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Authors

Wilson, Natalie L
Hoffman, Thomas J
Heath, Sonya L
et al.

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Original Article

HIV Symptom Clusters are Similar Using the Dimensions of Symptom Occurrence and Distress

Natalie L. Wilson, PhD, DNP, MPH, Thomas J. Hoffman, PhD, Sonya L. Heath, MD, Michael S. Saag, MD, and Christine Miaskowski, RN, PhD

Department of Community Health Systems (N.L.W.), School of Nursing, University of California, San Francisco, California, USA; Department of Epidemiology and Biostatistics (T.J.H.), School of Medicine, University of California, San Francisco, California, USA; Division of Infectious Diseases (S.L.H., M.S.G.), School of Medicine, University of Alabama, Birmingham, Alabama, USA; Department of Physiological Nursing (C.M.), School of Nursing, University of California, San Francisco, California, USA

Abstract

Context. People living with HIV infection (PLWH) in the United States continue to experience a high symptom burden despite improvements in antiretroviral therapy.

Objectives. The purpose of this study was to determine if the number and types of symptom clusters differed based on whether symptom occurrence rates or distress ratings were used to create the clusters.

Methods. Data from 2,000 patients with complete symptom occurrence rates and distress scores on the 20-item HIV Symptom Index from their first ambulatory clinic visit at one of six national HIV centers of excellence in the Center for AIDS Research Network of Integrated Clinical Systems were used in these analyses. Exploratory factor analysis was used to create the symptom clusters.

Results. The same four symptom clusters (i.e., gastrointestinal, psychological, pain, body image) were identified using occurrence rates and distress ratings. For both dimensions of the symptom experience, the psychological, pain, and body image clusters each had the same symptoms. For the gastrointestinal cluster, four symptoms loaded on the occurrence dimension and six symptoms loaded on the distress dimension.

Conclusion. The number and types of symptom clusters were relatively similar across the occurrence and distress dimensions of the symptom experience. Symptom clusters in PLWH may provide insights into the development of targeted interventions for multiple co-occurring symptoms. J Pain Symptom Manage 2022;63:943–952.

Key Words

Symptoms, symptom clusters, exploratory factor analysis, HIV, occurrence, distress, HIV Symptom Index

Key Message

HIV symptoms experienced by patients living with HIV infection co-occur together in clusters. The number and types of symptom clusters are relatively similar and consistent when measured by the dimensions of occurrence and distress in patients living with HIV infection.

Introduction

Over the past 40 years, HIV disease has transitioned to a chronic and manageable condition. Despite the shift in preferred antiretroviral therapy (ART) to integrase inhibitors, approximately 70% of the 1.2 million people living with HIV infection (PLWH) experience a relatively high symptom burden associated with the disease itself and/or its treatments.[1–4] Unrelieved

Address correspondence to: Natalie L. Wilson, PhD, DNP, MPH, Department of Community Health Systems, School of Nursing, University of California, 2 Koret Way – N531, San Francisco, CA 94143, USA. E-mail: natalie.wilson@ucsf.edu

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symptoms can decrease patients' adherence with ART and result in decrements in quality of life.[5]

A new and emerging area of symptom science research is the evaluation of symptom clusters.[6] A symptom cluster is defined as "two or more symptoms that are related to each other, occur together, composed of stable groups of symptoms, are independent of other clusters, and may reveal specific underlying dimensions of symptoms."[7] An underlying rationale for this line of scientific inquiry is that symptoms that cluster together may share a common etiology or mechanism(s).[6,8]

As noted in an expert panel report,[6] the majority of symptom cluster research was conducted in oncology patients. This panel noted that to advance this area of scientific inquiry, research is needed on the types of symptom clusters associated with other chronic medical conditions. As noted in a recent systematic review,[9] only 13 studies have evaluated for "symptom clusters" in PLWH. Two of these studies were done pre-ART;[10,11] one evaluated only depressive symptoms;[12] one evaluated for changes over time in a pre-specified symptom cluster (i.e., muscle aches, numbness of feet/toes, and fatigue);[13] and three evaluated for subgroups of patients with distinct symptom profiles.[14–16]

Of the six remaining studies,[4,17–21] the assessment instruments and dimensions of the symptom experience that were used to create the symptom clusters, *de novo*, were variable. In terms of instruments, three studies used English[17,18] or Chinese[19] versions of the Sign and Symptom Checklist for Persons with HIV disease with 26 to 42 symptom severity ratings included in the analysis. In another study,[20] the severity of 27 symptoms was evaluated using an investigator-developed tool. The remaining two studies evaluated for symptom clusters using distress ratings for the 20 items on the HIV Symptom Index.[4,21] All six of these studies used principal components analysis to create the symptom clusters. Significant variability was found in the number of items (i.e., symptoms) and dimensions used to create symptom clusters *de novo*, across these studies in PLWH.[4,17–21] Therefore, the number of symptom clusters identified ranged from two[4] to 11.[18] The most common symptom cluster identified across four of these six studies was a gastrointestinal cluster.[17–19,21]

Given that PLWH present with multiple co-occurring symptoms, additional research on symptoms clusters is warranted. As noted by the expert panel convened by the National Institute of Nursing Research,[6] studies are needed to determine if symptom clusters differ depending on the dimension of the symptom experience that is evaluated (e.g., occurrence versus distress) across a variety of chronic conditions. In addition, based on an evaluation of the numerous symptom clusters studies done in oncology patients,[22] the recommended analytic approach to create symptom clusters is exploratory factor analysis (EFA). Given that none of the previous studies used EFA to identify symptom clusters in PLWH, as well as the paucity of research on this topic, the purpose of this study was to determine if the number and types of symptom clusters differed based on whether symptom occurrence rates or distress ratings were used to create the clusters. Based on previous studies of oncology patients,[23–25] we hypothesized that the number and types of symptom clusters would be similar using the dimensions of occurrence and distress.

Methods

Patients and Settings

This study is a cross-sectional analysis of data collected from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) between 2015 and 2018. CNICS is a national research network of eight HIV clinics across the United States.[26] Patients (n = 2,000) from six CNICS sites who had complete symptom data were included in this analysis.

Study Procedures

The study was considered exempt by the University of California, San Francisco Institutional Review Board (IRB). The CNICS parent study collected and integrated longitudinal demographic, clinical, and patient-reported outcomes data from over 33,000 PLWH. Each CNICS site obtained IRB approval for data collection. Written informed consent was obtained from all patients. Demographic and symptom data used for these analyses were obtained during the patients' first clinic visit between 2015 and 2018. Clinical data were obtained within 180 days of the patients' initial clinic visit. Clinical data were considered missing if the report was >180 days before or after the completion of the HIV Symptom Index.

Instrument

The 20-item HIV Symptom Index evaluates the occurrence and distress of 20 common symptoms that occurred over the past four weeks.[27] Patients rated each symptom using a 0 to 4 Likert scale. The validity and reliability of the HIV Symptom Index is well established in studies of outpatients living with HIV infection.[27]

Data Analyses

All statistical analyses were conducted using the Statistical Package for the Social Sciences version 27 (IBM Corporation, Armonk, NY) and R version 3.3.2.[28] Descriptive statistics and frequency distributions were calculated for all of the demographic and clinical characteristics, as well as for the ratings of symptom

occurrence and distress. All 20 symptoms from the HIV Symptom Index were used in the EFAs.

Creation of Symptom Clusters

EFAs were done for the dichotomous (i.e., occurrence) and ordinal (i.e., distress) items in R.[29] While it is more common to describe the results of an EFA as "factors," the "factors" for this study are referred to as symptom clusters. Factor loadings were considered meaningful if they were ≥0.40.[30] In addition, factors (i.e., symptom clusters) were considered to be adequately defined if at least two items had loadings of ≥0.40. While it is common to require that each item load strongly on only one factor, items that cross-loaded on two factors were allowed if the symptom fell within our pre-set criteria of ≥0.40. These items were retained and used to define both factors (i.e., symptom clusters). The cross loading of symptoms on more than one factor may be beneficial in the interpretation of potential causal mechanism(s) underlying a symptom cluster.[6,31]

For the EFA using the dichotomous symptom occurrence responses (i.e., had versus did not have the symptom) or the ordinal distress ratings, we constructed the correlation matrix using polychoric correlations with the R package polycor v0.7-10.[32,33] The Kaiser-Meyer-Olkin test, using the R package psych v1.9.2,[34] was a high .93 for occurrence and .94 for distress, indicating our data were well-suited for EFA. The simple structure for the occurrence and distress EFAs were estimated using the method of unweighted least squares with geomin (i.e., oblique) rotation.[31,32] Oblique rotation allows factors to be correlated, as is likely true for associations in the population.[32,35] This rotational method provided an improved representation of how the factors were correlated and improved the interpretability of each factor solution.

The EFA for distress was done using distress ratings that included a zero (i.e., 0, 1, 2, 3, 4). If a patient indicated that s/he did not have the symptom (i.e., occurrence), a distress score of zero was selected. Factor solutions were estimated for two through seven factors. After examining all of the solutions, the factor solution with the greatest interpretability and clinical meaningfulness was selected, given that it met the criteria set for evaluating simple structure (i.e., size of item loadings, number of items on a factor). The four factor solution was preferred for both symptom dimensions because of the leveling off of the eigen values on the scree plot and having a simple structure of at least two items (i.e., symptoms) per factor with loadings of ≥0.40. Then, each factor solution was examined to determine a clinically appropriate name for the symptom cluster. The name of the symptom cluster was based on the majority of the symptoms in the cluster.

Differences in Number and Types of Symptom Clusters

We used the criteria proposed by Kirkova and Walsh to evaluate the agreement among the symptoms within the same cluster using occurrence and distress ratings.[36] Kirkova and Walsh suggested that to achieve agreement with each other, at least 75% of the symptoms in the cluster should be present and include the most prominent and important symptom, namely the symptom with the greatest weight from the factor analyses.

Results

Sample Characteristics

Of the total sample of 2,000, 82.9% identified as male, 86.8% reported assigned male at birth, 1.8% identified as transgender, 68.0% were Caucasian, and their mean age was 46.0 (±11.7) years. Over half of the patients (63.0%) had a CD4 count of >500 cells/mm^3 (mean 628 (±333) cells/mm^3), 13.7% had Hepatitis C, 45.6% were ART naïve, and 76.0% were prescribed an integrase-inhibitor based regimen (Table 1).

Symptom Occurrence and Distress

Mean number of symptoms was 9.7 (±5.4, range 2−20). Occurrence rates and distress ratings for each of the symptoms are listed in Table 2. Symptoms with the highest occurrence rates were fatigue or loss of energy; difficulty falling or staying asleep; muscle aches or joint paint; felt sad, down or depressed; and felt nervous and anxious. Symptoms with the highest distress ratings were: fatigue or loss of energy; difficulty falling or staying asleep; muscle aches or joint pain; pain and numbness or tingling in the hands or feet; changes in the way your body looks such as fat deposits or weight gain; problems with having sex; and feeling sad, down, and depressed.

Symptom Clusters Based on Occurrence or Distress

Four symptom clusters were identified using occurrence rates (Table 3). Factor 1, with four symptoms, was named the gastrointestinal cluster. Factor 2, with four symptoms, was named the psychological cluster. Factor 3, with three symptoms, was named the pain cluster. Factor 4, with four symptoms, was named the body image cluster.

Four clusters were identified using distress ratings (Table 4). Factor 1, with 6 symptoms was named the gastrointestinal cluster. Factor 2, with four symptoms, was named the psychological cluster. Factor 3, with three symptoms, was named the pain cluster. Factor 4, with four symptoms, was named the body image cluster.

Similarities and Differences in the Number and Types of Symptom Clusters

Four symptom clusters were identified using the two symptom dimensions of occurrence and distress

Table 1
Demographic and Clinical Characteristics ($n = 2000$)

Characteristic	*n*	%
Age (years) mean = 46.0 (±11.7)		
18–24	32	1.6
25–34	385	19.3
35–44	432	21.6
45–54	637	31.9
55–64	422	21.1
65–83	92	4.6
Birth sex		
Male	1637	86.8
Female	249	13.2
Gender		
Man	1294	82.9
Woman	239	15.3
Transgender	28	1.8
Race		
Caucasian	1330	68.0
African American	478	24.4
American Indian	30	1.5
Asian Pacific Islander	64	3.3
Other/Unknown	54	2.8
Ethnicity		
Hispanic	366	20.3
Non-Hispanic	1437	79.7
Risk factors		
Heterosexual	381	19.3
Men who have sex with men	1314	66.5
Intravenous drug use	93	4.7
Men who have sex with men and intravenous drug use	130	6.6
Other	57	2.9
Unknown	25	1.3
Insurance		
Private	469	23.5
Public	830	41.5
Uninsured	281	14.1
Ryan-White	128	6.4
Site		
Case Western Reserve University	166	8.3
Fenway	272	13.6
University of Alabama at Birmingham	116	5.8
University of California, San Diego	731	36.6
University of North Carolina	248	12.4
University of Washington	467	23.4
Antiretroviral therapy naïve (% yes)	912	45.6
Antiretroviral therapy class		
Integrase-inhibitor based regimen	1453	76.0
Non-nucleoside reverse transcriptase inhibitors	268	14.0
Other	191	10.0
CD4 Count in cells/mm^3 $n = 1481$		
Mean = 628 (±333)	126	8.5
≤200		
201–500	422	28.5
>500	933	63.0
Viral Load in copies/mL $n = 607$		
Range [19–502,700]		
<50	523	86.2
51 to ≤200	21	3.5
201 to ≤499	8	1.3
500 to ≤10,000	19	3.1
>10,000	36	5.9
Hepatitis C (% yes)	273	13.7

Abbreviations: mm^3 = millimeter cubed; mL = milliliter.

Table 2
Rank Order of Symptom Occurrence and Distress Ratings (n = 2,000)

		Occurrence	Distress[a]		
Rank	Symptom	%	Mean	SD	Rank
1	Fatigue or loss of energy	73.8	2.48	1.00	1
2	Difficulty falling or staying asleep	68.3	2.47	1.04	2
3	Muscle aches or joint pain	62.7	2.47	1.04	2
4	Felt sad, down, or depressed	60.7	2.36	1.02	5
5	Felt nervous or anxious	59.7	2.35	1.01	6
6	Trouble remembering	54.2	2.27	1.00	8
7	Pain, numbness or tingling in the hands or feet	53.4	2.45	1.03	3
8	Changes in the way your body looks such as fat deposits or weight gain	52.6	2.43	1.08	4
9	Problems with having sex, such as loss of interest or lack of satisfaction	49.1	2.43	1.11	4
10	Headache	48.5	2.15	0.97	12
11	Bloating, pain, or gas in stomach	48.3	2.25	0.99	10
12	Skin problems, such as rash, dryness, or itching	45.5	2.26	1.00	9
13	Diarrhea or loose bowel movements	45.4	2.13	1.01	13
14	Feeling dizzy or lightheaded	42.7	2.10	0.91	16
15	Cough or trouble catching your breath	40.2	2.11	0.99	15
16	Loss of appetite or change in the taste of food	36.3	2.16	1.02	11
17	Fever, chills, or sweats	34.1	2.16	0.96	11
18	Hair loss or changes in the way your hair looks	32.6	2.12	1.08	14
19	Problems with weight loss or wasting	31.5	2.33	1.10	7
20	Nausea or vomiting	27.3	2.04	0.94	17

Abbreviation: SD = standard deviation.
[a]Mean distress ratings were calculated based on the patients who reported the occurrence of the symptom on the following scale: 1 = I have this symptom and it does not bother me; 2 = I have this symptom and it bothers me a little; 3 = I have this symptom and it bothers me; or 4 = I have this symptom and it bothers me a lot.

(Table 5). Regardless of the dimension used, the psychological, pain, and body image clusters had the identical number and types of symptoms in the cluster. In terms of the gastrointestinal cluster, four symptoms were included in this cluster for both dimensions (i.e., nausea or vomiting; diarrhea or loose bowel movements; loss of appetite or change in the way food tastes; and fever, chills, or sweats). For the distress dimension, two additional symptoms were included in the gastrointestinal cluster (i.e., feeling dizzy or lightheaded; headache). Specific symptoms within each cluster were relatively similar between the occurrence and distress dimensions with three of the four clusters having 100.0% agreement.

Discussion

This study is the first to evaluate for differences in the number and types of symptom clusters using ratings of occurrence and distress from the HIV Symptom Index. Consistent with our *a priori* hypothesis and congruent with studies of oncology patients,[24,25,37] the symptom clusters identified were relatively similar

Table 3
Exploratory Factory Analysis Using Ratings of Symptom Occurrence

	Factor 1	Factor 2	Factor 3	Factor 4
Symptom	Gastrointestinal Cluster	Psychological Cluster	Pain Cluster	Body Image Cluster
Nausea or vomiting	**0.888**[a]	0.018	-0.163	-0.144
Diarrhea or loose bowel movements	**0.599**[a]	0.028	-0.105	0.028
Loss of appetite or a change in the taste of food	**0.506**[a]	0.091	-0.033	0.128
Fever, chills, or sweats	**0.496**[a]	-0.075	0.245	-0.071
Felt nervous or anxious	0.067	**0.779**[a]	-0.178	-0.004
Felt sad, down, or depressed	-0.007	**0.750**[a]	-0.082	0.008
Difficulty falling or staying asleep	0.048	**0.465**[a]	0.066	-0.032
Fatigue or loss of energy	-0.067	**0.460**[a]	0.235	-0.041
Pain, numbness or tingling in the hands or feet	-0.093	-0.066	**0.775**[a]	0.025
Muscle aches or joint pain	-0.049	0.005	**0.593**[a]	0.075
Feeling dizzy or lightheaded	0.334	0.042	**0.477**[a]	-0.134
Changes in the way your body looks such as fat deposits or weight gain	-0.186	-0.033	0.067	**0.686**[a]
Problems with weight loss or wasting	0.210	-0.095	-0.030	**0.515**[a]
Hair loss or changes in the way your hair looks	0.156	-0.043	-0.023	**0.490**[a]
Problems with having sex, such as loss of interest or lack of satisfaction	-0.073	0.187	-0.029	**0.467**[a]
Trouble remembering	0.074	0.320	0.150	0.073
Skin problems, such as rash, dryness, or itching	0.289	0.032	0.122	0.105
Headache	0.332	0.020	0.218	-0.029
Bloating, pain, or gas in your stomach	0.349	0.004	0.124	0.187
Cough or trouble catching your breath	0.397	0.039	0.120	0.102
Total number of symptoms in the cluster	4	4	3	4

Extraction method: Unweighted least squares. Rotation method: Promax oblique rotation.
[a]Factor loadings ≥ 0.4 are in **bold**. Items were allowed to load on more than on factor.

across the two dimensions of the symptom experience. In the two previous studies that used the HIV Symptom Index with relatively large sample sizes,[4,21] two or three symptom clusters were identified using PCA (i.e., physical and psychological;[4] and psychological and neurological, gastrointestinal and flu-like, and physical changes in body appearance[21]). Of note, the "psychological" cluster, that included felt sad, down, or

Table 4
Exploratory Factory Analysis Using Ratings of Symptom Distress

Symptom	Factor 1	Factor 2	Factor 3	Factor 4
	Gastrointestinal Cluster	Psychological Cluster	Pain Cluster	Body Image Cluster
Nausea or vomiting	**0.885**[a]	0.014	-0.133	-0.163
Diarrhea or loose bowel movements	**0.617**[a]	0.068	-0.181	0.079
Loss of appetite or a change in the taste of food	**0.582**[a]	0.077	-0.079	0.140
Fever, chills, or sweats	**0.558**[a]	-0.032	0.168	-0.081
Feeling dizzy or lightheaded	**0.416**[a]	0.038	**0.410**[a]	-0.114
Headache	**0.408**[a]	0.010	0.217	-0.044
Felt sad, down, or depressed	-0.050	**0.889**[a]	-0.086	0.021
Felt nervous or anxious	0.085	**0.877**[a]	-0.139	-0.081
Fatigue or loss of energy	0.013	**0.451**[a]	0.289	0.051
Difficulty falling or staying asleep	0.153	**0.437**[a]	0.116	-0.050
Pain, numbness or tingling in the hands or feet	-0.083	-0.064	**0.819**[a]	-0.009
Muscle aches or joint pain	-0.069	-0.018	**0.722**[a]	0.067
Problems with having sex, such as loss of interest or lack of satisfaction	-0.086	0.250	-0.013	**0.427**[a]
Changes in the way your body looks such as fat deposits or weight gain	-0.211	0.012	0.022	**0.762**[a]
Problems with weight loss or wasting	0.200	-0.102	-0.070	**0.551**[a]
Hair loss or changes in the way your hair looks	0.059	-0.056	0.051	**0.482**[a]
Trouble remembering	0.063	0.346	0.184	0.090
Skin problems, such as rash, dryness, or itching	0.254	-0.014	0.121	0.195
Cough or trouble catching your breath	0.378	-0.025	0.190	0.130
Bloating, pain, or gas in your stomach	0.390	0.002	0.026	0.302
Total number of symptoms in the cluster	6	4	3	4
% agreement with the symptom occurrence dimension	66.7	100.0	100.0	100.0

Extraction method: Unweighted least squares. Rotation method: Promax oblique rotation.
[a]Factor loadings ≥ 0.4 are in **bold**. Items were allowed to load on more than on factor.

depressed; felt nervous or anxious; and difficulty falling or staying asleep, was the only symptom cluster that was common across our study. Given that all three studies used the HIV Symptom Index, our findings suggest that the use of EFA compared to PCA, that is a data reduction technique,[38,39] allowed for the identification of four distinct symptom clusters.

Consistent with a previous report of PLWH,[4] fatigue or loss of energy; difficulty falling or staying asleep; muscle aches or joint pain; feeling sad, down, or depressed; and felt nervous or anxious were the five symptoms with the highest occurrence rates. In contrast, in a study of PLWH and diabetes,[21] only fatigue or loss of energy was in the top five most commonly reported symptoms. The other four most commonly reported symptoms in the sample of PLWH and diabetes included: nausea, diarrhea, headache, and loss of appetite. Given that the prevalence of diabetes in the current sample was only 11%, potential reasons for these differences in symptom occurrence rates between the two studies include the influence of diabetes on symptom burden, as well as differences in the mean age (46.0 vs. 55[21] years) and race/ethnicity (24.4% vs. 37% Black[21]) of the patients that are characteristics that are known to influence symptom burden.[40,41]

Consistent with previous reports in oncology patients,[25,37,42,43] the four symptom clusters identified using EFA were relatively similar regardless of whether occurrence or distress was used to create the clusters (Table 5). The remainder of this discussion will describe each of these symptom clusters.

Gastrointestinal Symptom Cluster

Consistent with previous reports in the oncology[24,43,44] and HIV[17–19,21] literature, a gastrointestinal symptom cluster was identified using both the occurrence and distress dimensions. Four symptoms, (i.e., nausea or vomiting; diarrhea or loose bowel movements; loss of appetite or change in the way food tastes; and fever, chills, or sweats) were common across both dimensions. For the distress dimension, feeling dizzy or lightheaded and headache were included in this cluster. However, diarrhea was the only symptom that was consistent in three[17–19] of the four[21] studies of PLWH that identified a gastrointestinal cluster using PCA.

The underlying etiology for the gastrointestinal symptom cluster in PLWH may be related to the disease itself and/or its treatments. For example, the ongoing replication of the HIV virus in gut-associated lymph tissue,[45] the decrease in $CD4^+$ cells,[46] and changes in the diversity of the gut microbiota contribute to the development of gastrointestinal symptoms.[47–51] In addition, ongoing dysbiosis in the gastrointestinal tract leads to chronic immune activation and systemic inflammation.[52] While 76% of patients in our study were taking integrase inhibitors, that have a relatively low gastrointestinal side effect profile, other medications may result in gastrointestinal symptoms.[53,54]

Psychological Symptom Cluster

A psychological symptom cluster was identified in previous studies that used the HIV Symptom Index.[4,21] Of note, the four symptoms identified in our study (i.e., felt sad, down, or depressed; felt nervous or anxious; fatigue or loss of energy; and difficulty falling or staying asleep were among the most common and distressing) were found in the psychological symptom cluster identified in the two previous studies.[4,21] This cluster is not surprising given that numerous systematic reviews have described relationships between and among depressive symptoms, anxiety, fatigue, and sleep disturbance in PLWH.[55–59]

The high occurrence rates for these four symptoms across multiple studies,[4,9,21] is not surprising given the high levels of stress associated with a diagnosis of HIV infection,[60,61] as well as internal and external perceptions of stigma and discrimination.[62–64] A variety of mechanisms may underlie the development of this symptom cluster including disruptions in the gut-brain-axis[65–67] and/or the hypothalamic-pituitary-adrenal axis.[68,69] In addition, recent evidence suggest that neuropsychiatric adverse effects are common with ART[59] and with the integrase inhibitors.[58]

Pain Cluster

For both dimensions, the pain cluster included three symptoms, namely: pain, numbness or tingling in the hands or feet; muscle aches or joint pain; and feeling dizzy or lightheaded. In PLWH, pain prevalence rates range from 39% to 85%.[70] In our study, pain, numbness, or tingling in the hands and feet was reported by 53.4% of the patients and was the third most distressing symptom. While not objectively evaluated in our study, this group of symptoms is commonly reported by patients with HIV-associated sensory neuropathy (HIV-SN). While the causes (e.g., inflammatory changes in the peripheral and central nervous systems, mitochondrial dysfunction) and prevalence rates of HIV-SN have changed over the course of the epidemic,[71] this type of pain has a significant impact on patients' ability to function and results in significant decrements in quality of life.

In addition, 62.7% of the patients in our study reported muscle aches or joint pain and this symptom had the second highest distress rating. As noted in a recent review,[72] musculoskeletal pain is common in PLWH. Patients can develop inflammatory rheumatic disease (e.g., rheumatoid arthritis) or experience common joint problems associated with aging (e.g., osteoarthritis). Additional research is warranted to determine why dizziness or light-headedness was associated with the pain cluster.

Table 5
Comparison of Symptom Clusters Created Using Ratings of Occurrence and Distress

Symptom Cluster	Symptoms Within the Cluster	Occurrence	Distress
Gastrointestinal cluster	Nausea or vomiting	X	X
	Diarrhea or loose bowel movements	X	X
	Loss of appetite or change in taste of food	X	X
	Fever, chills, or sweats	X	X
	Feeling dizzy or lightheaded		X
	Headache		X
Percent agreement = 66.7%			
Psychological cluster	Felt sad, down, or depressed	X	X
	Felt nervous or anxious	X	X
	Fatigue or loss of energy	X	X
	Difficulty falling or staying asleep	X	X
Percent agreement = 100.0%			
Pain cluster	Pain, numbness or tingling in hands or feet	X	X
	Muscle aches or joint pain	X	X
	Feeling dizzy or lightheaded	X	X
Percent agreement = 100.0%			
Body image cluster	Changes in the way your body looks such as fat deposit or weight gain	X	X
	Problems with weight loss or wasting	X	X
	Hair loss or changes in the way your hair looks	X	X
	Problems with having sex, such as loss of interest or lack of satisfaction	X	X
Percent agreement = 100.0%			

Body Image Cluster

For both the occurrence and distress dimensions, the body image cluster included the same four symptoms (i.e., problems with weight loss or wasting; changes in the way your body looks such as fat deposit or weight gain; hair loss or changes in the way your hair looks; and problems with having sex, such as loss of interest or lack of satisfaction). Only one of the previous studies that used the HIV Symptom Index,[21] identified a similar symptom cluster that was called physical changes. Common symptoms included in this cluster were: problems with weight loss or wasting; changes in the way your body looks such as fat deposit or weight gain; and hair loss or changes in the way your hair looks.

Ranked as the fourth most distressing symptom, 52.5% of our sample reported changes in the way your body looks such as fat deposits or weight gain. Given that this single item on the HIV Symptom Index contains two distinct symptoms, one cannot determine the occurrence of each symptom. However, prevalence rates for lipodystrophy range from 31% to 81% and more than a third of patients report that three or more areas of the body are affected (e.g., increased waist (58%) or chest (39%) circumferences).[73,74] While originally associated with ART, recent evidence suggests that the fat alterations in PLWH are complex, likely to be multifactorial, and are not completely understood. As noted in a recent review, fat alterations including weight gain may be related to: direct effects on HIV proteins and antiretroviral agents on adipocytes, genetic factors, increased microbial translocation, increased tissue inflammation and fibrosis, and changes in adaptive immune processes.[75] Equally important, lipodystrophy has been linked to depression, decreased self-esteem, sexual dysfunction, and social isolation, as well as decrements in quality of life in PLWH.[76]

While only 31.5% of the patients in our sample reported problems with weight loss or wasting, this symptom can have a significant impact on patients' physical and psychological well-being. While more common early in the HIV epidemic, cachexia and/or malnutrition can occur in PLWH. These changes in nutritional status are often associated with varying stages of immunosuppression.[77,78] Another symptom that can effect a person's perception of their body image is hair loss. While age-related changes can result in alopecia,[79] some antiretroviral drugs can produce alopecia.[80]

Almost half of our patients reported problems with having sex, such as loss of interest or lack of satisfaction and it ranked fourth in terms of symptom distress. This symptom fits well within the body image cluster because all of the symptoms listed above can have a negative impact on a person's perceptions of their attractiveness and sexual health. As noted in one study of gay and bisexual men living with HIV,[81] the severity of lipodystrophy and appearance orientation were associated with an increase in body image disturbance. In addition, a higher level of body image disturbance was associated with poorer adherence with ART and increased HIV sexual transmission risk behaviors.

Limitations

Several study limitations need to be acknowledged. While information on symptom occurrence and associated distress were evaluated, future studies need to determine the severity, duration, and causes of each of the symptoms. Another limitation of the HIV Symptom Index is that multiple symptoms are aggregated in a single item. For example, while a patient may have muscle aches, they may not have joint pain. This aggregation of symptoms may have influenced the number and types of symptom clusters identified. In addition,

the occurrence of symptoms and symptom clusters may vary based on patients' viral load. Because our sample had only a small group of patients with a detectable viral load, we were not able to perform an analysis on this sub-sample. Finally, due to the cross-sectional design, changes in symptom clusters over time warrant evaluation. These longitudinal studies will provide insights into the stability of patients' symptom experiences that can be used to guide clinical management. Future studies need to evaluate which patient characteristics are associated with differences in symptom clusters in PLWH.

Despite these limitations, our study is the first to provide detailed information on the relative stability of four distinct symptom clusters based on the occurrence and distress dimensions of the symptom experience. Because our large sample is representative of PLWH, the generalizability of our findings is enhanced. Additional studies are needed to confirm our findings; to evaluate the stability of clusters over time; and to evaluate for underlying mechanisms associated with each of these clusters. Given the relatively high rates of co-occurring symptoms in this sample, clinicians can use the HIV Symptom Index to assess patients and develop appropriate symptom management interventions. In addition, as is being done in oncology,[82,83] researchers need to develop interventions to address the various symptom clusters that PLWH experience.

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