

REHABILITATION SECTION

Brief Research Report

Pain is Independently Associated with Impaired Physical Function in HIV-Infected Patients

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Abstract

Introduction. Human immunodeficiency virus (HIV)-infected patients in the current treatment era can achieve normal life expectancies but experience a high degree of medical and psychiatric comorbidity. Impaired physical function and pain, often in the context of mood disorders and substance abuse, are common in HIV-infected patients. The objective of this study was to investigate the relationship of pain, a modifiable condition, to functional impairment in HIV-infected patients, independent of mood disorders and substance abuse.

Methods. Participants in a prospective cohort of HIV-infected patients at the University of Alabama at Birmingham were included. Patient-reported outcome measures were used to cross-sectionally assess pain and physical function (EuroQOL), mood disorders (PHQ), and substance abuse (ASSIST). Univariate and multivariable models were built with pain as the principal independent variable of interest and three domains of physical function (mobility, self-care, and usual activities) as outcomes. Covariates included mood, substance abuse, age, race, sex, insurance status, HIV transmission risk factor, and CD4+ T-cell count.

Results. Among 1,903 participants, 693 (37%) reported pain; 509 (27%) had a mood disorder; and 157 (8.4%) reported current substance abuse. In multivariable models, pain was independently associated with increased odds of impairment in all three domains of physical function investigated—mobility (aOR 10.5, 95% CI 7.6–14.6), self-care (aOR 4.1, 95% CI 2.2–7.4), and usual activities (aOR 5.4, 95% CI 4.0–7.4).

Discussion. Pain was associated with substantially increased odds of impairment in physical function. Pain should be an important consideration in HIV primary care. Interventions to address pain and impaired physical function should be investigated.

Key Words. HIV; Pain; Physical Function; Mental Health; Substance Abuse

Introduction

In the current human immunodeficiency virus (HIV) treatment era, HIV-infected patients' life expectancy approaches normal [1]. However, contemporary HIV-infected patients experience a high degree of medical and psychiatric comorbidity [2]. In this context, health-related quality of life (HR-QOL) outcomes have become an increasingly important area of investigation [3]. HR-QOL is defined by the Centers for Disease Control and Prevention as "aspects of overall quality of life that can be clearly shown to affect health—either physical or mental" (<http://www.cdc.gov/hrqol/>). Going beyond traditional endpoints of morbidity and mortality, HR-QOL can be used to understand the nature of disability in the setting of chronic illness [4].

Physical function is an important component of HR-QOL in HIV [5], and is an active area of investigation in HIV-infected patients. Impaired physical function in HIV-infected patients is common, and is associated with comorbidities such as heart failure, pulmonary disease, and depression, more so than CD4+ T-cell count [6,7]. This suggests that physical function may be influenced more by non-HIV-specific factors than markers of HIV disease progression. Furthermore, multiple studies in HIV-infected patients link functional impairment to depression, substance use/abuse, adherence to antiretroviral therapy, emergency department visits, hospital admissions, and mortality [3,8–11]. Therefore, it is imperative to identify modifiable factors that may inform interventions to maximize functionality and reduce morbidity and mortality in HIV-infected patients.

There is a large body of evidence in the general population linking chronic pain with HR-QOL, including impaired physical function [12]. However, the relationship between chronic pain and physical function has not been explored in patients with HIV. The relationship of chronic pain to physical function in HIV merits investigation, because chronic pain is a common comorbidity in HIV-infected patients. Prevalence estimates of pain range from 39–85% [13–20], chronic pain substantially higher than values from large epidemiologic studies of the general population [21–24]. In addition, mood and substance abuse disorders are often comorbid with chronic pain in HIV [18,19] and the general population [25–28], complicate pain treatment [29], and can be associated with worse pain prognosis [30,31]. For this reason, we sought to better understand the relationship between pain and physical function in HIV-infected patients, controlling for mood and substance abuse. We hypothesized that pain would be independently associated with impaired physical function.

Methods

Study Participants

The University of Alabama at Birmingham (UAB) 1917 Clinic Cohort is an HIV cohort that includes nearly 2,000 participants actively engaged in primary HIV medical care

(<http://www.uab1917cliniccohort.org>) [32]. Historically, over 85% of cohort participants have provided consent and participate in electronic Patient Reported Outcome (PRO) questionnaires [32]. PROs include standardized, well-validated instruments that span a variety of topics, including health-related quality of life, psychiatric symptoms, substance abuse, and health behaviors such as antiretroviral adherence [32–34]. The Cohort and this study were approved by the UAB Institutional Review Board.

This was a cross-sectional study of electronic medical record and PRO data captured between April 2008 and June 2011. Inclusion criteria for this study included HIV infection, speaking English, and age ≥ 19 years at the date of the PRO. For participants in whom follow-up data were available, presence of pain at any follow-up visit during the study period was assessed as a crude measure of the pain's chronicity.

Functional Measures

The EuroQOL includes three measures of physical function, each of which was considered separately as an outcome variable: 1) *Mobility* evaluates the participant's ability to "walk about"; 2) *Self-care* evaluates the participant's ability to wash or dress himself; and 3) *Usual activities* evaluates the participant's ability to work, study, or perform housework, family, or leisure activities [35]. Response options are: no problems, some problems, or unable to perform the domain of physical function. As very few patients reported being completely unable to perform each domain of physical function, being unable to perform and having some problems with performance were merged into one variable. Combining these response options into "no problems" and "problems" is a common way to analyze EuroQOL data (http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-3L.pdf).

Independent Variables and Covariates

Pain was the principal independent variable of interest. Pain was measured using the EuroQOL. The EuroQOL includes a single question about pain "today," and response options are no discomfort, moderate discomfort, or extreme discomfort. As with functional measures, participants' responses to the EuroQOL pain question were dichotomized as moderate/extreme discomfort vs no pain/discomfort.

In the general population, up to half of patients with chronic pain also have depression, anxiety, or substance abuse disorders [25,27,28], and pain is often investigated in the context of these comorbid disorders. There is emerging evidence that the link between pain, psychiatric, and substance comorbidities is also strong in HIV-infected patients. Recent data suggest that pain, mood disorders, and substance abuse comorbidities commonly co-occur in patients with HIV [36–41] and impact health outcomes such as adherence and no-show visits [42–46]. Therefore,

mood disorders and substance abuse were also included as covariates. A mood disorder was defined as the presence of either depression, anxiety, or both on the PHQ (<http://www.phqscreeners.com>). Participants with moderate, moderately severe, and severe depressive symptoms (PHQ-9 > 10) were considered to be depressed [47,48]. Participants with anxiety symptoms or panic syndrome on the PHQ were considered to have anxiety [49]. Substance abuse was measured using the ASSIST questionnaire and categorized as current or prior/never [50]. Other covariates were also selected based on their association with study outcomes and clinical relevance. These included age, race, sex, insurance status, HIV transmission risk factor, and CD4+ T-cell count.

Statistical Analyses

The statistical analyses performed in this article followed the same analysis plan as a previously published paper by Merlin et al. [19]. Briefly, separate univariate and multivariable logistic regression models (which included all covariates listed) were built for each outcome. All variables were included in the multivariable model.

Given the close relationship between pain, mood, and substance abuse, we evaluated the two and three-way interactions between pain, mood, and substance abuse.

Results

Study participants had a median age of 44 years, and 430 (23%) were female. The majority were uninsured (619, 33%) or had public insurance (570, 30%). Most had CD4+ T-lymphocyte counts > 350 cells/mL (1,198, 63%) and were virologically suppressed (1,084, 58%; see Table 1). Pain was common, occurring in 693 (37%) participants. Mood disorders occurred in 509 (27%), and substance abuse occurred in 157 (8%). Pain, mood disorders, and substance abuse sometimes co-occurred but not always: 278 (15%) had pain and a mood disorder, 35 (2%) had pain and substance abuse, and 42 (2%) had all three. However, many participants reported pain alone (328, 18%). The prevalence of impaired physical function was 19% for mobility, 5% for self-care, and 20% for performing usual activities. In addition, of the 444 patients who initially reported moderate or extreme pain and who had a pain measurement at a subsequent visit, 326 (73%) again reported moderate or extreme pain, suggesting that the majority of pain was chronic. There was no evidence of interaction between pain, mood disorders, or substance abuse in any of our models (*P* for interaction > 0.05). Because the interaction term was not statistically significant, it was not included in the regression models.

Detailed results of the adjusted and unadjusted models, with odds ratios (ORs) and 95% confidence intervals (CIs), are presented in Tables 2–4. Pain was independently associated with impairment in all three domains of physical function in both adjusted and unadjusted models. OR estimates in the adjusted models were slightly lower than

Table 1 Characteristics of 1903 HIV-infected patients seen for outpatient medical care at the UAB HIV Clinic, April 2008–June 2011*

Characteristic	Sample (N = 1,903)
Age, years	43.6 (35.6–50.1)
Non-white race	998 (52.8%)
Female sex	430 (22.6%)
Health insurance	
Uninsured	619 (32.7%)
Public	570 (30.1%)
Private	704 (37.2%)
Baseline CD4+ T-lymphocyte count (cells/mL)	
Overall	445.0 (263.0–644.0)
<200 cells/mL	342 (18.1%)
200–350 cells/mL	350 (18.5%)
>350 cells/mL	1,198 (63.4%)
HIV viral load < 200 copies/mL	1,084 (57.7%)
HIV transmission risk factor	
Injection drug use	179 (9.4%)
Men who have sex with men	1,003 (52.7%)
Other/unknown	62 (3.3%)
Heterosexual	659 (34.6%)
Pain	693 (36.9%)
Mood	509 (27.0%)
Substance abuse	157 (8.4%)
Pain-mood-substance categories	
Only pain	328 (17.7%)
Only mood	147 (7.9%)
Only substance abuse	48 (2.6%)
Pain and mood	278 (15.0%)
Pain and substance	35 (1.9%)
Mood and substance	27 (1.5%)
Pain, mood, and substance	42 (2.3%)
None	951 (51.2%)
EuroQOL outcomes (some problems/unable)	
Mobility	359 (19.2%)
Self-care	89 (4.8%)
Usual activities	370 (19.7%)

*Data are presented as medians and interquartile ranges or frequencies (column percent). Baseline HIV RNA and CD4+ T-lymphocyte count measurements were the value closest to the date of the initial clinic visit, with a window of –210 to +14 days. Missing data: race/sex 13, insurance status 10, CD4+ T-lymphocyte count 13, HIV viral load 23, pain 27, substance abuse 23, mobility 33, self-care 34, usual activities 25. UAB = University of Alabama at Birmingham.

the unadjusted models across the board. The adjusted OR for pain was highest for impairment in mobility (aOR 10.5 [95% CI 7.6–14.6]), and somewhat lower for self-care (aOR 4.1 [95% CI 2.2–7.4]) and usual activities (aOR 5.4 [95% CI 4.0–7.4]).

Mood was also consistently associated with impairment in physical function (mobility aOR 2.3 [95% CI 1.7–3.2],

Table 2 Mobility*

Characteristic	% Impaired Mobility [†]	Unadjusted OR (95% CI), <i>P</i> Value	Adjusted OR (95% CI), <i>P</i> Value N = 1,802
Pain			
Yes	42.8%	14.1 (10.4–19.1)	10.5 (7.6–14.6)
No	5.0%	1.0	1.0
Mood			
Yes	36.1%	3.8 (3.0–4.8)	2.3 (1.7–3.2)
No	13.1%	1.0	1.0
Substance			
Yes	24.7%	1.4 (1.0–2.1)	1.1 (0.7–1.7)
No	18.5%	1.0	1.0
CD4+ T cell (cells/mL)			
<200 cells/mL	26.1%	1.7 (1.3–2.2)	1.4 (1.0–2.0)
200–350 cells/mL	18.3%	1.1 (0.8–1.4)	0.9 (0.6–1.4)
>350 cells/mL	17.5%	1.0	1.0
Age (per 10 years)	N/A	1.7 (1.5–1.9)	1.8 (1.6–2.1)
Non-white race	19.2%	1.0 (0.8–1.2)	1.3 (0.9–1.8)
White	19.5%	1.0	1.0
Female	22.1%	1.3 (1.0–1.7)	0.7 (0.4–1.0)
Male	18.3%	1.0	1.0
HIV transmission risk factor			
IVDU	24.0%	1.1 (0.7–1.6)	0.7 (0.4–1.2)
MSM	16.3%	0.7 (0.5–0.9)	0.7 (0.4–1.0)
Other/unknown	19.4%	0.8 (0.4–1.6)	0.8 (0.4–1.9)
Heterosexual	22.4%	1.0	1.0
Health insurance			
None	17.0%	1.3 (1.0–1.8)	1.3 (0.9–2.0)
Public	28.8%	2.6 (2.0–3.5)	1.6 (1.1–2.3)
Private	13.3%	1.0	1.0

* Event = Limited mobility. Bolded results are statistically significant, *P* < 0.05. Adjusted model includes age, race, sex, insurance status, HIV transmission risk factor, and CD4+ T-cell count, mood, and substance abuse.

[†] % impaired mobility is the percentage of participants with the characteristic listed in the row who have impaired mobility (defined as being somewhat or unable to “walk about”).

IVDU = intravenous drug user; MSM = men who had sex with men.

self-care aOR 4.3 [95% CI 2.5–7.3], usual activities aOR 6.6 [95% CI 4.9–8.9], as was age (mobility aOR 1.8 [95% CI 1.6–2.1], self-care aOR 1.6 [95% CI 1.3–2.1], usual activities aOR 1.3 [95% CI 1.1–1.6]). CD4 count less than 200 cells/mL was associated with impairment in two domains of physical function (self-care aOR 2.0 [95% CI 1.1–3.4], usual activities aOR 2.0 [95% CI 1.4–2.8]), as was public insurance (mobility aOR 1.6 [95% CI 1.1–2.3], usual activities aOR 1.4 [95% CI 1.0–2.1]). In the multivariable models, substance abuse was not associated with impairment in any domain of physical function.

Discussion

To our knowledge, this is the first study to investigate the association of pain and physical function in HIV-infected patients. In this study, pain was associated with up to 10 times greater odds of impaired physical function, even after adjusting for other covariates including age, mood,

and substance abuse. Given that physical function is an important component of HR-QOL, and the association between impaired physical function and endpoints such as mortality in HIV-infected patients, our results suggest that pain should be an important primary care consideration in HIV-infected patients.

Our findings are similar to prior studies' findings with respect to physical function. For example, in a study describing functional status in the context of frailty, defined as a syndrome of functional impairment assessed by a combination of self-reported weight loss, fatigue, and clinically observed decreased grip strength and walking ability, impaired physical function occurred in up to 32% of HIV-infected individuals [10]. In our cohort, nearly 20% of participants had impairment in mobility or usual activities. Like our study, prior studies of frailty and other measures of physical function have also found that advanced age is associated with impaired physical function [6,7,51,52].

Table 3 Self-care*

Characteristic	% Impaired Self-Care [†]	Unadjusted OR (95% CI), <i>P</i> Value	Adjusted OR (95% CI), <i>P</i> Value N = 1,802
Pain			
Yes	10.3%	7.8 (4.6–13.4)	4.1 (2.2–7.4)
No	1.5%	1.0	1.0
Mood			
Yes	11.7%	5.7 (3.4–9.0)	4.3 (2.5–7.3)
No	2.3%	1.0	1.0
Substance			
Yes	9.2%	2.3 (1.3–4.2)	1.9 (1.0–3.6)
No	4.3%	1.0	1.0
Age (per 10 years)			
CD4+ T cell (cells/mL)		1.5 (1.2–1.9)	1.6 (1.3–2.1)
<200	8.3%	2.2 (1.3–3.5)	2.0 (1.1–3.4)
200–350	3.4%	0.9 (0.5–1.8)	0.9 (0.4–1.7)
>350	4.0%	1.0	1.0
Non-white race	4.6%	0.9 (0.6–1.5)	1.1 (0.7–1.9)
White	4.9%	1.0	1.0
Female	6.1%	1.4 (0.9–2.3)	0.7 (0.4–1.5)
Male	4.4%	1.0	1.0
HIV transmission risk factor			
IVDU	8.1%	1.5 (0.8–2.9)	1.1 (0.5–2.6)
MSM	3.7%	0.7 (0.4–1.1)	0.7 (0.4–1.5)
Other/unknown	4.9%	0.9 (0.3–3.0)	0.6 (0.1–2.7)
Heterosexual	5.4%	1.0	1.0
Health insurance			
None	3.6%	1.1 (0.6–1.9)	0.8 (0.4–1.6)
Public	7.5%	2.2 (1.3–3.8)	1.2 (0.7–2.2)
Private	3.5%	1.0	1.0

* Event = impaired self-care. Bolded results are statistically significant, $P < 0.05$. Adjusted model includes age, race, sex, insurance status, HIV transmission risk factor, and CD4+ T-cell count, mood, and substance abuse.

[†] % impaired self-care is the percentage of participants with the characteristic listed in the row who have impaired self-care (defined as being somewhat or unable to wash or dress oneself).

IVDU = intravenous drug user; MSM = men who had sex with men.

Although other studies have found a relationship between physical function and traditional non-HIV-associated medical and psychiatric comorbidities, our study is the first to investigate the relationship of physical function and comorbid pain in HIV-infected patients. Our results also suggest that individuals with lower CD4+ T-cell counts, which in the current treatment era represent not only HIV disease severity but CD4 nadir prior to initiation of antiretroviral therapy and degree of immune reconstitution, may be more likely to have functional impairment regardless of pain.

Like other studies before it, this study adds to the growing body of evidence that pain is a common comorbidity in HIV-infected patients in the current treatment era [13–20]. Additionally, by 2015, over half of people living with HIV will be over the age of 50, which is considered the geriatric age cutoff for HIV-infected patients [53]. Current evidence suggests that pain is especially in common in older as compared to younger adults [54]. Therefore, it stands to reason

that over the next 10 years, as the HIV epidemic ages, the burden of pain among HIV-infected patients will likely increase. Pain will therefore be an increasingly important comorbidity to consider in HIV outcomes research.

Despite pain's importance and association with impaired physical function, approaches to managing pain in patients with HIV have not been rigorously studied. There is evidence that opioids in HIV-infected patients are commonly used [55], and may actually be associated with worse pain [56]. One recent study suggests that HIV providers who prescribe opioids, which are commonly used in conjunction with other pharmacologic and non-pharmacologic management approaches for chronic pain, infrequently follow safe-prescribing practices such as routine screening for substance abuse, and have limited confidence in their ability to recognize opioid abuse [57]. We are only aware of one study of a behavioral intervention for chronic pain in HIV-infected patients, which showed only very modest benefit, had serious

Table 4 Usual activities*

Characteristic	% Impaired Usual Activities [†]	Unadjusted OR (95% CI), <i>P</i> Value	Adjusted OR (95% CI), <i>P</i> Value N = 1,811
Pain			
Yes	41.4%	9.6 (7.3–12.6)	5.4 (4.0–7.4)
No	6.9%	1.0	1.0
Mood			
Yes	47.4%	8.6 (6.7–11.0)	6.6 (4.9–8.9)
No	9.5%	1.0	1.0
Substance			
Yes	26.8%	1.6 (1.1–2.3)	1.1 (0.7–1.7)
No	18.6%	1.0	1.0
Age (per 10 years)			
CD4+ T cell (cells/mL)		1.3 (1.1–1.4)	1.3 (1.1–1.6)
<200	30.8%	2.2 (1.6–2.8)	2.0 (1.4–2.8)
200–350	17.7%	1.0 (0.8–1.4)	0.9 (0.6–1.3)
>350	17.2%	1.0	1.0
Non-white race			
White	17.9%	0.8 (0.6–1.0)	0.9 (0.7–1.3)
Female	21.9%	1.0	1.0
Male	22.5%	1.2 (1.0–1.6)	0.7 (0.5–1.1)
HIV transmission risk factor			
IVDU	18.9%	1.0	1.0
MSM	24.6%	1.2 (0.8–1.8)	0.7 (0.4–1.3)
Other/unknown	17.7%	0.8 (0.6–1.0)	0.6 (0.4–0.9)
Heterosexual	19.7%	0.9 (0.5–1.7)	0.6 (0.3–1.4)
Health insurance			
None	21.5%	1.0	1.0
Public	19.9%	1.6 (1.2–2.1)	1.3 (0.9–1.9)
Private	27.4%	2.4 (1.8–3.2)	1.4 (1.0–2.1)
	13.5%	1.0	1.0

* Event = Impairment in usual activities. Bolded results are statistically significant, $P < 0.05$. Adjusted model includes age, race, sex, insurance status, HIV transmission risk factor, and CD4+ T-cell count, mood, and substance abuse.

[†] % impaired usual activities is the percentage of participants with the characteristic listed in the row who have impaired usual activities (defined as being somewhat or unable to work, study, housework, family, or leisure activities).

methodologic limitations (pre-post study), and suffered from poor adherence (median number of sessions attended 4 of 12) [58].

Currently, there are no guidelines by infectious diseases or HIV professional societies to guide care providers on management of pain in HIV-infected patients. The association between pain and physical function found in this study suggests a need for pain-related research and discussions on a national level. Furthermore, interventions that incorporate pain management and address physical function, in addition to co-morbid mood and substance abuse disorders when present, may be important for improving health outcomes in patients living with HIV infection.

We acknowledge that pain can co-occur with mood disorders and substance abuse. In our study, although substance abuse was not associated with impaired physical function, mood disorders were associated with up to six times the odds of impaired physical function. However, in this study, we found that independent of mood, pain alone

was associated with impaired physical function. Further, while some participants had pain in conjunction with a mood disorder or substance abuse, many had pain alone, which suggests that pain itself, separate from these comorbidities, merits separate consideration.

This study has limitations. The EuroQOL questionnaire assessed pain “today,” and did not distinguish between acute and chronic pain. Acute pain, which is a symptom that may be related to recent painful events such as an injury, is different from chronic pain, the clinically important syndrome, which is defined as persistent pain that lasts longer than the period of active tissue injury, usually defined as 3–6 months [29,59–62]. Nevertheless, a majority of subjects (73%) reported pain at two consecutive visits. Future prospective studies should distinguish between acute and chronic pain, and evaluate the impact of chronic pain as a comorbid condition on HIV-related outcomes. In addition, this study does not characterize the type of pain, or explain the reasons behind the association between pain and impaired physical function.

Studies using quantitative and qualitative methods should explore the mechanisms by which this association occurs. One possible unmeasured confounder not addressed by this study is medical comorbidity/multimorbidity, which may independently lead to both chronic pain and impaired physical function. Additional research in HIV and multimorbidity that incorporates pain is needed.

There are also limitations related to the instruments used to assess mood, substance abuse, and physical function. Mood disorders are assessed using a one-time measure of symptoms of depression and anxiety, and substance abuse is assessed using a proxy of current substance use; these measures may overestimate the true prevalence of these comorbidities. This study used a subjective self-assessment of physical function rather than exercise physiology-based testing or clinician observation of patients' physical function.

In conclusion, pain is strongly associated with impairment in physical function. Future research focusing on pain itself as an important comorbid condition in HIV-infected patients, and the effects of pain on health outcomes, is needed.

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