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Pain and Physical and Psychological Symptoms in Ambulatory HIV Patients in the Current Treatment Era

Jessica S. Merlin, MD, MBA, **Liyi Cen, MS**, **Amy Praestgaard, MS**, **Michelle Turner, MS**, **Aura Obando, MD**, **Craig Alpert, MD**, **Sophie Woolston, MD**, **David Casarett, MD, MA**, **Jay Kostman, MD**, **Robert Gross, MD, MSCE**[*], and **Ian Frank, MD**[*]
Division of Infectious Diseases (J.S.M., M.T., A.O., C.A., S.W., J.K., R.G., I.F.), Center for Clinical Epidemiology and Biostatistics (L.C., A.P., R.G.), and Division of Geriatric Medicine (D.C.), Hospital of the University of Pennsylvania and Penn-Presbyterian Medical Center, Philadelphia, Pennsylvania

Abstract

Context—HIV infection has become a manageable chronic disease. There are few studies of pain and symptoms in the current treatment era.

Objectives—The primary objective was to determine the prevalence of and risk factors for pain and physical and psychological symptoms in a population of ambulatory HIV patients.

Methods—We performed a cross-sectional study using the Brief Pain Inventory and the Memorial Symptom Assessment Scale.

Results—We evaluated 156 individuals with a median age of 47.5 years (range 21–71), median time since HIV diagnosis of 11 years (range <1–25), and median CD4+ cell count of 502 cells/mm^3 (interquartile range [IQR] 308–683). The majority (125, 80.6%) had an undetectable viral load. Seventy-six (48.7%) reported pain, of whom 39 (51.3%) had moderate to severe pain, and 43 (57.3%) had pain that caused moderate to severe interference with their lives. The median number of symptoms was eight (IQR 5–14.5) of 32 queried. In multivariable analyses, patients with psychiatric illness were 39.8% more likely to have pain (P<0.001). Psychiatric illness was associated with 0.7 and 1.2 point higher MSAS subscale scores, and intravenous (IV) drug use was associated with 0.4 and 0.5 higher subscale scores (out of four).

Conclusion—Pain and other physical and psychological symptoms were common among ambulatory HIV patients. Pain and symptoms were strongly associated with psychiatric illness and IV drug use. Future investigation should evaluate interventions that include psychiatric and substance abuse components for HIV patients with pain.

Keywords

HIV; pain; symptoms

Address correspondence to: Jessica S. Merlin, MD, MBA, Brookdale Department of Geriatrics and Palliative Medicine, Mt. Sinai School of Medicine, 1 Gustave L. Levy Place, Box 1070, New York, NY 10029, USA, jessicasarahmerlin@gmail.com.
[*]These authors contributed equally to this manuscript.

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Introduction

Before combination antiretroviral therapy (ART), pain and physical and psychological symptoms in patients with HIV were common [1–7], often missed by providers [3, 8], and undertreated when found [9].

More effective ART has resulted in fewer opportunistic infections, and ART regimens with fewer side effects are now standard initial therapy [10]. Also, current recommendations are to initiate therapy at CD4+ cell counts of 500 cells/mm3, and perhaps even higher [11]. As a result, HIV has become a chronic disease, with a near normal life expectancy [12]. Yet, HIV patients face complications resulting from effects of therapy or disease, including cardiometabolic abnormalities [13], frailty [14], neurocognitive impairment [15, 16], and increased risk of malignancies [17–19]. At this new stage in the HIV epidemic, it is important to investigate whether pain and symptoms have changed along with changes in the trajectory of HIV disease.

The aims of this study were to determine the prevalence and severity of pain and other symptoms experienced in an ambulatory population of HIV patients, to investigate risk factors that may be related to pain and symptoms in this population, and to determine whether patients' pain and symptoms were recognized and treated by providers.

Methods

Study Population

Patients were recruited from the University of Pennsylvania's Center for AIDS Research (CFAR) Clinical Core Cohort. The CFAR cohort includes 2981 patients. They were seen by CFAR staff every six months for five years, and then annually for five years, at which time laboratory, demographic, and other survey-based data were collected.

For our study, patients were excluded if they had neurologic or cognitive impairments rendering them incapable of completing the survey or providing informed consent. Between October 2009 and January 2010, eligible patients were approached after their clinic visits and interviewed by study staff not responsible for their clinical care. Patients who were eligible but did not stay for the interview, such as patients not referred by their provider or patients who declined to be interviewed, were not consented for the study. No data from this group are available. However, data from the overall CFAR cohort were gathered for the purposes of comparison to our study group.

The study was approved by the University of Pennsylvania Health System Institutional Review Board, and all patients provided written informed consent.

Measures

We assessed pain using the Brief Pain Inventory-Short Form (BPI), a validated tool that has been used to assess cancer and non-cancer pain, including that from HIV [7, 20]. The BPI asks patients whether they have had pain other than "everyday" kinds of pain during the last day. Patients with pain were asked to rate their pain on a scale of 0 to 10, at its worst, least, average, and right now. Patients also reported the medications they have received for pain, and relief provided on a scale of 0% to 100%. Study staff categorized medications into opioids, nonsteroidal anti-inflammatories, acetaminophen, and medications for neuropathic pain.

We assessed other physical and psychological symptoms using the Memorial Symptom Assessment Scale Short Form (MSAS), which has been used in patients with and without cancer, including those with HIV [21, 22]. The MSAS asks patients to report whether they have had any of 26 physical symptoms and 6 psychological symptoms over the past week. For each symptom, patients were asked either about distress (0=symptom not present, 0.8=not at all, 1.6=a little bit, 2.4=somewhat, 3.2=quite a bit, and 4.0=very much) or frequency (0=symptom not present, 1=rarely, 2=occasionally, 3=frequently, and 4=almost constantly). Mean symptom scores were calculated by averaging the distress or frequency associated with each symptom. Based on prior studies, we defined high distress associated with physical symptoms as quite a bit or very much, and high frequency associated with psychological symptoms as frequently or almost constantly [21, 23].

The CFAR database was queried for multiple variables, including each patient's age, most recent CD4+ cell count, viral load, race, tobacco use, psychiatric history (whether a psychologist, therapist, physician, or other clinician has ever told the patient that they were depressed, schizophrenic, or bipolar), and history of intravenous (IV) drug use (whether they have ever injected any drugs). Viral load was further divided into viral load less than 75 copies/mL, the therapeutic goal of ART, and viral load less than 1000 copies/ml. "Blips" up to 1000 copies/mL are unlikely to be clinically significant [24].

A chart review was performed to determine whether pain was mentioned anywhere in the progress from the day of the interview. Trained reviewers used standardized forms to systematically review charts. Reviewers were blinded to the questionnaire results for the patients whose charts they reviewed.

Based on work regarding pain severity clustering using the BPI [25], we categorized pain as mild (1–4), moderate (5–6), or severe (7–10). Patients rated the amount pain interferes with their lives on a scale of 0 to 10, with regard to general activity, mood, walking ability, work, relations with other people, sleep, and enjoyment of life. A patient's overall pain interference was calculated by averaging these domains of interference. The proportions of patients with moderate to severe pain interference were determined using the same cutoffs as above.

Analysis

Dichotomous variables were compared using Chi-squared and Fisher's exact tests, and continuous variables were compared using *t*-tests and the Wilcoxon rank sum test. Tests of trend were assessed with the Cochran-Armitage Test of Trend for dichotomous variables and the Jonckheere-Terpstra test for continuous variables.

Multivariable analyses assessing risk factors for presence of pain were performed using logistic regression. Multivariable analyses assessing risk factors for MSAS subscale scores as continuous variables (0–4) (physical symptom subscale or MSAS-PHYS, psychological symptom subscale or MSAS-PSYCH, total MSAS score or TMSAS, and global distress index or GDI) were performed using linear regression [26]. Risk factors assessed included psychiatric illness, IV drug use history, tobacco use, race, CD4 category, and low viral load (viral load < 1000 copies/ml). In all models, risk factors associated with the primary outcome variable with a $P<0.05$ were assessed as primary variables. Potential confounders included all of the baseline characteristics and were retained in the models if they changed the association of the primary variable and the outcome by more than 15%.

Because MSAS subscales are calculated for an individual patient by adding the distress associated with distress-related symptoms to the frequency associated with frequency-

related symptoms [26], we considered distress and frequency to be measures of the symptom's severity and reported them together.

Data were analyzed using SAS v 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

We enrolled 156 patients from three sites. Patients were mostly male, middle-aged, African American, knew of their diagnosis of HIV infection for several years, and had high CD4+ cell counts and undetectable viral loads. Many patients had a history of psychiatric illness or IV drug use. In comparison to the full CFAR cohort, patients in this study were less likely to have a history of injection drug use or psychiatric illness, and more likely to have a history of tobacco use, but otherwise were very similar (Table 1).

Seventy-six (48.7%) reported having pain other than "everyday aches and pains" in the past day. Median pain was 6/10 "on average" (interquartile range [IQR] 3–7). Of patients with pain, 39 (51.3%) were in moderate to severe pain during the interview. Overall median pain interference was 4.6 on a scale of 0 to 10 (IQR 4.1–7.0), with 43 (57.3%) patients with pain reporting moderate to severe overall interference.

Patients experienced a median number of eight physical and psychological symptoms during the past week (IQR 5.0–14.5). The most prevalent physical symptoms other than pain were lack of energy and numbness or tingling in the hands and feet (Table 2). These also were the most common "high distress" physical symptoms. A substantial number of patients (61, 39.1%) experienced "high distress" from three or more physical symptoms. More than half the cohort experienced four of the six psychological symptoms (worrying, feeling sad, difficulty sleeping, feeling irritable). Nearly half of all patients (74, 47.7%) experienced "high distress" or "high frequency" from at least one psychological symptom.

Fifty-six (73.7%) of the patients reporting pain took analgesic medications; 32 (42.1%) were prescribed opioids. Patients reported a median of 50% relief of pain after taking medication (IQR 10%-80%). Of the 76 patients who reported pain, pain was documented in 51 (67.0%) of the provider notes on that day. Providers were more likely to document pain of higher severity; mild pain was documented in 14 (50.0%), moderate pain in 16 (76.2%), and severe pain in 21 (80.8%) (P=0.007, Cochran-Armitage test of trend). As pain severity increased, there was a trend toward more pain medication use, although it did not reach statistical significance; 18 (64.3%) patients with mild pain took pain medication, as compared to 17 (77.3%) patients with moderate pain and 21 (80.8%) patients with severe pain (P=0.08, Cochran-Armitage test of trend). Patients with severe pain were more likely to take opioids (18/26, 69.2%) than patients with moderate (8, 36.4%) or mild pain (6, 21.4%) (P=0.001, Cochran-Armitage test of trend).

Risk Factors for Pain

Patients with a history of IV drug use who had pain were more likely to have severe (6, 60%) or moderate (4, 40%) pain than patients without a history of IV drug use (P=0.005, Cochran-Armitage test of trend). Also, patients with more psychological symptoms were more likely to report pain. The frequency of pain in patients with one symptom was 31.8%, two symptoms 42.1%, three symptoms 38.9%, four symptoms 58.3%, five symptoms 63.6%, and six symptoms 85.2% (P=0.0016, Cochrane-Armitage test of trend). None of the other factors were associated with pain in univariate analyses. Thirty-seven (71.2%) patients with psychiatric illness had pain, compared to 39 (37.9%) without psychiatric illness (P=0.0002, Chi-square). In multivariable analyses, pain was 39.8% more common in

patients with a history of psychiatric illness ($P<0.001$) and there were no confounders of this association.

Risk Factors for Symptoms

Psychiatric illness was associated with a 0.7 point higher MSAS-PHYS subscale score ($P<0.001$), and IV drug use was associated with a 0.5 higher MSAS-PHYS subscale score ($P<0.0005$). There was no confounding of this association in the multivariable models. Low viral load was associated with higher MSAS-PHYS ($P=0.04$); however, in the multivariable model, the relationship between low viral load and MSAS-PHYS was no longer statistically significant ($P=0.06$), and was associated with a change from 0.32 points on the MSAS-PHYS subscale to 0.27.

Having a diagnosis of a psychiatric illness was associated with a 1.2 point higher MSAS-PSYCH subscale score ($P<0.001$). There was no confounding in multivariable models. Having a diagnosis of a psychiatric illness also was associated with a 0.7 point higher T-MSAS subscale score ($P<0.0001$), and IV drug use was associated with a 0.4 point higher T-MSAS subscale score ($P<0.006$). There was no confounding of these relations.

Psychiatric illness was associated with a 1.0 point higher GDI subscale score ($P<0.0001$), and IV drug use was associated with a 0.5 point higher GDI subscale score ($P<0.02$). No confounding was identified. Low viral load was associated with a higher GDI ($P=0.04$) but the relationship between viral load and GDI was no longer statistically significant when psychiatric illness was included as a confounder ($P=0.07$), and was associated with a change from 0.4 points on the GDI subscale to 0.3.

Discussion

There have been several studies of pain and symptoms in the current HIV treatment era. These studies established that pain and symptoms are still common [27–31], and suggested weak relationships between pain and symptoms and sleep disturbances, fatigue, and ever having AIDS. The relationship between pain and symptoms and CD4 count and race is less clear [21, 32, 33].

Our results confirm that pain and symptoms are still prevalent and cause a significant amount of distress and interference. We found that although providers documented moderate to severe pain, patients reported only modest relief from pain medications. Studies from the early treatment era suggest that providers often underestimate pain in patients with HIV [3]. Barriers to pain management, as identified in prior studies, are patient-related, such as patients' fear of addiction and medication side effects [34], and provider-related, such as providers' fear of addiction, lack of knowledge about pain management, and lack of access to pain management experts [35]. Other potential barriers to adequate pain management include inappropriately low doses or frequency of prescribed opioids, inadequate adherence, or the pain being psychological and, therefore, unresponsive to opioid therapy. Regardless, this study suggests that despite attempts at pharmacologic management, pain in this group of ambulatory HIV patients is not under good control. This is a serious issue that merits attention.

This is the first study in the current treatment era to suggest a strong relationship between pain and symptoms and psychiatric illness and IV drug use. In this study, patients with psychiatric illness were 40% more likely to have pain. Both psychiatric illness and IV drug use were associated with higher MSAS-PHYS, TMSAS, and GDI subscales, ranging from 0.4–1.2. Although there is no consensus about what constitutes a clinically significant

difference in MSAS subscale scores, it is striking that psychiatric illness and IV drug use are consistently related to these measures of symptom burden.

Psychiatric illness and IV drug use are common comorbidities in patients with HIV [36]. Some studies from before the current treatment era suggest that HIV infected patients with a history of IV drug use have a higher prevalence of pain and increased symptom-related distress [7, 20, 37]. The relationship of pain and symptoms to psychiatric history and IV drug use shown in this study also is consistent with data from early in the current treatment era [36].

Our study has a few important limitations. It was done at a single academic medical center, which may limit its generalizability. It is possible that patients who had pain and symptoms were more likely to participate in this study, causing overestimates of pain and symptoms. Although the BPI does ask about location of pain, this is a difficult question to interpret, so we were unable to include these results. Knowing the location of pain, and whether more than one site of pain was present, would have given us more insight into the patient's pain experience.

Numerous studies have shown that management of symptoms of chronic HIV disease, such as pain, fatigue, and insomnia, results in improved quality of life [7, 38–41]. There is also evidence that symptom management improves virologic suppression and adherence [42, 43, 22]. Therefore, understanding risk factors for pain and symptoms is an important part of improving outcomes in patients with HIV.

We propose that HIV providers systematically screen for pain and symptoms, just as they routinely screen for other prevalent, treatable comorbid conditions. Given the association between pain and symptoms and IV drug use and psychiatric illness in this study, these comorbidities must be addressed when treating HIV-infected patients with pain. Future research should focus on interventions that combine pain management with psychiatric and substance abuse treatment.

As urgent mortality issues in the management of chronic HIV disease wane, we believe that the diagnosis and treatment of HIV patients' pain and symptoms, with close attention to psychiatric and IV drug use comorbidities, should be a part of routine HIV care.

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Table 1

Characteristics of Participants and Target Population

Characteristics	Study Sample, *n*=156	CFAR Cohort, *n*=2981
Median age (range)	47.5 (21–71)	50 (19–95)
Female gender (%)	43 (27.7%)	682 (22.9%)
Median years since diagnosis (range)	11 (0–25)	14 (0–28)
Median CD4 count (range)	497.5 (7.0–1512.0)	438.5 (0–2058.0)
CD4+ cell count category (%), cells/mm^3		
<50	7 (4.5%)	187 (6.5%)
50–199	12 (7.7%)	394 (13.7%)
200–499	56 (35.9%)	1131 (39.3%)
≥500	81 (51.9%)	1114 (38.7%)
VL < 75 copies/ml (%)	125 (80.6%)	1313 (44.0%)
VL < 1000 copies/ml (%)	136 (87.7%)	1629 (54.6%)
African-American (%)	90 (58.4%)	1798 (60.3%)
History of Intravenous Drug Use (%)	15 (9.9%)	622 (21.5%)[a]
History of Psychiatric Illness (%)	52 (33.5%)	715 (48.2%)[b]
History of Tobacco Use (%)	104 (67.5%)	1282 (45.6%)[c]

[a] *n*=2891 because of missing data.

[b] *n*=1484 because of missing data; questions regarding psychiatric illness were introduced in a later version of the CFAR study questionnaire.

[c] *n*=2809 because of missing data; questions regarding tobacco use were introduced into a later version of the CFAR study questionnaire.

Table 2

Memorial Symptom Assessment Scale Results by Symptom

Symptom	Prevalence *n* (%)	Mean Symptom Score ± SD	High Distress or f Frequency *n* (%)[a]
Physical Symptoms			
Pain	96 (61.9)	1.5 ± 1.5	48 (31.0)
Lack of energy	89 (57.1)	1.2 ± 1.4	30 (19.2)
Numbness/tingling in hands and feet	72 (46.2)	1.0 ±1.4	29 (18.6)
Feeling drowsy	58 (37.2)	0.7 ± 1.2	17 (10.9)
Sweats	53 (34.0)	0.6 ± 1.2	15 (9.6)
Cough	52 (33.3)	0.6 ± 1.1	16 (10.3)
Dry mouth	51 (32.7)	0.6 ± 1.1	14 (9.0)
Diarrhea	49 (31.4)	0.7 ± 1.2	21 (13.5)
“I don’t look like myself”	42 (27.1)	0.6 ± 1.3	21 (13.5)
Feeling bloated	39 (25.2)	0.5 ± 1.1	15 (9.7)
Shortness of breath	39 (25.0)	0.5 ± 1.1	14 (9.0)
Itching	37 (23.7)	0.5 ± 1.2	16 (10.3)
Lack of appetite	36 (23.1)	0.4 ± 1.0	10 (6.4)
Problems with sexual interest or activity	35 (22.6)	0.6 ± 1.2	20 (12.9)
Nausea	35 (22.4)	0.4 ± 0.9	11 (7.1)
Problems with urination	35 (22.4)	0.5 ± 1.1	15 (9.6)
Changes in skin	32 (20.5)	0.4 ± 1.1	13 (8.3)
Weight loss	28 (17.9)	0.3 ± 0.9	8 (5.1)
Dizziness	27 (17.3)	0.3 ± 0.8	8 (5.1)
Constipation	22 (14.1)	0.3 ± 0.8	5 (3.2)
Change in the way food tastes	19 (12.2)	0.2 ± 0.8	6 (3.8)
Hair loss	19 (12.2)	0.2 ± 0.8	6 (3.8)
Swelling of arms or legs	15 (9.6)	0.2 ± 0.7	6 (3.8)
Difficulty swallowing	13 (8.3)	0.1 ± 0.6	4 (2.6)
Vomiting	13 (8.3)	0.1 ± 0.5	4 (2.6)
Mouth Sores	12 (7.7)	0.1 ± 0.6	4 (2.6)
Psychological Symptoms			
Worrying	98 (62.8)	1.5 ± 1.4	45 (28.8)
Feeling sad	86 (55.1)	1.1 ± 1.3	27 (17.3)
Difficulty sleeping	86 (55.1)	1.4 ± 1.5	45 (28.8)
Feeling irritable	82 (52.6)	1.1 ± 1.2	22 (14.1)
Feeling nervous	67 (42.9)	1.0 ± 1.3	21 (13.5)
Difficulty concentrating	63 (40.4)	0.8 ±1.3	20 (12.8)

[a]Frequency reported for worrying, feeling sad, feeling irritable, and feeling nervous; distress reported for the remainder.