ORIGINAL ARTICLE

OPEN

Pain Is Associated With Depressive Symptoms, Inflammation, and Poorer Physical Function in Older Adults With HIV

Heather M. Derry-Vick, PhD, Carrie D. Johnston, MD, Mark Brennan-Ing, PhD, Chelsie O. Burchett, MA, Nina Glesby, Yuan-Shan Zhu, MB, PhD, Eugenia L. Siegler, MD, and Marshall J. Glesby, MD, PhD

ABSTRACT

Objective: People living with HIV (PLWH) frequently experience pain, which often co-occurs with psychological symptoms and may impact functional outcomes. We investigated cross-sectional associations between pain, depressive symptoms, and inflammation, and then explored whether pain was related to poorer physical function among older PLWH.

Methods: We examined data from PLWH aged 54 to 78 years ($n = 162$) recruited from a single outpatient program for a larger study on HIV and aging. Participants reported depressive symptoms (10-item Center for Epidemiological Studies Depression Scale) and then attended a biomedical visit in which they reported past-month pain (Medical Outcomes Study-HIV pain subscale), completed physical function assessments, and provided blood samples (assayed for interleukin 6, interferon-γ, tumor necrosis factor α, and C-reactive protein). Links between pain, depressive symptoms, inflammation, and physical function were tested using linear regression models.

Results: PLWH with greater depressive symptoms experienced more pain than did those with fewer depressive symptoms ($B = 1.31$, SE $= 0.28$, $p < .001$), adjusting for age, sex, race, body mass index, smoking, disease burden, time since HIV diagnosis, and medication use. Higher composite cytokine levels were associated with worse pain ($B = 5.70$, SE $= 2.54$, $p = .027$ in adjusted model). Poorer physical function indicators, including slower gait speed, weaker grip strength, recent falls, and prefrail or frail status, were observed among those with worse pain. Exploratory mediation analyses suggested that pain may partially explain links between depressive symptoms and several physical function outcomes.

Conclusions: Pain is a potential pathway linking depressive symptoms and inflammation to age-related health vulnerabilities among older PLWH; longitudinal investigation of this pattern is warranted. PLWH presenting with pain may benefit from multidisciplinary resources, including behavioral health and geriatric medicine approaches.

Key words: HIV, aging, pain, inflammation, depression, frailty, gait speed, grip strength, falls.

INTRODUCTION

Modern antiretroviral therapy (ART) has improved health and longevity for people living with HIV (PLWH). Despite substantial progress in medical management of HIV, PLWH experience elevated physical and psychosocial burdens. For example, more than 50% of PLWH experience pain (1), which continues to be a problematic and underaddressed symptom among PLWH (2) that detracts from their quality of life (3).

Bodily pain among PLWH can commonly include unique HIV-associated patterns, such as sensory neuropathy associated with HIV infection and early-generation ART, as well as patterns with less clear etiologies including musculoskeletal and multisite pain (4,5). Overall, PLWH report higher levels of pain than their HIV-negative peers (3,6). In a large cohort study, PLWH reported higher pain levels than those without HIV, and pain was associated with missed days of work and lower quality of life (3). PLWH who are older and those who have been receiving ART for longer periods of time seem to experience pain at higher rates than those who are younger or their similarly aged counterparts without HIV (4,6). This pattern may be due in part to greater accumulated physiological damage or exposure to earlier-generation ART medications that contribute to peripheral neuropathy. Pain is also associated with outcomes that signal vulnerability to poor health during the aging process, including greater healthcare utilization (4), higher likelihood of exhibiting prefrail or frail phenotypes (7), and lower

ART = antiretroviral therapy, **BMI** = body mass index, **CRP** = C-reactive protein, **IL-6** = interleukin 6, **IFN-γ** = interferon-γ, **MOS-HIV** = Medical Outcomes Study-HIV survey, **PLWH** = people living with HIV, **SSRI** = selective serotonin reuptake inhibitor, **TNF-α** = tumor necrosis factor α

self-rated physical function (8,9). Accordingly, studies of pain among older PLWH, typically defined as 50 years and older in the HIV literature, is especially needed.

In a recent publication that summarized input from a global task force, high-priority areas for advancing the science and clinical management of pain included understanding its etiology and exploring the influence of psychosocial factors on pain (10). The biopsychosocial model (11), which has been applied to pain in PLWH (12), is a well-established approach to guiding such work. This framework posits that biological, psychological, and social factors interact dynamically to impact the pain experience, which can in turn affect health outcomes and quality of life. As a result, investigating biobehavioral contributors to pain may inform avenues for improving quality of life for the growing number of older adults with HIV, who are at risk for poor pain-related health outcomes. Here, we focus on psychological symptoms and systemic inflammation as potential contributors, given that they are elevated among PLWH and consistently linked to pain in the broader literature.

PLWH often experience elevated rates of mental health symptoms, a pattern that likely has key consequences for bodily pain in older PLWH. Depression and pain frequently co-occur; higher rates of pain have been observed among individuals with depression (13,14). In a 4-year population-based study of older adults, those with more psychological symptoms (as measured by a composite of depressive and anxiety symptoms) were more likely to have worsening pain and other somatic symptoms than those fewer psychological symptoms; the effects of these symptoms were similar to or larger than the effects of obesity and smoking (15). Among PLWH on long-term opioid therapy, baseline depressive symptoms contributed to increases in pain interference (i.e., impact on functioning and normal activities) over the course of 1 year (16). The relationship between depressive symptoms and bodily pain is also bidirectional, such that experiencing pain is often a distressing experience that can worsen mental health over time (17,18).

Inflammation is another likely contributor to pain among PLWH (19). Even in the context of viral suppression, PLWH experience elevated levels of systemic inflammation compared with their counterparts without HIV (20). Multiple factors, including residual low-level viral replication, other coinfections (e.g., cytomegalovirus), and chronic immune activation, are posited to drive the persistent low-grade inflammation experienced by PLWH (21). Although the relationships between pain and inflammation are complex (spanning acute and chronic patterns, as well as peripheral and central mechanisms), studies suggest that systemic inflammation can promote pain along with other sickness behaviors (22), as well as alter pain perception and signaling pathways (23). For example, in experimental study designs, participants who received endotoxin to induce an inflammatory response had lower pain thresholds on several standardized pain tasks than those in a control condition (24,25); higher levels of cytokines interleukin 6 (IL-6) and interleukin 8 (IL-8) were related to higher pain ratings (25). In addition, systemic inflammation has been linked to various pain-related conditions (26–28) and depressive symptoms (29), suggesting that these factors are interconnected. However, the literature on links between systemic inflammation and pain in PLWH is relatively small. In initial studies among PLWH, pain was associated with higher levels of IL-6 and interleukin 1ß (30,31).

In summary, PLWH experience elevated levels of bodily pain that persists in the context of viral suppression with modern ART,

which can negatively impact physical function. In addition, they experience higher levels of depressive symptoms and inflammation that may contribute to pain. Determining the extent to which depressive symptoms and inflammation are related to pain could inform novel approaches to assessment and intervention, especially for older adults who are most affected by pain yet are often underrepresented in HIV research. In the current study, we investigated links between biobehavioral factors and pain among older adults with HIV. We tested whether depressive symptoms and systemic inflammation were associated with bodily pain and investigated the relationship between pain and physical function, as indicated by subjective and objective measures. Based on a biopsychosocial conceptual model (12,19) and evidence suggesting that depressive symptoms and inflammation can contribute to pain (15,25), we then explored this potential pathway using cross-sectional data to test whether depressive symptoms and inflammation were associated with poorer physical function in part through worse pain.

METHODS

Participants

Participants were older adults with HIV who were recruited from the outpatient HIV clinics at Weill Cornell Medicine as part of the larger Research on Older Adults with HIV study (32). Data for this analysis are drawn from a substudy, which included a biomedical assessment; participants were invited to complete this portion of the study if they were 55 years or older, were English speaking, and had documented HIV infection. Exceptions were made to enroll two individuals who were 54 years of age and met the other inclusion criteria. Data were collected between June 2016 and March 2019. The analytic sample is composed of the 162 participants who had available data for the primary variables, pain and depressive symptoms; of these, inflammation data were available for 160 participants. Informed consent was obtained, and the study procedures were approved by the Weill Cornell Medicine Institutional Review Board.

Participants and Procedures

In an initial study visit, participants completed a survey focusing on psychosocial factors as part of the Research on Older Adults with HIV study. They reported sociodemographic characteristics and depressive symptoms on the survey. Next, they attended a separate study visit to complete biomedical assessments, which were administered by trained research staff at the Weill Cornell Clinical and Translational Science Center. Participants were instructed to arrive fasting for 8 hours to the visit; blood samples were drawn and processed, and serum was stored at −80°C and then later assayed for inflammatory markers. At the visit, participants also completed objective measures of physical functioning (frailty, including grip strength, and gait speed) and answered self-report questions about past-month pain and physical functioning, as summarized below.

Measures

Bodily Pain

Participants reported bodily pain on the Medical Outcomes Study-HIV (MOS-HIV) survey (33). The bodily pain subscale is composed of two items; participants rated pain severity ("none" to "very severe") and pain interference with normal activities ("not at all" to "extremely") they experienced in the past month. To facilitate interpretation for this analysis, the bodily pain subscale was reverse-scored such that higher scores reflect worse pain.

Depressive Symptoms

Participants reported depressive symptoms on the 10-item Center for Epidemiological Studies Depression Scale (CESD-10) at the survey visit (34).

They were asked to rate items such as "I was bothered by things that usually don't bother me" and "I felt hopeful about the future (reverse-scored)," on a 0 to 3 scale. Continuous, total scores were calculated and used for analysis, with higher scores indicating greater depressive symptoms. Cronbach's alpha was .83 in this sample.

Inflammation Levels

Inflammation levels were measured using biomarker data for C-reactive protein (CRP) and proinflammatory cytokines IL-6, tumor necrosis factor α (TNF-α), and interferon-γ (IFN-γ). The biomarker data were available as part of a larger study on psychosocial factors and inflammation, in which the cytokines were selected based on their expected relationships with depressive symptoms, loneliness, and stigma (29). Electrochemiluminescence-based assays were performed in the Weill Cornell Clinical and Translational Science Center Core Laboratory according to Meso Scale Discovery (Rockville, Maryland) kit instructions (K151STG and K15052G, respectively) using the MESO QuickPlex SQ120 Analyzer. Assays were run in duplicate with quality controls, with 10% repeated for confirmation. The intra-assay coefficients of variation for CRP, IL-6, TNF-α, and IFN-γ ranged from 2.4% to 6.4%, and the interassay coefficients of variation ranged from 5.0% to 10.2%. The detection limits of CRP, IL-6, TNF-α, and IFN-γ were 0.01 ng/ml, 0.10 pg/ml, 0.20 pg/ml, and 0.40 pg/mL, respectively. After examining inflammation data for outliers, winsorizing each biomarker variable to 3 standard deviations (SDs) from the mean (35,36), then log-transforming because of positive skew, a composite score for cytokine levels was computed as previously described (29). This strategy was used given moderate-to-strong correlations between IL-6, TNF-α, and IFN-γ cytokine levels ($r = 0.25$ to $r = 0.52$), and to facilitate interpretation and limit the number of statistical comparisons.

Physical Function Indicators

Gait Speed

Participants completed two 4-m walk trials at their usual speed (with assistive devices as needed), and gait speed was computed using the participant's fastest trial time (37,38).

Grip Strength

Grip strength was measured using a dynamometer; participants completed three trials with their dominant hand, and the average of the trials was computed (39).

Frailty

Frailty was assessed according to the well-established Fried phenotype (40). Weak grip (assessed via dynamometer), slow walk (assessed via 4-m walk), unintentional weight loss (assessed via self-report), low physical activity (assessed via self-report), and exhaustion (assessed via self-report) components were assessed at the biomedical visit. Frailty criteria for each component were classified according to the cutoffs applied in a large cohort study of older adults with HIV (39). Participants who met the frailty criteria for 0 components were categorized as robust, those who met the criteria for 1 or 2 components were categorized as prefrail, and those who met the criteria for 3 or more components were categorized as frail. Participants with missing data on one or two components were considered evaluable (40) if their final frailty category would remain unchanged by the addition of the remaining scores.

Recent Falls

To assess history of recent falls, participants were asked "In the past six months, have you had a fall?" with response options of "yes" or "no."

Self-Reported Physical Function

Participants completed the MOS-HIV survey, a well-validated quality-of-life instrument (33). Scores were computed for the Physical Function subscale according to the instrument manual. Participants were asked to rate how much their health limited them in a variety of daily activities (e.g., walking uphill or climbing a few flights of stairs), with response options "no, not limited at all," "yes, limited a little" and "yes, limited a lot." Higher subscale scores indicate better self-reported physical function, and Cronbach's alpha was .86.

Covariates

Body mass index (BMI; in kilograms per meter squared) was calculated using height and weight measured at the biomedical visit. Smoking status was assessed via self-report on the psychosocial survey. Participants self-reported their gender identity on the survey; there was one transgender woman in the sample, and her data are included under female gender identity. To measure disease burden of HIV and comorbid conditions, scores on the validated Veterans Aging Cohort Study Index were calculated, a widely used measure of accumulated organ system injury among PLWH (41). Dichotomous variables indicating medication use were coded for selective serotonin reuptake inhibitor (SSRI) medications, analgesic opioid medications, and regular use of systemic anti-inflammatory medications (immunosuppressants, systemic glucocorticoids, antigout medications, and statins). These variables used medication lists that were reconciled by nurses at the biomedical study visit and were coded using the World Health Organization Anatomical Therapeutic Chemical classification system.

Statistical Analysis

Analyses were conducted in SPSS, version 24.0 (IBM Corp., Armonk, New York). Pearson correlations were used to evaluate bivariate associations between depressive symptoms, inflammation, pain, and physical function measures. In follow-up adjusted analyses, depressive symptoms were tested as the key independent variable associated with pain levels while adjusting for age, sex, race, BMI, smoking, disease burden, SSRI use, opioid use, and years since HIV diagnosis. Covariates were selected based on their theoretical and established relationships with pain levels. Using the same covariates, relationships between pain and physical function indicators were examined in adjusted linear regression models for continuous outcomes (gait speed, grip strength, self-reported physical function) and adjusted logistic regression models for dichotomous outcomes (recent falls, prefrail or frail status). Similarly, adjusted linear regression models were used to test the relationship between pain and inflammation levels. We also conducted ancillary analyses adjusting for anti-inflammatory medication use and ancillary sensitivity analyses among those with CRP levels less than 10 mg/l (a common threshold for acute illness and analyses that focus on low-grade inflammation) (35,42,43), to determine whether the patterns were consistent in this subgroup. To determine whether the relationship between pain and the cytokine composite were driven by one or more of the individual cytokines, we conducted ancillary analyses to test the relationship between pain and individual cytokines in unadjusted and adjusted regression analyses.

Based on the observed relationships in the primary analyses and guided by the biopsychosocial model, exploratory analyses were conducted to examine pain as a mechanism linking depressive symptoms (or inflammation) and physical function. The PROCESS macro (version 3; model 4) was used to conduct mediation analyses (44), using mean-centered continuous variables and 10,000 bootstrap samples. Separate models included depressive symptoms (or inflammation levels) as the key predictor (x), bodily pain as the mediator (M), and continuous physical function measures individually as outcomes (y) in separate models, while adjusting for the same covariates as listed previously. Cases with missing data were excluded listwise for all models.

RESULTS

On average, participants were 61 years of age (SD = 5.66 years; range, 54–78 years) and had been diagnosed with HIV 23 years ago (SD = 5.69 years; range, 4–37 years). Other participant characteristics were: male (67%), Black (49%), and nonsmoking (84%). Most participants (85%) had undetectable virus levels (indicated by HIV-1 viral load <20 copies/ml).

On the MOS-HIV survey, 48% of participants rated their past-month bodily pain in the moderate to very severe range, 38% rated their pain as very mild or mild, and 14% reported having no pain in

the past month. Pain interference with normal activities was rated as moderate or greater among 38% of participants. Fifty percent endorsed clinically significant levels of depressive symptoms, indicated by CES-D-10 scores of 10 or greater (34). Additional sample characteristics are summarized in Table 1.

Associations Between Depressive Symptoms and Bodily Pain

Bivariate analyses are summarized in Table 2. Those with more depressive symptoms had worse pain than those with fewer depressive symptoms ($r = 0.33$, $p < .001$). The association between depressive symptoms and pain remained statistically significant in the adjusted regression model, as detailed in Table 3 ($B = 1.31$, $SE = 0.28$, $p < .001$). The set of independent variables in the adjusted model (age, sex, race, BMI, disease burden, current smoking, opioid medication, SSRI medication, time since HIV diagnosis, and depressive symptoms) explained 30.5% of the variance in pain levels ($F_{(10,148)} = 6.48$, $p < .001$). The pattern of results did not change when anti-inflammatory medication use was added to the model. Bivariate correlations were also consistently observed between depressive symptoms and physical function indicators (Table 2).

Associations Between Inflammation and Bodily Pain

Higher composite cytokine levels were associated with worse pain ($r = 0.25$, $p = .002$). There were not statistically significant associations between CRP levels and pain levels. The association between composite cytokine levels and pain remained statistically significant in the adjusted regression models, as detailed in Table 4 ($B = 5.70$, $SE = 2.54$, $p = .027$). The set of independent variables in the adjusted model (age, sex, race, BMI, disease burden, current smoking, opioid medication, SSRI medication, time since HIV diagnosis, and composite cytokine levels) explained 21.6% of the variance in pain levels ($F_{(10,146)} = 4.03$, $p < .001$). We also conducted ancillary sensitivity analyses in the subset of participants with CRP values less than 10 mg/l ($n = 143$). Using this common approach for focusing on chronic low-grade inflammation, the pattern of results was the same as discussed previously. Similarly, the pattern of results did not change when anti-inflammatory medication use was added to the model.

In ancillary analyses to determine whether the association between pain and the composite cytokine levels was driven by one or more of the individual cytokines, pain was associated with TNF-α ($B = 4.04$, $SE = 1.93$, $p = .038$) and IFN-γ ($B = 6.84$, $SE = 1.84$, $p < .001$) in unadjusted models. There was a positive but statistically nonsignificant association between pain and IL-6 in the unadjusted model ($B = 3.11$, $SE = 1.92$, $p = .11$). In adjusted models, the relationships between pain and IL-6 and TNF-α were weaker and not statistically significant. The relationship between pain and IFN-γ remained statistically significant in the adjusted model ($B = 5.95$, $SE = 1.78$, $p = .001$). In summary, the ancillary analyses align with the results using the cytokine composite score; positive associations with pain were observed across the individual cytokines, and these results additionally indicate that links between IFN-γ and pain may have driven the relationship between pain and the composite score in the primary analysis.

Associations Between Bodily Pain and Physical Function

Worse pain was related to poorer physical function indicators, including slower gait speed, weaker grip strength, recent falls, and

TABLE 1. Demographic and Key Variables for Participants in Sample ($n = 162$)

Characteristic	Mean (SD), Mdn (IQR), or n (%)
Age, y	61.01 (5.66)
Gender	
Female	53 (33%)
Male	109 (67%)
Race	
Black	80 (49%)
White	51 (32%)
Asian or Pacific Islander	3 (2%)
Biracial or multiracial	25 (15%)
Ethnicity	
Hispanic/Latino	42 (26%)
Non-Hispanic/Latino	100 (62%)
Education level	
≤12 y	48 (30%)
>12 y	111 (68%)
Viral load	
<20 copies/mL	137 (85%)
20–50 copies/mL	9 (5%)
≥50 copies/mL	16 (10%)
Time since HIV diagnosis, y	23.36 (5.69)
Disease burden (VACS Index score)	33.15 (18.21)
BMI, kg/m^2	28.35 (7.07)
Current smoking (yes)	26 (16%)
SSRI medication use (yes)	18 (11%)
Opioid medication use (yes)	31 (19%)
Anti-inflammatory medication use (yes)[a]	85 (53%)
Pain (MOS-HIV subscale, reverse-coded)	35.66 (24.76)
Depressive symptoms (CESD-10 scores)	10.00 (6.37)
Inflammation biomarkers, Mdn (IQR)	
CRP (raw values), mg/l	2.47 (1.19 to 5.53)
IL-6 (raw values), pg/ml	0.92 (0.61 to 1.42)
TNF-α (raw values), pg/ml	3.01 (2.38 to 3.94)
IFN-γ (raw values), pg/ml	3.39 (1.99 to 6.18)
Composite cytokine levels[b]	−0.01 (−0.54 to 0.52)
Gait speed (best trial), m/s	0.90 (0.23)
Grip strength (average of 3 trials), kg	31.68 (8.72)
Self-reported physical function (MOS-HIV subscale)	65.81 (26.74)
Fall in past 6 mo (yes)	36 (22%)
Prefrail or frail status	109 (67%)

SD = standard deviation; Mdn = median; IQR = interquartile range; VACS = Veterans Aging Cohort Study Index; BMI = body mass index; SSRI = selective serotonin reuptake inhibitor; MOS-HIV = Medical Outcomes Study-HIV survey; CESD-10 = 10-item Center for Epidemiological Studies Depression Scale; CRP = C-reactive protein; IL = interleukin; TNF-α = tumor necrosis factor α; IFN-γ = interferon-γ.

% indicates percentage of those with available data for each variable. Data were missing for some participants for race ($n = 3$), ethnicity ($n = 20$), education ($n = 3$), gait speed ($n = 1$), falls ($n = 2$), grip strength ($n = 5$), and frailty status ($n = 2$).

[a] Indicates regular use of systemic anti-inflammatory medications (immunosuppressants, systemic glucocorticoids, antigout medications, and statins).

[b] Composite cytokine levels were computed by standardizing the log-transformed, winsorized inflammation variables to index z scores for each cytokine (IL-6, TNF-α, and IFN-γ), then averaging these three standardized variables.

TABLE 2. Bivariate Pearson Correlations Between Pain, Depressive Symptoms, Inflammation, and Physical Function Indicators

	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]
[1] Bodily pain subscale	—								
[2] Depressive symptoms	0.33**	—							
[3] Composite cytokine levels	0.25*	0.24*	—						
[4] CRP (log-transformed)	0.03	−0.05	0.40**	—					
[5] Gait speed	−0.32**	−0.23*	−0.17*	−0.13	—				
[6] Grip strength	−0.25*	−0.20*	−0.10	−0.11	0.26*	—			
[7] Fall in past 6 mo	0.39**	0.31**	0.06	−0.02	−0.21*	0.02	—		
[8] Self-rated physical function	−0.60**	−0.35**	−0.31**	−0.19*	0.42**	0.29*	−0.34**	—	
[9] Prefrail/frail status	0.44**	0.43**	0.18*	0.02	−0.40**	−0.30**	0.21*	−0.50**	—

CRP = C-reactive protein.

* $p < .050$.

** $p < .001$.

lower self-reported physical function in bivariate analyses, as shown in Table 2. The association between pain levels and physical function indicators remained statistically significant in the separate adjusted linear and logistic regression models, which adjusted for age, sex, race, disease burden, BMI, smoking, SSRI medication, opioid medication, and time since HIV diagnosis. Specifically, those with worse

pain were more likely to report recent falls (adjusted odds ratio = 1.06, 95% confidence interval [CI] = 1.03–1.09, $p = <0.001$) and more likely to meet the criteria for prefrail or frail phenotype status (adjusted odds ratio = 1.06, 95% CI = 1.03–1.08, $p < .001$). In adjusted models, worse pain remained associated with lower self-reported physical function ($B = −0.64$, SE = 0.07, $p < .001$), weaker grip

TABLE 3. Unadjusted and Adjusted Linear Regression Models Testing the Relationship Between Depressive Symptoms and Pain

Dependent Variable: MOS-HIV Pain Subscale

Independent Variable	B	SE	t	p	R^2
Unadjusted model					
Depressive symptoms	1.26	0.29	4.35	<.001	0.11
Adjusted model					
Step 1					0.20
Age (years)	−0.61	0.38	−1.64	.10	
Gender (male)	−6.17	4.30	−1.44	.15	
Race (White)	5.82	4.31	1.35	.18	
BMI (kg/m²)	0.43	0.27	1.62	.11	
Disease burden (VACS)	0.22	0.12	1.74	.083	
Current smoking (yes)	8.57	5.00	1.72	.088	
Opioid medication (yes)	19.35	4.80	4.04	<.001	
SSRI medication (yes)	−3.67	5.95	−0.62	.54	
Time since HIV diagnosis (years)	0.28	0.34	0.82	.42	
Step 2					0.31
Age (years)	−0.61	0.35	−1.76	.081	
Gender (male)	−6.18	4.01	−1.54	.13	
Race (White)	3.23	4.07	0.79	.43	
BMI (kg/m²)	0.44	0.25	1.76	.081	
Disease burden (VACS)	0.14	0.12	1.20	.23	
Current smoking (yes)	6.83	4.68	1.46	.15	
Opioid medication (yes)	20.92	4.49	4.66	<.001	
SSRI medication (yes)	−6.58	5.59	−1.18	.24	
Time since HIV diagnosis (years)	0.25	0.32	0.78	.44	
Depressive symptoms	1.31	0.28	4.75	<.001	

MOS-HIV = Medical Outcomes Study-HIV survey; BMI = body mass index; VACS = Veterans Aging Cohort Study Index; SSRI = selective serotonin reuptake inhibitor.

TABLE 4. Unadjusted and Adjusted Linear Regression Models Testing the Relationship Between Composite Cytokine Levels and Pain

Dependent Variable: MOS-HIV Pain Subscale

Independent Variable	B	SE	t	p	R^2
Unadjusted model					
Composite cytokine levels	7.69	2.41	3.19	.002	0.06
Adjusted model					
Step 1					0.19
Age (years)	−0.59	0.38	−1.58	.12	
Gender (male)	−5.96	4.36	−1.37	.17	
Race (White)	5.60	4.40	1.27	.21	
BMI (kg/m²)	0.44	0.27	1.66	.10	
Disease burden (VACS)	0.19	0.13	1.48	.14	
Current smoking (yes)	8.61	5.09	1.69	.093	
Opioid medication (yes)	19.45	4.87	3.99	<.001	
SSRI medication (yes)	−4.57	6.11	−0.75	.46	
Time since HIV diagnosis (years)	0.28	0.34	0.81	.42	
Step 2					
Age (years)	−0.54	0.38	−1.44	.15	0.22
Gender (male)	−6.53	4.31	−1.52	.13	
Race (White)	4.78	4.36	1.10	.27	
BMI (kg/m²)	0.34	0.27	1.25	.21	
Disease burden (VACS)	0.07	0.13	0.53	.60	
Current smoking (yes)	7.22	5.06	1.43	.16	
Opioid medication (yes)	19.02	4.81	3.96	<.001	
SSRI medication (yes)	−3.32	6.06	−0.55	.58	
Time since HIV diagnosis (years)	0.25	0.34	0.75	.46	
Composite cytokine levels	5.70	2.54	2.24	.027	

MOS-HIV = Medical Outcomes Study-HIV survey; BMI = body mass index; VACS = Veterans Aging Cohort Study Index; SSRI = selective serotonin reuptake inhibitor.

strength ($B = −0.07$, SE = 0.03, $p = .010$), and slower gait speed ($B = −0.003$, SE = 0.001, $p = .001$).

Exploratory Mediation Analyses

Exploratory post hoc analyses tested whether depressive symptoms (x) were associated with physical function indicators (y), and whether these links were at least partially explained by worse pain (M). Consistent with the aforementioned adjusted models, these mediation models were adjusted for the following covariates: age, sex, race, BMI, disease burden, smoking, opioid medication, SSRI medication, and time since HIV diagnosis. Figure 1 shows the mediation model with gait speed as the dependent variable as an example; in the other models, physical function indicators were substituted for gait speed as the dependent variable. The total effect of depression on gait speed was statistically significant (total effect $c = −0.007$, 95% CI = −0.01 to −0.002). The indirect effect was also statistically significant, providing support for mediation (indirect effect $ab = −0.003$, 95% CI = −0.006 to −0.0005). Similarly, the indirect effect of pain was significant for separate models linking depressive symptoms to self-reported physical function, recent falls, and prefrail or frail status, as summarized in Table 5. The indirect effect of pain was not significant for the model testing the effect of depressive symptoms on grip strength.

As previously reported, higher levels of cytokines were associated with physical function indicators (29). Mediation analyses suggested that pain partially explained the relationship between cytokine levels and gait speed, grip strength, self-reported physical function, recent falls, and prefrail/frail status. Table 5 summarizes the indirect effects from these models.

DISCUSSION

In this study of older PLWH (ages, 54–78 years) recruited from a single outpatient HIV program, we observed that depressive symptoms and circulating cytokines were associated with pain, as indexed by the MOS-HIV subscale scores. These relationships remained significant when adjusting for key sociodemographic and health-related covariates. In addition, those with worse pain had poorer physical function than those with less pain, as indicated by slower gait speed, weaker grip strength, recent falls, lower self-reported physical function, and prefrail or frail phenotypes, all of which are hallmarks of vulnerability to poor health outcomes. In line with prior studies, a notable portion of the sample endorsed concerning pain characteristics, with 48% and 38% reporting moderate or higher levels of pain severity and pain interference, respectively. Overall, these findings highlight that pain is associated with depressive symptoms and inflammation over and above other relevant factors. The results are timely in the context of a recent

Indirect effect of pain (ab) = -.003, 95% CI = -.006 to -.0005
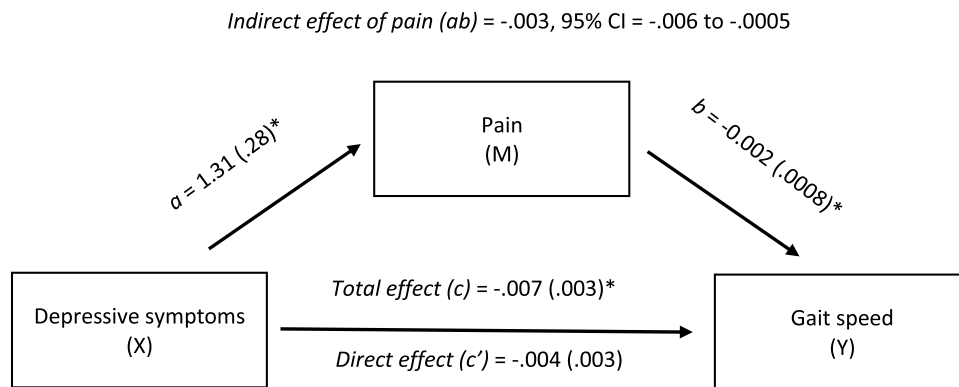
FIGURE 1. Exploratory mediation model suggesting that depressive symptoms are related to slower gait speed in part via worse pain. The figure notes the estimated effect for each path, with standard errors in parentheses. The * symbol indicates a statistically significant effect at an α level of .050. The model adjusted for age, sex, race, disease burden, body mass index, smoking status, selective serotonin reuptake inhibitor medications, analgesic opioid medications, and time since HIV diagnosis. CI = confidence interval.

expert-driven research agenda on pain in PLWH, which underscored the need to expand knowledge about pain-related etiologies and psychosocial factors (10).

These findings are consistent with the biopsychosocial model of pain and broader literature, suggesting that depressive symptoms and inflammation are both linked to pain and that pain is related to poorer physical function. For example, in a study of PLWH in primary care, 53% had chronic pain, and those with higher levels of depressive symptoms also had higher levels of pain (45). These findings are also consistent with emerging work suggesting that elevated inflammation plays a role in the pain experience for PLWH (31). In this study, cytokine levels had stronger associations with pain than CRP levels did, and additional studies are needed to determine whether this pattern is consistent across samples. As expected, those with worse pain also performed worse on physical function tasks and rated their physical function as lower than those with less pain. Although these links were not tested longitudinally in the current study, prospective studies would be useful for determining whether pain impairs physical function over time.

The exploratory mediation results further suggested that the links between depressive symptoms and physical function indicators were partially due to worse pain. These findings provide initial, preliminary evidence that pain may be a contributing pathway that links depressive symptoms with physical function; similar findings were observed in models with inflammation as the key independent variable. These results provide insight into the possible ways that links between biobehavioral factors, pain, and physical function may unfold or share common characteristics. However, these results should be interpreted with caution because of the post hoc, atemporal nature of the mediation analyses, which limits the conclusions that can be drawn and cannot be used to infer causality (46). A strong test of this potential pathway would involve measurement of these factors at three or more time points, which would also allow testing bidirectionality. Although we chose to test this particular pattern based on one configuration of the biopsychosocial model, alternate pathways likely exist; for example, it is quite possible that pain's effect on physical function outcomes could be due in part to depressive symptoms or inflammation. Although these results are

TABLE 5. Summary of Indirect Effects of Pain in Separate Post Hoc Mediation Models, Adjusted for Covariates

Effect	n	Estimate	95% CI	
			LL	UL
Key predictor: depressive symptoms				
Indirect effect of pain on gait speed	158	−0.003	−0.006	−0.001
Indirect effect of pain on grip strength	154	−0.065	−0.138	0.0005
Indirect effect of pain on self-reported physical function	159	−0.730	−1.119	−0.384
Indirect effect of pain on recent falls	157	0.0697	0.036	0.154
Indirect effect of pain on prefrail or frail status	157	0.050	0.024	0.112
Key predictor: composite cytokine levels				
Indirect effect of pain on gait speed	156	−0.014	−0.032	−0.002
Indirect effect of pain on grip strength	152	−0.358	−0.833	−0.036
Indirect effect of pain on self-reported physical function	157	−3.477	−6.424	−0.671
Indirect effect of pain on recent falls	157	0.070	0.037	0.151
Indirect effect of pain on prefrail or frail status	155	0.302	0.067	0.704

CI = confidence interval; LL = lower limit; UL = upper limit.

Models included age, sex, race, disease burden, body mass index, smoking status, selective serotonin reuptake inhibitor medications, opioid medications, and time since HIV diagnosis as covariates. Indirect effects for dichotomous outcome variables (recent falls, prefrail or frail status) are presented in log odds metric.

exploratory and should be viewed as hypothesis-generating information for future work, it is encouraging that similar patterns were seen across multiple physical function measures.

Although older adults (traditionally defined as those older than 50 years in the HIV literature) are the fastest-growing segment of PLWH (47) and experience higher levels of pain and pain-related disability compared with their younger counterparts (6), they are underrepresented in HIV research. Accordingly, the current study's focus on older PLWH provides valuable information about pain's links to biobehavioral factors in this group for whom it is particularly relevant. The study also included a diverse population of older PLWH. The sample was composed of 33% women and 52% Black participants, a strength that adds to the generalizability of the results. In addition, the study design provided a unique opportunity to investigate both psychological and biological contributors to pain among PLWH. Comprehensive measures of physical function included both objective and subjective measures, and the patterns of results were similar across both types of measures, suggesting that the findings are robust.

The primary limitation of this study is its cross-sectional nature. These data cannot inform conclusions about causality or directionality, which would be best tested in future longitudinal designs that consider the likely bidirectionality of these associations. Furthermore, although a validated pain measure was used (i.e., the pain subscale of the widely used MOS-HIV survey), information about specific pain types and locations was not gathered. It is likely that participants were experiencing heterogeneous types of pain; for example, musculoskeletal pain (38%) and neuropathic pain (11%) were the most common types of pain endorsed by PLWH in the primary care setting (4). Unique contributors and consequences might be relevant to each of these, an area for future work.

Implications of this work include the importance of integrating multidimensional pain assessment (including psychological factors and function) and interprofessional team approaches (48) to pain management into HIV care. Our results suggest that when PLWH present with pain, it may be important to consider ways to also address closely related problems of depressive symptoms, inflammation levels, and physical function. Because these factors can complicate pain management, accounting for and addressing them could strengthen treatment approaches. For example, a multicomponent intervention combining Tai Chi, cognitive-behavioral therapy, and motivational text messaging seemed promising for addressing pain in a pilot trial (49). These strategies could also improve mood, inflammation, and physical function (50,51). Another recent study concluded that integrated care for pain, including pairing pharmacological and nonpharmacological strategies to address biopsychosocial factors, would be useful (4). Given relationships between pain and depression, another key aspect of adequate pain management among older PLWH may be promoting mental health care access and engagement when needed. For example, among older HIV-positive Veterans who screened positive for depression, 45% were not receiving mental health services (although they were offered in 66% of these cases); several reported barriers included scheduling/availability, transportation, and stigma (52). Alternatively, incorporating psychosocial factors into pain management is both efficacious and well-received (53), which could serve as a pathway to engaging individuals in mental health care.

Overall, in addition to the goals set for achieving high rates of viral suppression among PLWH, recent calls have focused on prioritizing quality-of-life benchmarks for PLWH in the modern ART era (54).

The current study, along with the broader literature, highlights pain as a significant barrier to maximal quality of life among those aging with HIV. Indeed, PLWH identify pain as a high-priority, concerning symptom (2). These findings contribute information on likely biobehavioral drivers and consequences of pain among PLWH, which may be used to inform longitudinal study of these pathways to determine directionality. In line with the biopsychosocial model and the pattern of results in this study, approaches that incorporate strategies to manage depressive symptoms, limit chronic inflammation, or both, are likely to contribute to pain management and maximize physical function among older PLWH.

REFERENCES

1. Parker R, Stein DJ, Jelsma J. Pain in people living with HIV/AIDS: a systematic review. J Int AIDS Soc 2014;17:18719.
2. Bristowe K, Clift P, James R, Josh J, Platt M, Whetham J, et al. Towards person-centred care for people living with HIV: what core outcomes matter, and how might we assess them? A cross-national multi-Centre qualitative study with key stakeholders. HIV Med 2019;20:542–54.
3. Sabin CA, Harding R, Bagkeris E, Nkhoma K, Post FA, Sachikonye M, et al. Pain in people living with HIV and its association with healthcare resource use, well being and functional status. AIDS 2018;32:2697–706.
4. Jiao JM, So E, Jebakumar J, George MC, Simpson DM, Robinson-Papp J. Chronic pain disorders in HIV primary care: clinical characteristics and association with healthcare utilization. Pain 2016;157:931–7.
5. Madden VJ, Parker R, Goodin BR. Chronic pain in people with HIV: a common comorbidity and threat to quality of life. Pain Manag 2020;10:253–60.
6. Sabin CA, Harding R, Bagkeris E, Geressu A, Nkhoma K, Post FA, et al. The predictors of pain extent in people living with HIV. AIDS 2020;34:2071–9.
7. Petit N, Enel P, Ravaux I, Darque A, Baumstarck K, Bregigeon S, et al. Frail and pre-frail phenotype is associated with pain in older HIV-infected patients. Medicine (Baltimore) 2018;97:e9852.
8. Talaei-Khoei M, Fischerauer SF, Jha R, Ring D, Chen N, Vranceanu A-M. Bidirectional mediation of depression and pain intensity on their associations with upper extremity physical function. J Behav Med 2018;41:309–17.
9. Merlin JS, Westfall AO, Chamot E, Overton ET, Willig JH, Ritchie C, et al. Pain is independently associated with impaired physical function in HIV-infected patients. Pain Med 2013;14:1985–93.
10. Merlin JS, Hamm M, de Abril Cameron F, Baker V, Brown DA, Cherry CL, et al. Special Issue HIV and Chronic Pain (The Global Task Force for Chronic Pain in

People with HIV (PWH): developing a research agenda in an emerging field). AIDS Care 2021;1–9. doi:10.1080/09540121.2021.1902936.

11. Engel GL. The clinical application of the biopsychosocial model. Am J Psychiatry 1980;137:535–44.

12. Merlin JS, Zinski A, Norton WE, Ritchie CS, Saag MS, Mugavero MJ, et al. A conceptual framework for understanding chronic pain in patients with HIV. Pain Pract 2014;14:207–16.

13. Stubbs B, Vancampfort D, Veronese N, Thompson T, Fornaro M, Schofield P, et al. Depression and pain: primary data and meta-analysis among 237 952 people across 47 low- and middle-income countries. Psychol Med 2017;47:2906–17.

14. Arnow BA, Hunkeler EM, Blasey CM, Lee J, Constantino MJ, Fireman B, et al. Comorbid depression, chronic pain, and disability in primary care. Psychosom Med 2006;68:262–8.

15. Niles AN, O'Donovan A. Comparing anxiety and depression to obesity and smoking as predictors of major medical illnesses and somatic symptoms. Health Psychol 2019;38:172–81.

16. Serota DP, Capozzi C, Lodi S, Colasanti JA, Forman LS, Tsui JI, et al. Predictors of pain-related functional impairment among people living with HIV on long-term opioid therapy. AIDS Care 2021;33:507–15.

17. Euesden J, Matcham F, Hotopf M, Steer S, Cope AP, Lewis CM, et al. The relationship between mental health, disease severity, and genetic risk for depression in early rheumatoid arthritis. Psychosom Med 2017;79:638–45.

18. de Heer EW, ten Have M, van Marwijk HWJ, Dekker J, de Graaf R, Beekman ATF, et al. Pain as a risk factor for common mental disorders. Results from the Netherlands Mental Health Survey and Incidence Study-2: a longitudinal, population-based study. Pain 2018;159:712–8.

19. Slawek DE. People living with HIV and the emerging field of chronic pain-what is known about epidemiology, etiology, and management. Curr HIV/AIDS Rep 2021;18:436–42.

20. Peterson TE, Baker JV. Assessing inflammation and its role in comorbidities among persons living with HIV. Curr Opin Infect Dis 2019;32:8–15.

21. Gabuzda D, Jamieson BD, Collman RG, Lederman MM, Burdo TH, Deeks SG, et al. Pathogenesis of aging and age-related comorbidities in people with HIV: highlights from the HIV ACTION workshop. Pathog Immun 2020;5:143–74.

22. Watkins LR, Maier SF. The pain of being sick: implications of immune-to-brain communication for understanding pain. Annu Rev Psychol 2000;51:29–57.

23. Ren K, Dubner R. Interactions between the immune and nervous systems in pain. Nat Med 2010;16:1267–76.

24. de Goeij M, van Eijk LT, Vanelderen P, Wilder-Smith OH, Vissers KC, van der Hoeven JG, et al. Systemic inflammation decreases pain threshold in humans in vivo. PLoS One 2013;8:e84159.

25. Karshikoff B, Lekander M, Soop A, Lindstedt F, Ingvar M, Kosek E, et al. Modality and sex differences in pain sensitivity during human endotoxemia. Brain Behav Immun 2015;46:35–43.

26. Wang H, Schiltenwolf M, Buchner M. The role of TNF-α in patients with chronic low back pain—a prospective comparative longitudinal study. Clin J Pain 2008;24:273–8.

27. Parkitny L, McAuley JH, Pietro FD, Stanton TR, O'Connell NE, Marinus J, et al. Inflammation in complex regional pain syndrome: a systematic review and meta-analysis. Neurology 2013;80:106–17.

28. Bäckryd E, Tanum L, Lind A-L, Larsson A, Gordh T. Evidence of both systemic inflammation and neuroinflammation in fibromyalgia patients, as assessed by a multiplex protein panel applied to the cerebrospinal fluid and to plasma. J Pain Res 2017;10:515–25.

29. Derry HM, Johnston CD, Burchett CO, Brennan-Ing M, Karpiak S, Zhu Y-S, et al. Links between inflammation, mood, and physical function among older adults with HIV. J Gerontol B Psychol Sci Soc Sci 2022;77:50–60.

30. Schnall R, Jia H, Reame N. Association between HIV symptom burden and inflammatory cytokines: an analysis by sex and menopause stage. J Womens Health (Larchmt) 2020;29:119–27.

31. Merlin JS, Westfall AO, Heath SL, Goodin BR, Stewart JC, Sorge RE, et al. IL-1β levels are associated with chronic multisite pain in people living with HIV. J Acquir immune Defic Syndr 2017;75:e99–e103.

32. Erenrich R, Seidel L, Brennan-Ing M, Karpiak S. HIV and aging in San Francisco: findings from the Research on Older Adults with HIV (ROAH) 2.0 San Francisco Study. 2018.

33. Wu AW, Revicki DA, Jacobson D, Malitz FE. Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). Qual Life Res 1997;6:481–93.

34. 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;10:77–84.

35. Boylan JM, Ryff CD. Varieties of anger and the inverse link between education and inflammation: toward an integrative framework. Psychosom Med 2013;75:566–74.

36. Gouin JP, Wrosch C, McGrath J, Booij L. Interpersonal capitalization moderates the associations of chronic caregiving stress and depression with inflammation. Psychoneuroendocrinology 2020;112:104509.

37. Margolick JB, Bream JH, Martínez-Maza O, Lopez J, Li X, Phair JP, et al. Frailty and circulating markers of inflammation in HIV+ and HIV− men in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr 2017;74:407–17.

38. Kallen M, Slotkin J, Griffith J, Magasi S, Salsman J, Nowinski C, et al. NIH Toolbox 4-Meter Walk Gait Speed Test Technical Manual. 2012. Available at: https://staging.healthmeasures.net/images/nihtoolbox/Technical_Manuals/Motor/Toolbox_4-Meter_Walk_Gait_Speed_Test_Technical_Manual.pdf. Accessed August 11, 2022.

39. Erlandson KM, Wu K, Koletar SL, Kalayjian RC, Ellis RJ, Taiwo B, et al. Association between frailty and components of the frailty phenotype with modifiable risk factors and antiretroviral therapy. J Infect Dis 2017;215:933–7.

40. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–57.

41. Justice AC, Freiberg MS, Tracy R, Kuller L, Tate JP, Goetz MB, et al. Does an index composed of clinical data reflect effects of inflammation, coagulation, and monocyte activation on mortality among those aging with HIV? Clin Infect Dis 2012;54:984–94.

42. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499–511.

43. Wilson SJ, Woody A, Kiecolt-Glaser JK. Inflammation as a biomarker method in lifespan developmental methodology. In B. Knight (Ed.), The Oxford Research Encyclopedia of Psychology and Aging. New York, NY: Oxford University Press; 2019.

44. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. New York, NY: Guilford Publications; 2017.

45. Uebelacker LA, Weisberg RB, Herman DS, Bailey GL, Pinkston-Camp MM, Stein MD. Chronic pain in HIV-infected patients: relationship to depression, substance use, and mental health and pain treatment. Pain Med 2015;16:1870–81.

46. Winer ES, Cervone D, Bryant J, McKinney C, Liu RT, Nadorff MR. Distinguishing mediational models and analyses in clinical psychology: atemporal associations do not imply causation. J Clin Psychol 2016;72:947–55.

47. Centers for Disease Control and Prevention. HIV Surveillance Report, 2018 (Updated). 2020;31. Available at: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed August 11, 2022.

48. Scher C, Meador L, Van Cleave JH, Reid MC. Moving beyond pain as the fifth vital sign and patient satisfaction scores to improve pain care in the 21st century. Pain Manag Nurs 2018;19:125–9.

49. Moore AA, Lake JE, Glasner S, Karlamangla A, Kuerbis A, Preciado D, et al. Establishing the feasibility, acceptability and preliminary efficacy of a multi-component behavioral intervention to reduce pain and substance use and improve physical performance in older persons living with HIV. J Subst Abuse Treat 2019;100:29–38.

50. Shields GS, Spahr CM, Slavich GM. Psychosocial interventions and immune system function: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 2020;77:1031–43.

51. Irwin MR, Olmstead R. Mitigating cellular inflammation in older adults: a randomized controlled trial of Tai Chi Chih. Am J Geriatr Psychiatry 2012;20:764–72.

52. Moore RC, Marquine MJ, Straus E, Depp CA, Moore DJ, Schiehser DM, et al. Predictors and barriers to mental health treatment utilization among older veterans living with HIV. Prim Care Companion CNS Disord 2017;19:10.4088/PCC.16m02059. doi:10.4088/PCC.16m02059.

53. Miller TR, Halkitis PN, Durvasula R. A biopsychosocial approach to managing HIV-related pain and associated substance abuse in older adults: a review. Ageing Int 2019;44:74–116.

54. Lazarus JV, Safreed-Harmon K, Barton SE, Costagliola D, Dedes N, del Amo Valero J, et al. Beyond viral suppression of HIV—the new quality of life frontier. BMC Med 2016;14:94.