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Health-Related Quality of Life ‘Well-Being’ In HIV Distal Neuropathic Pain Is More Strongly Associated With Depression Severity Than With Pain Intensity

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Abstract

Background—Despite modern antiretroviral treatment, HIV-associated distal neuropathic pain (DNP) remains one of the most prevalent and debilitating complications of HIV disease. Neuropathic pain is often accompanied by depressed mood, and both pain and depression have been associated with decreased health-related quality of life (HRQOL) well-being. The relative contribution of depression and pain to worse life quality has not been addressed, however, even though a better understanding might sharpen intervention strategies.

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Methods—We used the Medical Outcomes Study HIV (MOS-HIV) Health Survey and the Beck Depression Inventory-II and linear regression models to investigate HRQOL well-being in HIV-infected patients with DNP (N=397) participating in an observational cohort study at six US sites (CNS HIV Antiretroviral Treatment Effects Research Study, CHARTER).

Results—For this sample of patients with HIV DNP, severity of depressed mood was more highly correlated with HRQOL well-being than was pain intensity.

Conclusions—These results suggest that interventions to improve HRQOL well-being in individuals with HIV-associated DNP may need to address not only pain intensity, but mood state as well.

Keywords

Quality of Life; Depression; HIV-Associated Distal Neuropathic Pain; Pain Intensity

INTRODUCTION

HIV-associated distal sensory neuropathy is the most prevalent neurologic complication of HIV-1 infection in the era of combination antiretroviral therapy (CART) ^{1,2}. Painful HIV distal sensory neuropathy affects 20% of all HIV cases and is often refractory to treatment ^{3,4,5}. Moreover, patients with chronic pain ^{6,7,8} including HIV DNP ^{3,9}, often have depression.

The introduction of CART has markedly increased survival in HIV disease, ^{10,11} turning some of the clinical focus towards longer-term management of pain and improving overall health related quality of life (HRQOL). The term HRQOL encompasses both the biological and psychological effects of illness and involves state of health, daily functioning, general “quality” of life ¹², everyday functioning and well-being ^{13,14}. Depressed mood has a significant adverse impact upon HIV HRQOL ^{14,15,16,17,18,19,20,21,22}, and the same negative effect is true for chronic pain in this population ^{23,24,25,17,26,27,28}.

Although evaluation of pain intensity is the foundation of pain assessment and the key target of management, few studies in HIV distal neuropathy attempt to relate pain intensity to life quality. Despite the prevalence of co-morbid depression and pain, the relative contributions of pain intensity and severity of mood disturbance to overall life quality are rarely examined ²⁵. In addition, in only a few studies are HIV pain diagnoses specified ³. These are important omissions since a better understanding of pain-depression relationships to life quality may help guide treatment strategy, especially since both these relationships and successful intervention may vary across different pain disorders.

In an effort to address this gap we performed a cross-sectional analysis of data on pain, mood, and life quality from a large multi-site cohort study of patients with HIV distal neuropathic pain enrolled in HIV clinical care. In order to assess the relative influence of depressed mood and pain on HRQOL, we compared the relationships between standardized measures of health related quality-of-life with measures of mood and with measures of pain intensity. We hypothesized that pain intensity, rather than mood disturbance, would be more robustly associated with worse life quality and worse sense of overall well-being.

METHODS

Participants

The participants in this study included 397 HIV-infected individuals reporting symptoms of distal neuropathic pain who were participating in the CNS (Central Nervous System) HIV

Anti-Retroviral Therapy Effects Research (CHARTER) study, a prospective multi-site cohort of patients in HIV care at six academic centers (Johns Hopkins University (Baltimore, MD); Mt. Sinai School of Medicine (New York, NY); University of California, San Diego (La Jolla, CA); University of Texas-Galveston (Galveston, TX), University of Washington (Seattle, WA); and Washington University (St. Louis, MO))³ The study protocol involved comprehensive standardized neuromedical, neuropsychological, and psychiatric assessments, including evaluation of health-related quality of life²⁹.

The Human Subjects Protection Committees of each participating institution approved the study procedures. Written informed consent was obtained from all study participants before enrollment into the study.

Measures

Diagnosis of HIV Distal Neuropathic Pain Severity—Using procedures described in detail elsewhere³, diagnosis of HIV distal neuropathic pain was made by physicians and nurses trained in neurological AIDS disorders based on a standardized neurological examination evaluating HIV-associated sensory neuropathy symptoms and signs. Neuropathy symptoms were assessed in the legs, feet, and toes and included neuropathic pain, paresthesias, and loss of sensation. Study clinicians classified neuropathic pain (defined as burning, aching, or shooting symptoms) into five categories of ‘clinician-rated pain severity’: none, slight (occasional, fleeting), mild (frequent), moderate (frequent, disabling), and severe (constant, daily, disabling, requiring analgesic medication or other treatment). Neuropathy signs were defined as diminished ability to recognize vibration and reduced sharp-dull discrimination in the feet and toes or reduced ankle reflexes. Of the 1433 CHARTER participants evaluated at entry, those (N = 397) with a clinician-rated pain severity rating of at least “slight” and who also reported at least “very mild” pain intensity over the past month (see below) qualified for the present study. Of these 397 participants, 301 had at least one sign bilaterally of sensory neuropathy.

HIV Health-Related Quality of Life Well-Being and Pain Intensity—The Medical Outcomes Study (MOS)-HIV Health Survey³⁰ is one of the most widely used instruments for assessing HIV HRQOL. It is internally consistent, correlates with concurrent measures of health, discriminates among distinct patient populations, and predicts outcomes^{31,32,33,34}. This 35-item questionnaire comprises ten scales (health perceptions, physical function, social function, role function, cognitive function, pain, vitality, mental health, health distress, and quality of life), scored as summated ratings from 0–100 (where higher values indicate better health). These scales are aggregated to yield summary scores of overall Physical Health and Mental Health, and are categorized into three major dimensions: General Health, Functional Status, and Well-Being, see Figure 1^{30,33}. Question #2 of the MOS-HIV Health Survey asks, “How much bodily pain have you generally had during the past four weeks” classified into six categories of intensity: none, very mild, mild, moderate, severe, and very severe. We used responses to this question as the index of self-reported pain intensity. This question is used to calculate the score for the MOS-HIV survey ‘pain’ scale, but is not used to calculate the score for any of the other MOS-HIV survey scales.

Medical Evaluation

Clinicians conducting the neurological examination also performed structured interviews with medical record reviews to ascertain HIV disease status and treatment history. We obtained information about exposure to combination antiretroviral drugs (CART) use, including current and past exposure to dideoxy nucleoside reverse transcriptase inhibitors (eg, zalcitabine, didanosine, and stavudine), since these agents are known to cause neuropathy), historical indicators of HIV disease (e.g., plasma viral load and current and

lowest ever (nadir) CD4 lymphocyte count); improvement in CD4 on CART; and serological evidence of infection with hepatitis C virus. Blood was collected by venipuncture to quantify plasma HIV concentration by reverse transcription polymerase chain reaction ultrasensitive assay (nominal lower quantitation limit, 50 copies/mL [Amplicor; Roche Diagnostic Systems, Indianapolis, Indiana]). Current peripheral blood CD4+ T cell concentration was measured by flow cytometry.

Depressed Mood

We used the Beck Depression Inventory second edition (BDI-II)³⁵ to assess degree of depressive symptomatology. The BDI-II consists of 21 questions, each having four graded statements (labeled 0 to 3) ordered to show increasing severity of symptoms of depression. These items can be categorized as reflecting both the affective/cognitive (eg, sadness, guilt) and somatic (eg, fatigue, weight loss) dimensions of depression. The reporting period was referenced to the past 14 days. Responses are summed to derive a total score; this provides categories of severity of depressed mood: 0–13 = Minimal; 14–19 = Mild; 20–28 = Moderate; 29–63 = Severe.

Current (e.g., within the last 30 days) and lifetime history of major depression was assessed by the computer-assisted Composite International Diagnostic Interview³⁶.

Statistical Methods

We computed the Pearson's correlation coefficient *R* between each of the 10 MOS-HIV scales and the BDI-II total score, and between each MOS-HIV scale and MOS self-reported category of pain intensity. The correlation coefficients between the BDI and self-reported pain intensity scores were compared using Hotelling's *t*-test³⁷. For all analyses unadjusted and adjusted calculations were performed. The unadjusted calculations used the raw data, while the comparison of the adjusted correlation coefficients was done by replacing the MOS-HIV scale scores, the BDI-II total score, and the self-reported pain intensity with their residuals from the multi-variable linear regressions using each of these variables as the dependent variable and age, gender, race/ethnicity, education, and CD4 nadir as independent variables. The correlation comparisons for the MOS-HIV global summary scores for Physical and Mental Health were conducted using the same approach. For all results the unadjusted and adjusted results were not significantly different. All of the reported results therefore are from the adjusted analyses. For each calculated correlation coefficient the statistical comparison with 0 used Fisher's *z*-transform test. All variables were considered on a numeric scale. All computations were done using JMP (SAS Institute, Cary, North Carolina, U.S.) and R statistical platforms (R Foundation, Vienna, Austria). All tests were two-sided, and *P*-values <0.05 after Bonferroni corrections were considered statistically significant.

RESULTS

The demographic and clinical characteristics of the study participants are given in Table 1. Most patients were middle-aged men of Caucasian and African-American ethnicity who had a history of AIDS and were currently on an antiretroviral regimen, with good immune recovery and fair virologic control. As might be expected given the stage of illness and presence of chronic pain, participants were on average experiencing at least "mild" depressive symptoms (as measured by the BDI-II); 183 participants had a history of a major depressive episode and 214 did not have a history of major depression. The burden of current pain was high, with nearly three in four individuals reporting their intensity in the "moderate" to "very severe" range.

The results of the comparison of the correlation of the 10 MOS-HIV Health Survey scales with mood and pain intensity scores are presented in Figure 1. In all cases, the depressed mood and self-reported pain intensity scores were negatively correlated with the MOS-HIV scales. When scales are considered according to their MOS-HIV dimensions of “Well-Being” and “Function” the correlations with depressed mood are significantly larger than for pain intensity in four out of five MOS-HIV scales comprising “Well-Being” (with the only exception being, as expected, for the Pain scale). The P-values reported in Figure 1 were corrected for multiple comparisons within each dimension using Bonferroni’s correction. Since depression may present as a report of pain rather than depressed mood (“masked depression”) we were concerned that a depressive diathesis might confound our analyses. In an attempt to address this issue we repeated our analyses by restricting the sample to patients with at least one objective sign of bilateral neuropathy, and by comparing results in patients with and without lifetime histories of major depressive disorder. The results for the correlation of five MOS-HIV scales in the “Well-Being” dimension with mood and pain intensity, shown in Figure 1, were not significantly changed when the sample of 397 participants with distal neuropathic pain were reduced to the 301 with at least one sign of bilateral neuropathy. The pattern of results was also similar between the 183 participants with a history of major depression and the 214 participants with no history of major depression. The results were also the same when we censored the “somatic” items from the BDI-II total score (eg, items 14–21, which might be elevated by somatic symptoms due to physical illness rather than depressed mood).

When the MOS-HIV Health Survey global summary scores were considered, both Physical Health Scores (PHS) and Mental Health Scores (MHS) were negatively and significantly correlated with BDI-II total score (severity of depressive symptoms) and pain intensity. Pain intensity was more strongly correlated with PHS ($r = -.611$) than was severity of depressed mood ($r = -.447$) ($P = 0.0005$). Depressed mood was more correlated with MHS ($r = -.778$) than was pain intensity ($r = -.314$) ($P < 0.0001$).

DISCUSSION

In a cohort of individuals with HIV-associated distal neuropathic pain we hypothesized that pain intensity, rather than depressed mood, would be more strongly associated with worse life quality and worse sense of overall well-being. Contrary to this hypothesis our results suggest that greater severity of depression symptoms is more highly correlated with worse well-being than is pain intensity. The result supports the psychiatric consultants position that efforts to improve well-being in this population should consider mood disturbance, as well as pain intensity, as part of a comprehensive approach to treatment.

Painful HIV-associated neuropathy is recognized as a prevalent and growing world health problem³⁸. As described in the results, the burden of current pain was high, with nearly three in four individuals reporting their intensity in the “moderate” to “very severe” range. This burden of pain intensity is in the range reported in one recent epidemiologic survey for acute and chronic pain of diverse etiology in ambulatory HIV-infected individuals²⁷. HIV neuropathy pain is often resistant to standard therapy with antidepressants, anticonvulsants, opioids, and topical agents⁴. This implies that a comprehensive approach addressing factors beyond pain intensity may be important to improving life quality outcomes. HIV disease status is one clear target, since disease symptom complaints are linked to worse life quality²¹, and disease status is customarily the primary treatment focus. But, mood disturbance is known to have significant impact upon HIV HRQOL^{3,15,16,17,18,19,20,21,22}.

One of the difficulties in better understanding relationships between life quality, HIV disease, mood, and HIV-associated pain is that each of these variables is often studied in

relative isolation. Studies of HIV and life quality may omit assessment of either mood or pain or both³⁹, making it impossible to assess their relative contributions. In turn, studies relating pain intensity to mood and HIV-disease variables may omit assessment of life quality²¹. Furthermore, pain syndromes in HIV have diverse etiologies²⁴, but research relating pain, mood, and life quality does not routinely report diagnosis of specific pain syndromes nor differentiate acute pain from chronic pain. Pain symptoms may affect over 25% of HIV-infected men and women^{27,21}, and presence of pain may be related to worse HIV outcomes, including life quality³ as well as disability in everyday function and unemployment³ despite the advances of modern treatment. Pain may be linked to worse immune function (CD4+ lymphocyte count) and worse mood^{25,17,21} while depressed mood itself is associated with lower overall and painrelated life quality¹⁷. The relation of pain intensity to mood is uncertain: some work finds no correlation³, but other evidence suggests a relation between intensity of pain and severity of mood disturbance^{17,21}, particularly in socioeconomically disadvantaged patients with high rates of substance abuse²⁷. Other carefully conducted research, on the other hand, suggests overall life satisfaction is similar in those with and without pain, at least for mild pain intensity²⁵. Part of this variability of results among studies with regard to pain intensity may as well be related to the study entry criteria in terms of chronicity and diagnostic heterogeneity. In this regard there is evidence that patients with neuropathic pain differ from those with nociceptive pain in responses to and beliefs about pain, major problems experienced and factors increasing pain⁴⁰. It may be important to evaluate carefully diagnosed, more homogeneous pain samples in future work.

Limitations of the present study include its cross-sectional design, which leaves us unable to explore possible cause and effect relationships among life quality, pain intensity and mood. Another limitation is that this multi-site cohort was drawn from individuals enrolled in HIV care, rather than from a random sample, and therefore may not be generalizable to all HIV-infected individuals. Because participants in this cohort underwent extensive assessments, and were modestly reimbursed for time and travel, it is probable that unemployed persons were more likely to enroll. One set of limitations includes the fact that our study group was defined as HIV patients with clinician-rated neuropathic pain severity rated as of at least “mild” severity. Participant self-reported pain intensity was derived from the MOS-HIV question regarding intensity of “body pain”. Given the definition of the cohort, it is likely that participants reported “body pain” in reference to “neuropathic pain,” but we cannot be certain of this in all cases. Also the correlations between pain intensity and Well-Being may be artificially restricted since we limited the range of pain to include only individuals with at least mild symptoms. Finally, Well-Being may be more highly correlated with the BDI-II than with pain intensity since well-being components such as mental health, fatigue, and health distress are likely to reflect depression symptoms, at least in part. Compensating for some of these limitations may be the fact that this was a large cohort drawn from diverse geographic sites, which included a wide range of HIV disease status, and which underwent rigorous standardized assessment of pain diagnosis, pain intensity, mood, and life quality.

Given the prevalence and impact of HIV neuropathic pain, and the need to improve everyday outcomes in those living with HIV disease, these results suggest that additional research may be warranted to assess effects of depression treatment on life quality in painful HIV neuropathy.

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Figure 1.

Comparison of Beck Depression Inventory (BDI-II) correlation coefficient R with pain intensity correlation coefficient R, where y-axis = negative correlation coefficient R and x-axis = MOS-HIV Health Survey Scales and Dimensions. The BDI-II R is statistically larger than the pain intensity R for four out of five of the Well-Being dimension MOS-HIV Health Survey scales. Asterix (*) indicates that BDI-II R and self-reported pain intensity R are statistically different with $P < 0.0001$. For MOS-HIV Survey scales General Health, Physical Function, Role Function, and Social Function, BDI-II R and pain intensity R are not statistically different with P-values respectively (0.11, 0.33, 1.0, and 0.053).

TABLE 1**Demographic and Clinical Characteristics of Participants**

Number of subjects	397
Age, mean (SD)	45.3 (7.6)
Male, No. (%)	293 (74)
Race/Ethnicity, No. (%)	180 (45)
Caucasian	170 (43)
African American	38 (10)
Hispanic	9 (2)
Other	
Hepatitis C Virus seropositive, No. (%)	103 (27)
One or more neuropathy sign, No. (%)	301 (76)
AIDS, No. (%)	263 (67)
Plasma HIV RNA Detectable, No. (%)	220 (56)
CD4, No. (%)	56 (14)
Current<200; Nadir<200	172 (44)
Current 200, Nadir<200	163 (42)
Current 200, Nadir 200	
Combination Antiretroviral Therapy Use, No. (%)	298 (75)
Current	56 (14)
Past	43 (11)
Naïve	
Current Antiretroviral Regimen, No. (%)	179 (60)
PI-based *	87 (29)
NNRTI-based *	15 (5)
PI+NNRTI-based	19 (6)
Other	
D-drug use, past or current, No. (%)	245 (62)
Beck Depression Inventory, Mean (SD)	18.2 (10.4)
Lifetime Major Depression (%)	183 (46)
Current Major Depression (%)	86 (21)
Clinician-Rated Pain Severity, No. (%)	N (%)
Slight	150 (38)
Mild	108 (27)
Moderate	65 (16)
Severe	74(19)
Self-Reported Pain Intensity, No. (%)	N (%)
Very Mild	40 (10)
Mild	62 (16)
Moderate	178 (45)
Severe	99 (25)
Very Severe	18 (5)

*
PI = Protease Inhibitor; NNRTI = Non-nucleoside reverse-transcriptase inhibitor