severe chronic pain (i.e., pain severity was ≥ 40 in the past week and pain for at least 6 months). A combination of a question about past-week pain severity plus a similar (to our own) retrospective question about whether pain has lasted for 6 months or longer has been found to show a high level of sensitivity and specificity when compared to a classification of chronicity of pain that was based on questions about pain severity asked repeatedly during the 6-month period of interest [28]. Further, the combination of a past-week question about severity and a question about chronicity is understandable to HIV-infected patients [29]. We chose the severity cutoff based on its use as a threshold for inclusion in clinical trials of pain [21]. We compared the three groups on: demographics, HIV-related factors, depression and substance use, and mental health and pain treatments using either a chi-square test or one-way ANOVA. For continuous dependent variables, we conducted a post hoc comparison of group differences using a Tukey HSD test. For discrete dependent variables, we conducted follow-up chi-square tests comparing two pain groups. We considered $P < 0.05$ to be statistically significant.

Next, we used multinomial logit models to estimate the adjusted associations between depression, substance use, treatment, and pain type while controlling for demographics, HIV variables, and other measured variables. The statistical significance of the overall association was tested using a likelihood ratio difference in chi-square test comparing models with and without each evaluated predictor. Specific variables included in the model included demographics (gender, race, ethnicity, employment status, age, and years of education), HIV variables available for all groups (years with HIV), depression (CES-D), substance use variables (use of crack, cocaine, or methamphetamine in the past month, binge drinking in the past month), mental health treatment variables (receiving mental health counseling, taking an antidepressant) and pain treatment (taking a nonopioid pain medication, taking an opioid pain medication), We present adjusted odds-ratios to describe the association between variables and pain type.

Results

Of 238 HIV-infected participants, 131 (53% of total participants) endorsed having chronic pain. Of the individuals with chronic pain, 24 had mild chronic pain, and 107 had moderate-severe chronic pain. Among participants with chronic pain, the most common primary pain sites in the past week were: multiple locations, joints, and back (Table 1). One hundred and seven participants denied having chronic pain; of these, 70 reported having no pain at all in the past week; the remaining 37 had pain severity levels ranging from 1 to 90, although only eight had levels of 40 or higher (moderate-severe acute pain).

We report results of bivariate comparisons of demographics, HIV characteristics, depression and substance use, and mental health and pain treatment in Table 2. With regard to *demographics*, participants with mild or moderate-severe chronic pain were less likely to be working and more likely to be on disability than those with no chronic pain. Sites also differed in proportions of patients in each of the three pain groups. In terms of *HIV-related* variables, participants with moderate-severe chronic pain reported a longer time as HIV diagnosis than those with mild chronic pain. People with moderate-severe chronic pain were more likely to report having had an AIDS-related infection than those with no chronic pain.

Relative to individuals in the no chronic pain group, those in the moderate-severe chronic pain group had higher levels of depression symptoms. The mild chronic pain group was not significantly different from either of the other two groups in terms of depression symptom

Table 1 Primary pain locations in the past week

	Participants with Acute but No Chronic Pain ($n = 38$; Remainder had No Pain At All)	Participants with Mild Chronic Pain ($n = 23$)*	Participants with Moderate or Severe Chronic Pain ($n = 102$)*
Location	*n* (%)	*n* (%)	*n* (%)
Back	6 (16%)	6 (26%)	18 (18%)
Neck	1 (3%)	0	2 (2%)
Headache/migraine	7 (18%)	0	2 (2%)
Stomach/abdomen	3 (8%)	1 (4%)	0
Lower extremities	10 (26%)	8 (35%)	32 (31%)
Chest	3 (8%)	0	0
Face	1 (3%)	0	0
Multiple sites primary/pain all over body	7 (18%)	8 (35%)	48 (47%)

* A total of six participants had missing data.

severity. Many more participants in the moderate-severe chronic pain group screened positive for depression on the PHQ-2 than in the mild chronic pain group, although this difference did not reach our predefined level of statistical significance. Participants with moderate-severe chronic pain were more likely to report pain interference with activities than participants with mild chronic pain, who in turn were more likely to report greater interference than persons without chronic pain. We did not find a significant association between chronic pain status and either the tendency to binge drink or use crack, cocaine, or methamphetamines in the last 30 days.

With regard to depression or pain *treatment*, participants with moderate-severe chronic pain were more likely to be taking an antidepressant medication and an opioid, compared to persons mild or no chronic pain groups. Rates of nonopioid pain medication receipt were higher in the mild chronic pain group when compared to the no chronic pain group. Of the 47 participants with chronic pain (mild, or moderate-severe) who were taking opioids, average pain in the past week ranged from 10 to 100, with a mean level of 67 and a median level of 70. No participant reported receiving counseling specifically targeted toward chronic pain.

The multinomial logit regression model (Table 3) shows associations between key variables and pain group (no pain, mild pain, and moderate-severe pain) while adjusting for demographic and HIV disease covariates and other variables. We found that the moderate-severe chronic pain group had significantly more depression than the no chronic pain group. As demonstrated previously, the mild chronic pain group was most likely to be receiving mental health counseling, and least likely to be taking an antidepressant. Both the moderate-severe and the mild chronic pain groups were more likely to be taking a nonopioid pain medication that the group with no chronic pain. Finally, the moderate-severe pain group was more likely than either of the other two groups to be taking an opioid pain medication.

Discussion

In this study, we examined differences between groups with no chronic pain, mild chronic pain, and moderate-severe chronic pain among HIV-infected people in the era of HAART. People with moderate-severe chronic pain had higher levels of depression symptoms and higher rates of screening positive for depression than participants in the no chronic pain group. Even when adjusting for other variables, differences in depression symptom severity between the moderate-severe chronic pain group and the no chronic pain group remained statistically significant. Contrary to our hypothesis, we did not find statistically significant differences between the moderate-severe pain group and the mild pain group in terms of depression, although the direction of the effect was as expected, and the mild pain group was also not significantly different from the no chronic pain group. The relationship of depression with chronic pain is well documented in other chronic conditions, and is likely bidirectional [30,31]. Banks and Kerns suggest that it is not just having a chronic medical condition that puts one at risk for depression, but it is the specific nature of chronic pain that places one at higher risk, noting that pain is "inextricably associated with negative affect." Because pain is aversive and "can pervade one's consciousness and seems psychologically inescapable," it follows that a substantial minority of patients with chronic pain (and particularly moderate-severe pain) experience extreme negative reactions, namely, depression. Conversely, being depressed predicts the development of chronic pain (e.g., the conversion of acute low back pain to chronic low back pain [32]), likely through varied mechanisms, including decreased engagement in physical activity interventions [33] or increased attention to somatic symptoms.

Table 2 Differences between people with no chronic pain, mild chronic pain, and moderate or severe chronic pain

	No Chronic Pain ($n = 107$) N (%) or *Mean* (*SD*)	Chronic Pain, Mild ($n = 24$) N (%) or *Mean* (*SD*)	Chronic Pain, Moderate or Severe ($n = 107$) N (%) or *Mean* (*SD*)	Chi-Square (df) or *F*(*df*)	*P* Value
Demographics					
Site	†	†,‡	‡	11.62 (4)	0.02
Site 1	40 (37%)	7 (29%)	20 (19%)		
Site 2	36 (34%)	8 (33%)	55 (51%)		
Site 3	31 (29%)	9 (38%)	32 (30%)		
Gender—Women	34 (32%)	10 (42%)	45 (42%)	2.61 (2)	0.27
Race				7.53 (6)	0.28
Caucasian	65 (62%)	15 (63%)	62 (68%)		
Black/African American	32 (31%)	6 (25%)	30 (28%)		
Native American/Alaskan Native	3 (3%)	2 (8%)	0		
Other	5 (5%)	1 (4%)	4 (4%)		
Ethnicity—Hispanic/Latino	21 (20%)	4 (17%)	15 (14%)	1.20 (2)	0.55
Work status	†	†,‡	‡	24.52 (6)	<0.001
Full time	30 (28%)	2 (8%)	9 (8%)		
Part-time	13 (12%)	3 (13%)	5 (5%)		
Disability	50 (47%)	16 (67%)	81 (76%)		
Other	14 (13%)	3 (13%)	12 (11%)		
Age	*51.0 (10.3)*	*50.0 (10.9)*	*51.0 (8.4)*	*0.27 (2,235)*	*0.76*
Years of Education	*12.7 (2.9)*	*12.1 (2.4)*	*11.9 (2.3)*	*2.48 (2,235)*	*0.09*
HIV-Related					
Transmission method				3.06 (6)	0.80
IV Drug use	20 (21%)	5 (21%)	30 (30%)		
Men who have sex with men	36 (37%)	9 (38%)	31 (31%)		
Heterosexual	35 (36%)	8 (33%)	33 (33%)		
Other/transfusion	6 (6%)	2 (8%)	5 (5%)		
Years with HIV	*16.0 (7.9)*†,‡	*12.8 (8.0)*†	*17.9*‡ *(9.5)*	*3.68 (2, 233)*	*0.03*
Taking HIV medications	100 (94%)	22 (92%)	104 (97%)	2.17 (2)	0.34
Has had an AIDS-related infection	10 (13%)†		22 (30%)‡	6.26 (2)	0.04
Ever taken neurotoxic medications	37 (49%)	9 (60%)	41 (59%)	1.66 (2)	0.44
Depression, Substance Use, and Interference Due to Pain					
CES-D score	*8.14*† *(5.96)*	*11.58*†,‡ *(7.64)*	*14.81*† *(8.09)*	*23.20 (2,235)*	*<0.001*
CES-D score > 10	41 (38%)†	13 (54%)†,‡	76 (71%)‡	23.10 (2)	<0.001
Positive screen on the PHQ-2	13 (12%)†	4 (17%)†,‡	40 (37%)‡	19.48 (2)	<.001
	9 (8.4%)	3 (12.5%)	12 (11.3%)	0.66 (2)	0.72

Table 2 Continued

	No Chronic Pain ($n = 107$) N (%) or *Mean* (*SD*)	Chronic Pain, Mild ($n = 24$) N (%) or *Mean* (*SD*)	Chronic Pain, Moderate or Severe ($n = 107$) N (%) or *Mean* (*SD*)	Chi-Square (df) or *F*(*df*)	*P* Value
Used crack, cocaine, or methamphetamine in past month					
Tends to binge drink in past month	10 (9%)	1 (4%)	10 (9%)	0.72 (2)	0.70
Interference due to pain (BPI)	*0.62*[†] *(1.82)*	*3.00*[‡] *(2.12)*	*5.93*[§] *(2.67)*	*145.94 (2, 234)*	*<0.001*
Treatment					
Receiving MH counseling (therapy)	24 (22%)	10 (42%)	24 (22%)	4.33 (2)	0.12
Taking an antidepressant	30 (28%)[†]	5 (21%)[†]	47 (44%)[‡]	8.17 (2)	0.02
Receiving counseling specifically for chronic pain	0	0	0		
Taking a non-opioid pain medication	16 (15%)[†]	10 (42%)[‡]	64 (62%)[‡]	47.35 (2)	<0.001
Taking an opioid pain medication	3 (3%)[†]	2 (8%)[†]	41 (38%)[†]	45.34 (2)	<0.001

Note. Same superscripts indicate no significant difference on post hoc tests; different superscripts indicate significant difference. Having had an HIV-related infection, having ever taken neurotoxic medications, and currently receiving counseling specifically for chronic pain were not assessed at site 3.
Continuous variables are in italics.

[†] Mild chronic pain group compared to the no chronic pain group.

[‡] Moderate+ chronic pain group compared to the no chronic pain group.

[§] Moderate+ chronic pain group compared to the mild chronic pain group.

* $P < 0.05$.

The comorbidity of depression and chronic pain is of special concern for many reasons. First, when compared to individuals with major depression but without chronic pain, those with chronic pain have depressive symptoms of longer duration [34] and greater severity [35]. Second, in comparison to those without chronic pain, individuals with chronic pain have twice the risk for suicide [36]. Even in depressed inpatients [37] and outpatients [34], chronic pain increases the risk of suicidal ideation. Third, comorbid chronic pain and major depressive disorder (MDD) is associated with more disability than either condition alone [10]. Fourth, the combination of chronic pain and MDD may increase health care costs in a multiplicative fashion [38]. Fifth, both pain and depression may increase risk for nonadherence to HAART [4,5,39], although it is unclear whether the presence of both problems will increase the risk of nonadherence above and beyond the risk inherent when only pain or only depression are present.

We turn next to antidepressant use at these HIV sites. It is worth noting that even among the primary care HIV-infected patients without chronic pain, antidepressant use was higher than the general population (28% in patients without chronic pain in our sample, compared to 16% of people aged 40–59 in the general population [40]). There were differences in rates of antidepressant medication use between groups, with a higher proportion of the moderate-severe pain group taking antidepressants, as compared to the no chronic pain group. This is not surprising, given the higher rates of depression, and indeed, was no longer statistically significant in the multivariate model which accounted for depression severity and other variables. Although antidepressants can have analgesic effects, and may be useful for treating fibromyalgia, some types of neuropathic pain, and headaches [41], these results are consistent with the idea that antidepressants were being primarily used in people with depressive symptoms in this sample.

Results regarding mental health counseling were unexpected. Despite the fact that the mild chronic pain group was intermediate in terms of depression symptom severity, this group was more likely to be receiving mental health counseling than the other two groups. It is unclear to us whether this is a spurious finding due to something unusual in a relatively small sample ($n = 24$). It is possible that the mild chronic pain group is more likely to receiving mental health counseling than the moderate-severe pain group because the mild pain group has fewer other medical appointments, less disability, and is more able to participate in therapy appointments. The fact that they are receiving counseling may make it less likely that they and their providers believe an antidepressant is needed.

Overall, 20% of our sample reported taking current opioid medication for pain. This is consistent with other data suggesting that 30% of HIV-infected patients receive an opioid prescription in a years' time [42], and up to 8% of HIV-infected patients have a long-term opioid prescription [43]. As one might expect, there was a relationship between having any chronic pain and nonopioid pain medication use. Contrary to our hypothesis, there were no statistically significant differences between people with moderate-severe pain and mild chronic pain. However, as hypothesized, relative to patients with no chronic pain or mild chronic pain, the patients who reported current moderate-severe pain had higher levels of current opioid pain medication use. This was confirmed in the multivariate analysis. For 45 patients in our sample (19% of the total sample), pain was reported as being moderate or severe despite the fact that they were taking opioids. This phenomenon has been documented in other samples [44] where persons who continued to have high pain levels despite opioid use were more likely to report neuropathic pain or symptoms of centralized pain such as symptoms consistent with fibromyalgia. Specifically in HIV-infected patients, Onen et al. [45] reported that, in a chart review study of 140 outpatients who were prescribed opioids, 63% of patients' charts documented no subjective improvement. As is well documented, prescription opioid use is not without risks, including the risk of accidental (or purposeful) overdose [46] and of aberrant drug-related behaviors or misuse [47]. Despite the fact the there is good evidence that psychotherapy, including cognitive-behavioral therapy (CBT) and mindfulness-based therapies, are effective for treatment of chronic pain [48], not one participant in the two sites where this variable was assessed reported receiving counseling specifically for chronic pain. Further, rates of any type of mental health counseling were fairly low overall in this sample.

Contrary to our hypotheses, we did not see an association between binge drinking or substance abuse and chronic pain. This may be due to the fact that reported rates of use of cocaine, crack, or methamphetamine were fairly low overall in our sample. We also used brief measures of amount of substance use rather than more extensively validated and lengthier measures of hazardous use such as the Alcohol Used Disorders Identification Test [49]. However, as discussed in Introduction, previous research on the relationship between past-week pain and current substance use has been mixed and certainly the relationship may not be as robust as the association between depression and chronic pain. Future research may focus on the conditions in which chronic pain does increase risk for illicit substance use in HIV-infected patients.

Between the three groups, the only demographic difference that we observed was employment status. Even though overall rates of participation in Social Security and Supplemental Security income disability programs were high in this sample, moderate-severe chronic pain was associated with a higher likelihood of being on disability. This is to be expected given that moderate-severe chronic pain may be judged to interfere with one's ability to work and thus qualify one for a disability program. However, we note that the association

Table 3 Multinomial logit model regressing chronic pain group on demographic characteristics, HIV characteristics, depression, substance use, and depression and pain treatment ($n = 238$)

	Mild vs. None[†] OR (95% CI)	Mod and Sev vs. None[‡] OR (95% CI)	Mod and Sev vs. Mild[§] OR (95% CI)	LR^2 ($P =$)
Site				
Site 1	1.23 (0.29; 5.16)	0.84 (0.28; 2.49)	0.6889 (0.15; 3.04)	7.84 (0.01)
Site 2	1.22 (0.31; 4.79)	2.78* (1.07; 7.24)	2.28 (0.57; 9.06)	
Site 3 [REF]	[1.00]	[1.00]	[1.00]	
Gender (Women)	1.28 (0.41; 4.01)	1.40 (0.62; 3.16)	1.09 (0.34; 3.49)	0.68 (0.71)
Race (Caucasian)	1.12 (0.34; 3.68)	1.36 (0.60; 3.09)	1.22 (.0.36; 4.09)	0.56 (0.76)
Ethnicity (Hispanic)	0.65 (0.15; 2.79)	0.65 (0.22; 1.89)	0.99 (0.22; 4.43)	0.75 (0.69)
Employment Status				
Part-Time	2.39 (0.26; 21.74)	0.91 (0.19; 4.36)	0.38 (0.03; 4.23)	
Disabled	7.70 (1.04; 57.17)	3.25 (0.88; 11.99)	0.42 (0.05; 3.60)	8.25 (0.220)
Other	2.70 (0.31; 23.26)	1.45 (0.32; 6.53)	0.54 (0.05; 5.57)	
Full-Time [REF]	[1.00]	[1.00]	[1.00]	
Age	1.00 (0.94; 1.06)	0.98 (0.94; 1.02)	0.98 (0.92; 1.05)	0.89 (0.64)
Years of education	0.99 (0.78; 1.27)	1.05 (0.88; 1.26)	1.06 (0.83; 1.36)	0.40 (0.82)
Years with HIV	0.91* (0.83; 0.98)	1.00 (0.95; 1.06)	1.11* (1.02; 1.20)	7.23 (0.03)
CESD-score	1.05 (0.97; 1.15)	1.13* (1.07; 1.20)	1.08 (0.99; 1.17)	20.48 (<0.001)
Used crack/coc/meth past month	1.43 (0.23; 9.06)	1.76 (0.49; 6.31)	1.23 (0.19; 8.07)	0.78 (0.68)
Tends to binge drink in the past month	0.08* (0.01; 1.09)	0.69 (0.18; 2.70)	8.12 (0.62; 106.68)	5.07 (0.08)
Receiving MH counseling (therapy)	5.62* (1.28; 24.70)	0.20* (0.07; 0.61)	0.04* (0.01; 0.18)	20.87 (<0.001)
Taking an antidepressant	0.11* (0.02; 0.63)	1.91 (0.73; 5.02)	16.14* (2.86; 91.14)	12.47 (0.002)
Taking a nonopioid pain medication	3.47* (1.16; 10.39)	5.83* (2.54; 13.38)	1.68 (0.56; 5.03)	19.51 (<0.001)
Taking an opioid pain medication	2.09 (0.24; 18.47)	21.37* (4.91; 93.05)	10.22* (1.50; 69.66)	27.81 (0.000)

[†] Mild chronic pain group compared to the no chronic pain group.
[‡] Moderate+ chronic pain group compared to the no chronic pain group.
[§] Moderate+ chronic pain group compared to the mild chronic pain group.
*$P < 0.05$.

between chronic pain and employment status was no longer statistically significant when we controlled for other variables including depression.

The overall rate of chronic pain that we found is similar to rates of pain (although not necessarily chronic pain) reported in the existing HAART-era literature. In the modern treatment era, reported rates of pain in the past week have ranged from 34% to 48% of ambulatory HIV clinic patients in the United States [14,50,51]. The two studies that document the percentage of participants with current pain who had chronic pain varied widely in estimates: in a study of homeless individuals with current pain, 90% with current pain had chronic pain [16], whereas in a small study of consecutive HIV clinic patients with current pain, only 27% reported that the pain was chronic [50]. It would be useful to conduct research to document the rate of chronic pain in in a more general sample of HIV-infected individuals.

We note limitations of this study. First, it is cross-sectional in nature, and therefore, it is impossible to disentangle cause and effect between pain and depression. Second, although we looked at particular symptoms (e.g., depression symptoms), we did not determine whether participants met formal diagnostic criteria for Diagnostic and Statistical Manual of Mental Disorders (DSM) disorders such as major depression or substance abuse/dependence, nor did we conduct urine toxicology screens. As evidenced by the fact that dichotomizing the CES-D at a recommended cutpoint resulted in a higher rate of positive screens for depression than what was found using the PHQ-2, there are limitations to the use of self-report questionnaires. We also did not seek to determine whether opioids were being misused. Related, the use of self-report data may contribute to underestimation of rates for certain items such as substance use or prior neurotoxic medication use. Chronic pain was assessed via self-report to a face-valid question that we developed, and not via chart

review or another method. Third, we did not ask about other important substances that may be associated with chronic pain: marijuana, benzodiazepines, or nonmedical use of opioids. We also do not have data on HIV viral load or Hepatitis C status. Finally, we note that there were slight differences in procedures between the three sites.

In sum, we found a robust association between depression symptom severity and chronic pain in HIV-infected patients, with clear differences between a group with moderate-severe chronic pain and no chronic pain. This association is consistent with that found in non-HIV populations, although the burden may be greater in HIV-infected individuals due to high baseline levels of depression and chronic pain. Finally, we documented that moderate-severe chronic pain clearly persists despite the fact that many people receive treatment with opioids and antidepressants. Thus, there is a clear need to better address the needs of this moderate-severe chronic pain group. In addition to improving quality of life and depressive symptoms, better treatment of pain may improve HAART adherence [4], which has implications for survival and HIV transmission. Although it is certainly not a panacea, greater (or any) access to nonmedication treatments such as CBT specifically targeted towards chronic pain as well as increasing medication adherence may reduce disability, depression, and the escalating use of opioid medication in this population. Across the 3 clinics and 238 people, we surveyed, no one reported receiving CBT for pain. Given the chronicity of the pain experienced, CBT and other nonmedication treatments shown to be efficacious for pain should be more available to HIV-infected patients.

Acknowledgment

We are grateful to Allison Borges, Meagan Durson, Michelle Rapoza, and Brittany Rizzo for their help in collecting these data.

References

1 Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: A World Health Organization study in primary care. JAMA 1998;280(2):147–51. PubMed PMID: 9669787.

2 Merlin JS, Zinski A, Norton WE, et al. A conceptual framework for understanding chronic pain in patients with HIV. Pain Pract 2014;14(3):207–16. PubMed PMID: 23551857.

3 Stavros K, Simpson DM. Understanding the etiology and management of HIV-associated peripheral neuropathy. Curr HIV/AIDS Rep 2014;11(3):195–201. PubMed PMID: 24969360.

4 Berg KM, Cooperman NA, Newville H, Arnsten JH. Self-efficacy and depression as mediators of the relationship between pain and antiretroviral adherence. AIDS Care 2009;21(2):244–8. PubMed PMID: 19229695. Pubmed Central PMCID: 2703292.

5 Surratt HL, Kurtz SP, Levi-Minzi MA, et al. Pain treatment and antiretroviral medication adherence among vulnerable HIV-positive patients. AIDS Patient Care STDs 2014;29(4):186–92. PubMed PMID: 24984142.

6 Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. J Gen Intern Med 2007;22(10):1453–8. PubMed PMID: 17668269. Pubmed Central PMCID: 2305860.

7 Grotle M, Foster NE, Dunn KM, Croft P. Are prognostic indicators for poor outcome different for acute and chronic low back pain consulters in primary care? Pain 2010;151(3):790–7. PubMed PMID: 20932646. Pubmed Central PMCID: 3398128.

8 Langley PC. The societal burden of pain in Germany: Health-related quality-of-life, health status and direct medical costs. J Med Econ 2012;15: 1201–15. PubMed PMID: 22835007.

9 Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur J Pain 2006;10(4):287–333. PubMed PMID: 16095934. eng.

10 Currie SR, Wang J. Chronic back pain and major depression in the general Canadian population. Pain 2004;107(1–2):54–60. PubMed PMID: 14715389. eng.

11 Licciardone JC, Gatchel RJ, Kearns CM, Minotti DE. Depression, somatization, and somatic dysfunction in patients with nonspecific chronic low back pain: Results from the osteopathic trial. J Am Osteopath Assoc 2012;112(12):783–91. PubMed PMID: 23212429.

12 Uebelacker LA, Weisberg RB, Strong DR, Smith M, Miller IW. Time-invariant and time-varying predictors of depression symptoms in primary care patients. Prim Care Companion J Clin Psychiatry. 2009;11: 322–9. PubMed PMID: 20098524. eng.

13 Aouizerat BE, Miaskowski CA, Gay C, et al. Risk factors and symptoms associated with pain in HIV-infected adults. J Assoc Nurses AIDS Care 2010; 21(2):125–33. PubMed PMID: 20116299. Pubmed Central PMCID: 2832225.

14 Merlin JS, Cen L, Praestgaard A, et al. Pain and physical and psychological symptoms in ambulatory HIV patients in the current treatment era. J Pain Symptom Manage 2012;43(3):638–45. PubMed PMID: 22115794. Pubmed Central PMCID: 3786171.

15 de Boer IM, Prins JM, Sprangers MA, Smit C, Nieuwkerk PT. Self-reported symptoms among HIV-infected patients on highly active antiretroviral therapy in the ATHENA cohort in The Netherlands. HIV Clin Trials. 2011;12(3):161–70. PubMed PMID: 21684856.

16 Miaskowski C, Penko JM, Guzman D, et al. Occurrence and characteristics of chronic pain in a community-based cohort of indigent adults living with HIV infection. J Pain 2011;12(9):1004–16. PubMed PMID: 21684218. Pubmed Central PMCID: 3164738.

17 Tsao JC, Stein JA, Ostrow D, Stall RD, Plankey MW. The mediating role of pain in substance use and depressive symptoms among Multicenter AIDS Cohort Study (MACS) participants. Pain 2011; 152(12):2757–64. PubMed PMID: 21962911. Pubmed Central PMCID: 3215839.

18 Ilgen MA, Perron B, Czyz EK, McCammon RJ, Trafton J. The timing of onset of pain and substance use disorders. Am J Addict 2010;19(5):409–15. PubMed PMID: 20716303.

19 Pence BW, Miller WC, Whetten K, Eron JJ, Gaynes BN. Prevalence of DSM-IV-defined mood, anxiety, and substance use disorders in an HIV clinic in the Southeastern United States. J Acquir Immune Defic Syndr 2006;42(3):298–306. PubMed PMID: 16639343.

20 Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113(1–2):9–19. PubMed PMID: 15621359. eng.

21 Dworkin RH, Turk DC, Peirce-Sandner S, et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. Pain 2012;153(6):1148–58. PubMed PMID: 22494920.

22 Cleeland CS, Ryan KM. Pain assessment: Global use of the brief pain inventory. Ann Acad Med Singapore 1994;23(2):129–38. PubMed PMID: 8080219. Epub 1994/03/01. eng.

23 Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 1994;10(2):77–84. PubMed PMID: 8037935. eng.

24 Kroenke K, Spitzer RL, Williams JB. The patient health questionnaire-2: Validity of a two-item depression screener. Med Care 2003;41(11):1284–92. PubMed PMID: 14583691.

25 National Institute on Alcohol Abuse and Alcoholism. National Institute of Alcohol Abuse and Alcoholism Council approves definition of binge drinking. NIAAA Newsletter. Bethesda, MA: Office of Research Translation and Communications, NIAAA, NIH, DHHS, Winter 2004.

26 Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. Primary care validation of a single-question alcohol screening test. J Gen Intern Med 2009;24(7): 783–8. PubMed PMID: 19247718. Pubmed Central PMCID: 2695521.

27 O'Farrell TJ, Fals-Stewart W, Murphy M. Concurrent validity of a brief self-report drug use frequency measure. Addict Behav 2003;28(2):327–37. PubMed PMID: 12573682.

28 Landmark T, Romundstad P, Dale O, Borchgrevink PC, Kaasa S. Estimating the prevalence of chronic pain: Validation of recall against longitudinal reporting (the HUNT pain study). Pain 2012;153(7):1368–73. PubMed PMID: 22575226.

29 Merlin JS, Walcott MM, Herbey I, et al. Qualitative investigation of a brief chronic pain screening tool in HIV-infected patients. AIDS Patient Care STDs 2014;28(4):176–82. PubMed PMID: 24621145. Pubmed Central PMCID: 3985507.

30 Banks SM, Kerns RD. Explaining high rates of depression in chronic pain: A diathesis-stress framework. Psychol Bull 1996;119:95–110.

31 Currie SR, Wang J. More data on major depression as an antecedent risk factor for first onset of chronic back pain. Psychol Med 2005;35(9):1275–82. PubMed PMID: 16168150. eng.

32 Melloh M, Elfering A, Egli Presland C, et al. Predicting the transition from acute to persistent low back pain. Occup Med 2011;61(2):127–31. PubMed PMID: 21199861.

33 Harkapaa K, Jarvikoski A, Mellin G, Hurri H, Luoma J. Health locus of control beliefs and psychological distress as predictors for treatment outcome in low-back pain patients: Results of a 3-month follow-up of a controlled intervention study. Pain 1991;46(1): 35–41. PubMed PMID: 1832753. eng.

34 Karp JF, Scott J, Houck P, et al. Pain predicts longer time to remission during treatment of recurrent depression. J Clin Psychiatry 2005;66(5):591–7. PubMed PMID: 15889945. eng.

35 Ohayon MM. Specific characteristics of the pain/depression association in the general population. J Clin Psychiatry 2004; 65(suppl 12):5–9. PubMed PMID: 15315471. eng.

36 Tang NK, Crane C. Suicidality in chronic pain: A review of the prevalence, risk factors and psychological links. Psychol Med 2006;36(5):575–86. PubMed PMID: 16420727. eng.

37 Meeks TW, Dunn LB, Kim DS, et al. Chronic pain and depression among geriatric psychiatry inpatients. Int J Geriatr Psychiatry 2008;23:637–42. PubMed PMID: 18041102. Eng.

38 Gameroff MJ, Olfson M. Major depressive disorder, somatic pain, and health care costs in an urban primary care practice. J Clin Psychiatry 2006;67(8): 1232–9. PubMed PMID: 16965201. eng.

39 Uthman OA, Magidson JF, Safren SA, Nachega JB. Depression and adherence to antiretroviral therapy in low-, middle- and high-income countries: A systematic review and meta-analysis. Curr HIV/AIDS Rep 2014;11(3):291–307. PubMed PMID: 25038748. Pubmed Central PMCID: 4359613.

40 Pratt LA, Brody DJ, Gu Q. Antidepressant Use in Persons Aged 12 and Over: United States, 2005-2008. NCHS Data Brief, No 76. Hyattsville, MD: National Center for Health Statistics; 2011.

41 Mercier A, Auger-Aubin I, Lebeau JP, et al. Evidence of prescription of antidepressants for non-psychiatric conditions in primary care: An analysis of guidelines and systematic reviews. BMC Fam Pract 2013;14:55. PubMed PMID: 23641784. Pubme d Central PMCID: 3648410.

42 Edelman EJ, Gordon K, Becker WC, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. J Gen Intern Med 2013;28(1):82–90. PubMed PMID: 22895747. Pubmed Central PMCID: 3539026.

43 Silverberg MJ, Ray GT, Saunders K, et al. Prescription long-term opioid use in HIV-infected patients. Clin J Pain 2012;28(1):39–46. PubMed PMID: 21677568. Pubmed Central PMCID: 3175344.

44 Wasserman RA, Brummett CM, Goesling J, Tsodikov A, Hassett AL. Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. Reg Anesth Pain Med 2014;39(1):13−7. PubMed PMID: 24310048. Pubmed Central PMCID: 3960717.

45 Onen NF, Barrette EP, Shacham E, et al. A review of opioid prescribing practices and associations with repeat opioid prescriptions in a contemporary outpatient HIV clinic. Pain Pract 2012;12(6):440–8. PubMed PMID: 22103269. Pubmed Central PMCID: 3943214.

46 Paulozzi LJ. Prescription drug overdoses: A review. J Saf Res 2012;43(4):283–9. PubMed PMID: 23127678.

47 Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. Pain Med 2008;9(4):444–59. PubMed PMID: 18489635.

48 Kerns RD, Sellinger J, Goodin BR. Psychological treatment of chronic pain. Annu Rev Clin Psychol 2011;7:411–34. PubMed PMID: 21128783.

49 Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT: The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Care, 2nd edition. Geneva, Switzerland: World Health Organization; 2001.

50 Cervia LD, McGowan JP, Weseley AJ. Clinical and demographic variables related to pain in HIV-infected individuals treated with effective, combination antiretroviral therapy (cART). Pain Med 2010; 11(4):498–503. PubMed PMID: 20210870.

51 Merlin JS, Westfall AO, Raper JL, et al. Pain, mood, and substance abuse in HIV: Implications for clinic visit utilization, antiretroviral therapy adherence, and virologic failure. J Acquir Immune Defic Syndr 2012; 61:164–1. Oct 70. PubMed PMID: 22766967. Pubmed Central PMCID: 3459261.