



Physical Activity Intensity is Associated with Symptom Distress in the CNICS Cohort

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Abstract

Symptom distress remains a challenging aspect of living with HIV. Physical activity is a promising symptom management strategy, but its effect on symptom distress has not been examined in a large, longitudinal HIV-infected cohort. We hypothesized that higher physical activity intensity would be associated with reduced symptom distress. We included 5370 people living with HIV (PLHIV) who completed patient-reported assessments of symptom distress, physical activity, alcohol and substance use, and HIV medication adherence between 2005 and 2016. The most frequent and burdensome symptoms were fatigue (reported by 56%), insomnia (50%), pain (46%), sadness (45%), and anxiety (45%), with women experiencing more symptoms and more burdensome symptoms than men. After adjusting for age, sex, race, time, HIV medication adherence, alcohol and substance use, site, and HIV RNA, greater physical activity intensity was associated with lower symptom intensity. Although individual symptoms may be a barrier to physical activity (e.g. pain), the consistent association between symptoms with physical activity suggests that more intense physical activity could mitigate symptoms experienced by PLHIV.

Keywords HIV · Symptoms · Physical Activity · Pain

Resumen

La carga de síntomas sigue siendo un aspecto problemático para personas que viven con VIH. La actividad física es una prometedora estrategia de manejo, pero su efecto sobre la carga de síntomas no ha sido examinado en estudios grande longitudinales de cohortes. Nuestra hipótesis es que una mayor intensidad de actividad física puede estar asociada con una reducción de la carga de síntomas. En este estudio, incluimos 5.370 personas viviendo con VIH (PVV) que completaron cuestionarios estandarizados de carga de síntomas, actividad física, uso de alcohol y drogas, y adherencia a medicamentos entre 2005 y 2016. Los síntomas más frecuentes y con mayor impacto fueron cansancio (descrito por 56%), insomnio (50%), dolor (46%), tristeza (45%), y ansiedad (45%). Las mujeres describieron mayor número y mayor carga de síntomas que los hombres. Después de ajustar por edad, sexo, raza, tiempo, adherencia a antiretrovirales, uso de alcohol y drogas, sitio y carga viral, una mayor actividad física estuvo asociada con una menor intensidad de síntomas. Aunque algunos síntomas individuales pueden ser una barrera para la actividad física (como el dolor, por ejemplo), la consistente asociación entre síntomas y actividad física en nuestro estudio sugiere que una mayor intensidad de actividad física podría mitigar algunos de los síntomas que experimentan las PVV.

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Introduction

Despite effective antiretroviral therapy (ART), symptom distress remains a challenging aspect of living with HIV. Symptoms, the subjective phenomena indicating one's perception of a departure from normal function [1], are among the most important health indicators for patients and practitioners [2]. Prior to the current HIV medication era, common symptoms reported by people living with HIV (PLHIV) included

anxiety and respiratory, gastrointestinal, and neurological symptoms, related to opportunistic infections and HIV medications [3, 4]. As HIV has transitioned from an acute to chronic disease, HIV-associated symptoms have also transitioned from symptoms related to illness progression and poorly tolerated ART medications, to symptoms associated with low grade inflammation, accelerated aging, better tolerated ART, and age-related co-morbidities. Symptom distress among PLHIV varies by gender and race [5–7]. This symptom distress significantly impacts daily functioning and quality of life. Specific symptoms such as depression and fatigue are implicated as important drivers of poor ART adherence [8, 9], underscoring a need for effective and targeted symptom management interventions in this population [10–14].

With widespread use of better tolerated HIV medications, the types of symptoms have changed, but the burden has not. Wilson et al. [15] conducted a clinic-based study of 1885 PLHIV and found that 31% of respondents reported at least seven symptoms, among which poor sleep, muscle aches, fatigue, anxiety, and depression were the most frequent and bothersome symptoms [15]. Schnall et al. [14] administered an online survey to 769 PLHIV with self-reported comorbidities and found that over the previous month, PLHIV experienced an average of eight symptoms with fatigue, muscle aches, depression, anxiety, and sleeping difficulties being the most frequent [16].

Despite their common co-occurrence, symptom management strategies often only target one symptom at a time [14]. Pharmacological interventions can individually treat depression, anxiety, pain, insomnia, and lipodystrophy with varying degrees of success, but their use by PLHIV can be limited by pill burden, prioritization of HIV medication, cost, and side effects [17–19]. Non-pharmacological strategies are promising but there is less evidence examining their effectiveness in a large, diverse aging HIV population experiencing multiple symptoms. Van Luenen et al. [20] reviewed the effectiveness of psychosocial interventions (e.g., Cognitive Behavioral Therapy, relaxation, meditation) on mental health symptoms in PLHIV and found small positive effects of the interventions on depression and anxiety [20]. Recently, Schnall et al. [21] tested an mHealth video app that provided 143 different self-care strategies for 13 commonly experience symptoms among 80 PLHIV and found that it improved both symptoms and HIV medication adherence [21]. However, few symptom management strategies are as promising as physical activity.

Physical activity is any skeletal muscle movement that results in energy expenditure [22]. Physical activity has shown promise as a multi-symptom self-management strategy with which individuals with chronic diseases can combat symptoms [23, 24], and may be more tolerable than medications. In non-HIV infected populations, physical activity has been shown to reduce pain severity [25], depression [26],

and fatigue [27], and to improve cognitive function [28], with response to physical activity varying by sex. Of note, systematic reviews report mixed results for this relationship, citing small sample sizes, measurement issues and variable study quality [25, 27, 28].

Among PLHIV, physical activity has been associated with reduced depressive symptoms [29, 30], pain [31], fatigue [32], and less neurocognitive impairment [33]. However, these studies are limited by a small sample size, convenience sampling, and strict eligibility criteria that may not be representative of PLHIV in the United States today. The CNICS cohort overcomes many of these limitations by collecting standardized data (including symptom and physical activity measures) from over 32,000 PLHIV from eight HIV clinics around the United States. Data are collected annually, as part of patients' routine clinic visit, and are integrated with high-quality clinical data obtained directly from the electronic medical record. This approach has led to a large, diverse database of PLHIV that is representative of U.S. HIV epidemic and, due to clinic-based sampling, is less vulnerable to bias than studies employing convenient sampling. Therefore, using the CNICS cohort, the purpose of this study was twofold: (1) To describe symptom distress and physical activity in PLHIV by sex and to examine the relationship between physical activity and symptom distress, controlling for sex, age, race, health status (Veteran's Aging Cohort Study (VACS) Index) [34], and substance use in a large, longitudinal HIV-infected cohort. We hypothesized that higher intensity and frequency of physical activity would be associated with reduced symptom distress.

Symptom distress is influenced by personal, health, and environmental factors. This study was guided by the UCSF Symptom Management model which conceptualizes the relationships among these factors and one's symptom experience [35]. In particular, we used this model to help us identify and conceptualize the factors that may influence the relationship between physical activity and symptom distress in PLHIV. Based on this model, available literature, and the data available in the CNICS cohort, we will control for sex, age, race, health status (Veteran's Aging Cohort Study (VACS) Index), study site, substance use, and medication adherence [1, 16, 28, 35, 36].

Methods

Sample and Setting

This study used data collected between 2000 and 2016 from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS). CNICS is a national research network of eight centers of excellence for HIV care in the United States. CNICS collects and integrates longitudinal

demographic, clinical, and patient reported outcomes (PROs) data from over 32,000 people living with HIV [37]. Data collection, validation, and processing procedures are described elsewhere [37, 38].

For the current study, CNICS participants were eligible for inclusion if they were aged 18 years or older, prescribed HIV antiretroviral therapy, completed at least one patient-reported outcome assessment, and were not on hormone therapy. These data were collected from six HIV clinics (Fenway Community Health in Boston; University of Alabama Birmingham; University of California San Diego; University of California, San Francisco; University of North Carolina, Chapel Hill; and University of Washington). Participants completed PRO assessments approximately every 12 months on touch-screen tablets or computers at their routine HIV clinic appointments [38]. CNICS data collection was approved by the Institutional Review Boards at each site and the University Hospitals, Cleveland Medical Center IRB approved this study on October 17, 2016.

Measures

Demographic and clinical data needed to calculate the VACS index (i.e., age, CD4 T cell count, HIV Viral Load, Hemoglobin, FIB4, eGFR and Hepatitis C coinfection) were collected from the electronic medical record. FIB4 was calculated using the participant's aspartate aminotransferase, platelet count, and alanine aminotransferase. We used the CKD-EPI adult equation to calculate eGFR [38]. Clinical data (e.g., CD4 T cell count, HIV Viral load) were merged to the exact date of the PRO assessment.

Patient-Reported Outcomes

HIV Symptoms

Our dependent variable was symptom distress, which was assessed with the 20-item *HIV Symptom Index* [39]. This HIV-specific scale has been widely used and validated in PLHIV [15, 40]. It assesses the presence and intensity of 20 common symptoms reported by PLHIV (e.g., pain, anxiety, fatigue, weight gain) over the past 4 weeks. All symptoms are measured on a 0–4 ordinal scale where 0 is “I do not have the symptom” and 4 is “I have this symptom and it bothers me a lot”. Each symptom was analyzed as a single item. The reliability of the *HIV Symptom Index* in this sample was 0.92, indicating high reliability.

Physical Activity

Our primary independent variable was physical activity. Physical activity was assessed using three items from the five-item *Lipid Research Clinics Physical Activity*

Questionnaire [41]. This scale has previously been used in analyses of PLHIV and has been associated with depression and increased metabolic conditions in this population [42, 43]. For this analysis we included three questions, all pertaining to physical activity in the past month. The first question, “what was your highest level of physical activity” was answered with three categorical options, none, moderate, or vigorous. The second question, “did you regularly engage in strenuous exercise or hard physical labor” and the third, “Do you exercise or labor at least three times per week” were answered with dichotomous yes or no responses. They were analyzed as single items.

Additionally, we controlled for several factors shown to influence symptom frequency and intensity including HIV medication adherence and substance use.

HIV Medication Adherence was measured via a single visual analog scale, “Touch or click the point along the line that most closely reflects how much of your HIV medications you have taken in the past months”. A 0% indicates that the respondent took none of his or her HIV medications and 100% indicates he or she took all of them. Because the distribution of these responses was heavily skewed, with 75% of subjects reporting 95–100% medication adherence, this item was dichotomized at 95% and included in the analysis as a dichotomous covariate.

Lifetime Substance Use was assessed with the *Alcohol, Smoking and Substance Involvement Screening Test* (ASSIST) [44–46]. A summary variable, “In your life, have you ever used cocaine, opiates, amphetamines, or marijuana?” was created where 0 indicates no use, 1 indicates past use, and 2 indicates current use.

Statistical Analyses

To describe baseline demographic (age, race) and medical (T Cell Count, HIV medication adherence, VACS Index, and smoking) characteristics, symptom distress and physical activity by sex, we presented summary statistics, and performed bivariate analyses using Wilcoxon rank sum tests with continuity correction, Pearson Chi squared tests, and Fisher's exact tests, as appropriate. We used generalized linear mixed effects models to examine the relationship between symptom distress and physical activity. Each model included a random intercept and slope for each subject to address individual variabilities and random phenomenon of the outcome trajectories. As our symptom outcome variables were measured on an ordinal scale, we applied a proportional odds model (POM) for longitudinal ordinal response with a multinomial distribution and a cumulative probit link [47]. Based on hypotheses, known associations and potential confounders, the POM is a suitable model for studying association between ordinal longitudinal symptom distress outcomes and physical activity

variable. In addition to age, sex, race, HIV Viral Load, and study site, we also included VACS index, substance use and medication adherence as the explanatory variables in the POM model. These confounding covariates effectively control the variability in the outcome variables when we studied the association between symptom distress outcomes and physical activity.

We generated estimates for three physical activity variables. First, we estimated the association between highest level of physical activity in the past three months (none vs moderate; none vs. vigorous) and odds of experiencing a lower level of the symptom. Next, we estimated the association between strenuous exercise and odds of experiencing a lower level of the symptom. Finally, for those who engaged in strenuous exercise, we estimated the association between exercising at least three times per week and odds of experiencing a lower level of the symptom. We repeated the models for each of the five most prevalent and burdensome symptoms. We also examined the association between physical activity and the subsequent measure of symptom distress (baseline, 180 days after baseline and 360 days after baseline) using Spearman rank-order correlations.

Bonferroni adjusted, two-tailed p values < 0.01 were considered significant.

Results

Demographics

Between 2000 and 2016, 5370 PLHIV completed the patient reported outcomes and met our inclusion criteria. Demographic characteristics of the sample by sex are presented in Table 1. The mean age of participants at their first PRO assessment was 36.8 (± 10.1) years. Most were male (85%) and white (61%). Overall, participants completed a median of three PRO assessments with an average of 376 (± 355) days between assessments.

Physical Activity

Overall, participated engaged in a moderate level of physical activity (65%) with men engaging in more vigorous physical activity than women (26% vs. 10% $p < 0.001$).

Table 1 Demographic characteristics of the sample, by gender

Variable	Overall sample <i>n</i> = 5370	Men <i>n</i> = 4588	Women <i>n</i> = 782	<i>p</i> -value
Median age in years (Q1, Q3)	36 (29, 44)	36 (29, 43)	38 (30, 46)	$< 0.001^a$
Race ^b				$< 0.001^c$
White (%)	3181 (60.8)	2901 (65.0)	280 (36.3)	
Black (%)	1619 (30.9)	1178 (26.4)	441 (57.2)	
Asian/Pacific (%)	181 (3.5)	167 (3.7)	14 (1.8)	
American Indian (%)	58 (1.1)	46 (1.0)	12 (1.6)	
Multiracial (%)	44 (0.8)	42 (0.9)	2 (0.3)	
Hispanic (%)	762 (14.3)	681 (14.9)	81 (10.4)	$< 0.001^d$
Median years since first HIV clinic visit (Q1, Q3)	2.47 (0.40, 7.58)	1.90 (0.31, 6.18)	3.46 (0.61, 8.33)	0.92
Median CD4 + T cell (Q1, Q3)	364 (175, 547.75)	360 (177, 543)	384 (168, 575)	0.173 ^a
HIV viral load (% undetectable < 200)	291 (6.0)	251 (6.0)	40 (5.6)	0.682 ^d
Median medication adherence (Q1, Q3)	99 (94, 100)	99 (94, 100)	98 (90, 100)	$< 0.001^a$
Median VACS index (Q1, Q3)	18 (10, 33)	17 (7, 30)	27 (17, 40)	$< 0.001^a$
Median restricted VACS index (Q1, Q3)	21 (11, 35)	21 (11, 35)	21 (11, 35)	0.016 ^a
Smoking status				$< 0.001^d$
Current smoker (%)	2036 (38.1)	1716 (37.6)	320 (41.3)	
Past smoker (%)	1240 (23.2)	1124 (24.6)	116 (15.0)	
Never smoking (%)	2066 (38.7)	1727 (37.8)	339 (43.7)	
Drug use in the past three months (%) ^e	2085 (56.6)	1880 (57.5)	205 (50.3)	0.006 ^a
Past drug use (%)	3790 (74.1)	3290 (76.7)	418 (59.0)	$< 0.001^a$

^aThe p -values were obtained from Wilcoxon rank sum tests

^b5234 participants reported race

^cThe p -value was obtained from a Fisher's exact test

^dThe p -values were obtained from Pearson Chi Square Tests

^eAt baseline only 3670 (3271 men and 408 women) completed the current drug use question on the ASSIST

Approximately one-third (34%) of participants engaged in strenuous activity and slightly fewer (31%) engaged in strenuous activity at least three times a week. Men engaged in more strenuous physical activity than women (36% vs. 20%, $p < 0.001$) and more regular strenuous physical activity (33% vs. 20%, $p < 0.001$) (Table 2).

Symptom Distress

Participants reported a high symptom burden (Table 3). Overall, PLHIV reported a median of 7 symptoms (Q1: 3, Q4: 12) with at least 1 symptom (0, 5) bothering them a

lot over the past month. Almost one-third of participants (32.5%) reported at least four symptoms that bothered them a lot. On average, women reported more symptoms than men (8 vs. 7, $p = 0.005$) and more highly burdensome symptoms (2 vs. 1, $p < 0.001$). The most frequent and bothersome symptoms were fatigue (reported by 55.5%), insomnia (50.4%), pain (muscle aches/joint pain) (45.9%), depression (sadness) (45.2%) and anxiety (45.2%). There were variations by sex with women reporting more pain and neuropathy than men. We focused the analyses examining the relationship of physical activity and symptom distress on these five prevalent, burdensome symptoms.

Table 2 Physical activity at baseline, by gender

	Overall sample	Men	Women	<i>p</i> -value
Median number of physical activity assessments (Q1, Q3)	3 (1, 5)	3 (1, 5)	3 (1, 7)	0.157 ^a
Mean days between the physical activity assessments	380.9 (301.5)	376.5 (286.2)	406.7 (379.2)	0.468 ^a
Highest level of physical activity				<0.001 ^b
None (%)	608 (11.3)	476 (10.4)	132 (16.9)	
Moderate (%)	3488 (65.1)	2922 (63.8)	566 (72.7)	
Vigorous (%)	1262 (23.6)	1181 (25.8)	81 (10.4)	
Engage in regular strenuous exercise (%)	1814 (34.0)	1658 (36.3)	156 (20.1)	<0.001 ^b
Exercise regular strenuous exercise ≥ 3 times per week (%)	1622 (30.5)	1498 (33.0)	153 (20.0)	<0.001 ^b

^aThe *p*-values were obtained from Wilcoxon rank sum tests

^bThe *p*-values were obtained from Pearson Chi Square Tests

Table 3 Symptom characteristics, by gender

	Overall sample	Men	Women	<i>p</i> -value
Median number of symptom assessments (Q1, Q3)	3 (2, 6)	3 (2, 6)	3 (2, 7)	0.014 ^a
Mean days between the symptom assessments	376.6 (355.3)	367.6 (323.2)	429.0 (500.1)	0.413 ^a
Median number of symptoms 2 or higher (Q1, Q3)	7 (3, 12)	7 (3, 12)	8 (3, 13)	0.005 ^a
Median number of symptoms 4 or higher (Q1, Q3)	1 (0, 5)	1 (0, 4)	2 (0, 7)	<0.001 ^a
Participants reporting ≥ 4 symptoms with the level ≥ 4 (most burdensome) (%)	1744 (32.5)	1414 (30.8)	330 (42.2)	<0.001 ^b
Most frequent symptoms over time				
Top reported symptom	Fatigue: 12,190 (55.5%)	Fatigue: 10,145 (55.1%)	Fatigue: 2045 (57.3%)	
Second most frequent reported symptom	Insomnia: 11,079 (50.4%)	Insomnia: 9244 (50.3%)	Pain: 1930 (54.0%)	
Third most frequent reported symptom	Pain: 10,093 (45.9%)	Anxiety: 8385 (45.6%)	Insomnia: 1835 (51.4%)	
Fourth most frequent reported symptom	Sadness: 9931 (45.2%)	Sadness: 8322 (45.2%)	Sadness: 1609 (45.1%)	
Fifth most frequent reported symptom	Anxiety: 9925 (45.2%)	Pain: 8163 (44.4%)	Neuropathy: 1585 (44.4%)	
Most bothersome symptom at baseline (> 4)				
Most Bothersome Symptom	Fatigue: 5334 (24.3%)	Fatigue: 4294 (23.3%)	Pain: 1204 (33.7%)	
Second most bothersome symptom	Insomnia: 5173 (23.5%)	Insomnia: 4107 (22.3%)	Insomnia: 1066 (29.9%)	
Third most bothersome symptom	Pain: 4843 (22.0%)	Pain: 3639 (19.8%)	Fatigue: 1040 (29.1%)	
Fourth most bothersome symptom	Anxiety: 4058 (18.5%)	Anxiety: 3276 (17.8%)	Neuropathy: 862 (24.1%)	
Fifth most bothersome symptom	Sadness: 3872 (17.6%)	Sadness: 3151 (17.1%)	Anxiety: 782 (21.9%)	

^aThe *p*-values were obtained from Wilcoxon rank sum tests

^bThe *p*-values were obtained from Pearson Chi Square Tests

Association of Physical Activity and Symptom Distress

Controlling for age, sex, race, HIV viral load, study site, substance use, and medication adherence, we found that increased physical activity was associated with reduced symptom distress for fatigue, insomnia, pain, depression, and anxiety ($p < 0.001$) and that this relationship strengthened as physical activity intensity increased. For example, physically inactive participants were twice as likely to experience more burdensome fatigue compared to those who engaged moderate physical exercise (OR = 2.22 [95% CI 1.92, 2.57]), and almost five times as likely when compared to those who engaged in vigorous exercise (OR = 4.69 [95% CI 3.92, 5.61]). We observed similar responses across symptoms (Table 4). Participants reporting that they did not regularly engage in strenuous exercise or hard physical labor were also more likely to have to have more burdensome symptoms (OR range: 1.49–2.03, $p < 0.001$). However, those who did not exercise at least three times a week were more likely to experience more burdensome fatigue and insomnia (OR = 1.74 [95% CI 1.33, 2.27] and 1.41 [95% CI 1.07, 1.86], respectively), compared to those who did exercise at least three times a week. There were no other associations between regular physical activity and symptom intensity. We further examined the effect of the health status (VACS index) on these relationships and found that it did not modify the relationship between physical activity intensity and symptom intensity; we excluded it from the final model.

The correlation coefficients between physical activity and subsequent symptom intensity were similar to when both variables were measured at the same visit (Supplemental Table 1). The correlations were slightly stronger when the measures were taken less than 6 months apart and may suggest that physical activity is more strongly associated with subsequent symptom intensity than with current symptom intensity.

Discussion

Our results demonstrated that PLHIV experience a high symptom distress with women experiencing both more symptoms and more burdensome symptoms. Additionally, we found that increased physical activity was associated with reduced symptom distress for the most frequent symptoms and that this relationship strengthened as physical activity intensity increased. These findings suggest that symptom management continues to be an unresolved and important clinical issue for PLHIV and that physical activity may be a useful component of a treatment strategy. It is possible that despite increasing age and multimorbidity, PLHIV can reduce their symptom burden by increasing physical activity intensity.

Physical activity can improve symptoms through several pathways, but among PLHIV its anti-inflammatory effects are likely significant. Physical activity can reduce inflammation that is often associated with fatigue, sleep disturbances, pain and depression in many populations. Regular moderate-to-vigorous physical activity can directly inhibit inflammation pathways by increasing anti-inflammatory myokines and reducing inflammatory adipose tissue [48, 49]. This results in lower levels of circulating inflammatory cytokines such as CRP, TNF α and IL-1 β [48, 50, 51]. These cytokines can signal the central nervous system and result in increased fatigue [52], depression [53], and pain [54, 55]. Physical activity is likely an effective symptom management strategy but to move it beyond a blunt tool and to developed targeted physical activity prescriptions, it is critical to understand the mechanism by which it works in PLHIV. To do so, well-designed experimental studies to examine the potential mediating effect of inflammation on the relationship between physical activity and symptoms are needed.

In examining symptom distress, our data confirm an ongoing shift in symptoms related to improved HIV treatment. Today, fatigue is the most prevalent and burdensome symptom followed by insomnia, pain, and depression, in contrast to the respiratory, gastrointestinal, and neurological symptoms experienced in an

Table 4 Estimated odds ratio of the association between physical activity and symptom distress after adjusting for age, sex, race, time, HIV medication adherence, alcohol and drug use, study site, and HIV viral load

Reduced Symptom Intensity	Physical activity intensity ($n = 5311$)				Strenuous exercise (Yes vs. No) ($n = 5310$)		Exercise or labor 3 times a week (Yes vs. No) ($n = 5310$)	
	Moderate vs. None		Vigorous vs. None		OR (95% CI)	p -value	OR (95% CI)	p -value
	OR (95% CI)	p -value	OR (95% CI)	p -value				
Fatigue	2.22 (1.92, 2.57)	<0.001	4.69 (3.92, 5.61)	<0.001	2.03 (1.81, 2.26)	<0.001	1.74 (1.33, 2.27)	<0.001
Insomnia	1.71 (1.47, 1.98)	<0.001	2.93 (2.44, 3.52)	<0.001	1.49 (1.33, 1.67)	<0.001	1.41 (1.07, 1.86)	0.014
Pain	1.58 (1.35, 1.85)	<0.001	2.23 (1.94, 2.81)	<0.001	1.48 (1.31, 1.67)	<0.001	1.04 (0.78, 1.39)	0.768
Depression	1.90 (1.62, 2.22)	<0.001	3.18 (2.62, 3.86)	<0.001	1.76 (1.56, 1.99)	<0.001	1.26 (0.92, 1.72)	0.143
Anxious	1.72 (1.46, 2.01)	<0.001	2.71 (2.23, 3.30)	<0.001	1.62 (1.43, 1.83)	<0.001	1.13 (0.84, 1.54)	0.417

Odds Ratio (OR) = $\exp(\beta)$

earlier era. Further, there are significant differences in the symptom experience by sex. Women experience more symptoms and more burdensome symptoms compared to men. While both men and women report fatigue as their most frequent symptom, women report more pain and neuropathy than men. They also report much more burdensome pain. This is in contrast to recent research by Wilson et al. [15] who did not find any differences in symptoms by sex [15]. Sex differences in symptom distress are poorly understood and warrant more research, in particular to understand the how sex hormones interact with inflammation to alter the symptom experience [56].

There are several implications of these findings. Symptoms are under-treated in this population. For example, in our clinic-based sample of over 5000 PLHIV 25% of the sample reported that they had fatigue and that it bothered them a lot. Additionally, one-third of women reported that they were experiencing pain and that it bothered them a lot. This may be because we lack effective symptom management strategies for this population or because symptoms are under-recognized in this population. To start to reduce these staggering symptoms, they should be systemically screened and tracked in all PLHIV. As in the CNICS sites, these data can inform the patient's medical visit and guide the patient-provider interaction. Further, such data can help develop a repertoire of symptom-management interventions that can be studied, tailored, and shared among clinics. The effectiveness of these interventions will vary by a number of factors including sex, age, employment status, substance use and pooling data on them and their outcomes can help to more efficiently reduce burdensome symptoms in this population.

Finally, these data confirm the relationship between physical activity intensity and symptom distress in PLHIV. Physical activity, in particular intense, regular exercise could help many, but not all, of the prevalent symptoms experienced by PLHIV. Reduced fatigue and insomnia were consistently associated with higher intensity activity at least three times per week. These results are similar to those observed in those with, or survivors of, cancer. Higher intensity exercise training reduces cancer-related fatigue [57] and in a recent clinical trial Adlard et al. found that regular, higher intensity physical activity significantly reduced fatigue more than regular moderate intensity physical activity in cancer survivors [58]. Similar results have been found in those with multiple sclerosis [59] and together these data suggest that further study into the effect of different types and intensities of physical activity in this population is needed.

Our study has many strengths including a large, heterogeneous sample representative of those in HIV care in the U.S. today, longitudinal data collection, and controlling for the potential modifying effect of health status (VACS index) on the relationship between physical activity and symptom distress. However, our study has several limitations that should be considered. First, we used a self-report, retrospective measure of physical activity which may have been limited by recall or

social desirability biases. To overcome this limitation, objective measures of physical activity such as accelerometry can be used. Second, the sample was predominantly male and had a young average age at baseline. To control for the effect of sex and age on the relationship between symptom intensity and physical activity, we included both age and sex in our proportional odds models. Third, the symptom and physical activity measures were collected simultaneously on a roughly annual basis, making it hard to examine if physical activity preceded symptom changes. We attempted to overcome this limitation by examining the correlation of physical activity on subsequent symptom distress. However, since not all participants completed subsequent measures < 180 days later, we cannot be certain that physical activity precedes changes in symptoms. Similarly, our analysis is a blunt, first step in trying to understand if and how physical activity improves symptom distress in this highly symptomatic population. While we demonstrate a clear association and start to provide evidence on the sequence, much more research is needed examining this relationship and the mechanisms underpinning this relationship, perhaps using a symptom cluster approach [60, 61]. Demonstrating a causal effect of physical activity on decreased symptom burden, however, will require rigorously timed and objective, rather than self-reported, assessments of physical activity together with equally controlled evaluations of subsequent symptom burden. This should be followed by interventional, randomized trials to demonstrate and quantify the potential therapeutic effect of physical activity on symptom distress in this population. Given the high burden, distress, and consequences of unaddressed symptoms in PLHIV, such research is clearly justified.

Conclusions

PLHIV continue to experience a high symptom distress with women experiencing more distress than men. However, there is little evidence on the mechanisms underpinning the high symptom distress or on interventions to reduce it in this population. We conducted this study to understand if a critical non-pharmacological intervention, physical activity, is associated with reduced symptom distress in large, representative, national cohort of PLHIV. We found that physical activity was consistently associated with lower symptom intensity suggesting it can help mitigate the symptoms experienced by PLHIV. These findings highlight physical activity as a promising strategy to start to explore in understanding the mechanisms underlying increased symptom burden among PLHIV.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no potential conflicts of interest that could influence or bias the material in this manuscript.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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