

# UCSF

## UC San Francisco Previously Published Works

### Title

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

### Permalink

<https://escholarship.org/uc/item/0921z1mj>

### Journal

Journal of Pain and Symptom Management, 63(6)

### ISSN

0885-3924

### Authors

Wilson, Natalie L  
Hoffman, Thomas J  
Heath, Sonya L  
[et al.](#)

### Publication Date

2022-06-01

### DOI

10.1016/j.jpainsymman.2022.02.337

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

**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. © 2022 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

**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.<sup>1–4</sup> 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](mailto:natalie.wilson@ucsf.edu)

*Accepted for publication:* 18 February 2022.

symptoms can decrease patients' adherence with ART and result in decrements in quality of life.<sup>5</sup>

A new and emerging area of symptom science research is the evaluation of symptom clusters.<sup>6</sup> 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."<sup>7</sup> An underlying rationale for this line of scientific inquiry is that symptoms that cluster together may share a common etiology or mechanism(s).<sup>6,8</sup>

As noted in an expert panel report,<sup>6</sup> 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,<sup>9</sup> only 13 studies have evaluated for "symptom clusters" in PLWH. Two of these studies were done pre-ART;<sup>10,11</sup> one evaluated only depressive symptoms;<sup>12</sup> one evaluated for changes over time in a pre-specified symptom cluster (i.e., muscle aches, numbness of feet/toes, and fatigue);<sup>13</sup> and three evaluated for subgroups of patients with distinct symptom profiles.<sup>14–16</sup>

Of the six remaining studies,<sup>4,17–21</sup> 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<sup>17,18</sup> or Chinese<sup>19</sup> 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,<sup>20</sup> 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.<sup>4,21</sup> 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.<sup>4,17–21</sup> Therefore, the number of symptom clusters identified ranged from two<sup>4</sup> to 11.<sup>18</sup> The most common symptom cluster identified across four of these six studies was a gastrointestinal cluster.<sup>17–19,21</sup>

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,<sup>6</sup> 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,<sup>22</sup> 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,<sup>23–25</sup> 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.<sup>26</sup> 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.<sup>27</sup> 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.<sup>27</sup>

### 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.<sup>28</sup> 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.<sup>29</sup> 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  $\geq 0.40$ .<sup>30</sup> In addition, factors (i.e., symptom clusters) were considered to be adequately defined if at least two items had loadings of  $\geq 0.40$ . 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  $\geq 0.40$ . 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.<sup>6,31</sup>

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.<sup>32,33</sup> The Kaiser-Meyer-Olkin test, using the R package psych v1.9.2,<sup>34</sup> 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.<sup>31,32</sup> Oblique rotation allows factors to be correlated, as is likely true for associations in the population.<sup>32,35</sup> 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  $\geq 0.40$ . 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.<sup>36</sup> 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 ( $\pm 11.7$ ) years. Over half of the patients (63.0%) had a CD4 count of  $>500$  cells/mm<sup>3</sup> (mean 628 ( $\pm 333$ ) cells/mm<sup>3</sup>), 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 ( $\pm 5.4$ , 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 pain; 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 <sup>3</sup> 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<sup>3</sup> = millimeter cubed; mL = milliliter.

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

Rank	Symptom	Occurrence %	Distress <sup>a</sup>		Rank
			Mean	SD	
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.

<sup>a</sup>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.

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,<sup>24,25,37</sup> the symptom clusters identified were relatively similar

(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

Table 3  
Exploratory Factor Analysis Using Ratings of Symptom Occurrence

Symptom	Factor 1	Factor 2	Factor 3	Factor 4
	Gastrointestinal Cluster	Psychological Cluster	Pain Cluster	Body Image Cluster
Nausea or vomiting	<b>0.888<sup>a</sup></b>	0.018	-0.163	-0.144
Diarrhea or loose bowel movements	<b>0.599<sup>a</sup></b>	0.028	-0.105	0.028
Loss of appetite or a change in the taste of food	<b>0.506<sup>a</sup></b>	0.091	-0.033	0.128
Fever, chills, or sweats	<b>0.496<sup>a</sup></b>	-0.075	0.245	-0.071
Felt nervous or anxious	0.067	<b>0.779<sup>a</sup></b>	-0.178	-0.004
Felt sad, down, or depressed	-0.007	<b>0.750<sup>a</sup></b>	-0.082	0.008
Difficulty falling or staying asleep	0.048	<b>0.465<sup>a</sup></b>	0.066	-0.032
Fatigue or loss of energy	-0.067	<b>0.460<sup>a</sup></b>	0.235	-0.041
Pain, numbness or tingling in the hands or feet	-0.093	-0.066	<b>0.775<sup>a</sup></b>	0.025
Muscle aches or joint pain	-0.049	0.005	<b>0.593<sup>a</sup></b>	0.075
Feeling dizzy or lightheaded	0.334	0.042	<b>0.477<sup>a</sup></b>	-0.134
Changes in the way your body looks such as fat deposits or weight gain	-0.186	-0.033	0.067	<b>0.686<sup>a</sup></b>
Problems with weight loss or wasting	0.210	-0.095	-0.030	<b>0.515<sup>a</sup></b>
Hair loss or changes in the way your hair looks	0.156	-0.043	-0.023	<b>0.490<sup>a</sup></b>
Problems with having sex, such as loss of interest or lack of satisfaction	-0.073	0.187	-0.029	<b>0.467<sup>a</sup></b>
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.

<sup>a</sup>Factor loadings  $\geq 0.4$  are in **bold**. Items were allowed to load on more than one 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,<sup>4,21</sup> two or three symptom clusters were identified using PCA (i.e.,

physical and psychological;<sup>4</sup> and psychological and neurological, gastrointestinal and flu-like, and physical changes in body appearance<sup>21</sup>). Of note, the “psychological” cluster, that included felt sad, down, or

Table 4  
Exploratory Factor 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	<b>0.885<sup>a</sup></b>	0.014	-0.133	-0.163
Diarrhea or loose bowel movements	<b>0.617<sup>a</sup></b>	0.068	-0.181	0.079
Loss of appetite or a change in the taste of food	<b>0.582<sup>a</sup></b>	0.077	-0.079	0.140
Fever, chills, or sweats	<b>0.558<sup>a</sup></b>	-0.032	0.168	-0.081
Feeling dizzy or lightheaded	<b>0.416<sup>a</sup></b>	0.038	<b>0.410<sup>a</sup></b>	-0.114
Headache	<b>0.408<sup>a</sup></b>	0.010	0.217	-0.044
Felt sad, down, or depressed	-0.050	<b>0.889<sup>a</sup></b>	-0.086	0.021
Felt nervous or anxious	0.085	<b>0.877<sup>a</sup></b>	-0.139	-0.081
Fatigue or loss of energy	0.013	<b>0.451<sup>a</sup></b>	0.289	0.051
Difficulty falling or staying asleep	0.153	<b>0.437<sup>a</sup></b>	0.116	-0.050
Pain, numbness or tingling in the hands or feet	-0.083	-0.064	<b>0.819<sup>a</sup></b>	-0.009
Muscle aches or joint pain	-0.069	-0.018	<b>0.722<sup>a</sup></b>	0.067
Problems with having sex, such as loss of interest or lack of satisfaction	-0.086	0.250	-0.013	<b>0.427<sup>a</sup></b>
Changes in the way your body looks such as fat deposits or weight gain	-0.211	0.012	0.022	<b>0.762<sup>a</sup></b>
Problems with weight loss or wasting	0.200	-0.102	-0.070	<b>0.551<sup>a</sup></b>
Hair loss or changes in the way your hair looks	0.059	-0.056	0.051	<b>0.482<sup>a</sup></b>
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.

<sup>a</sup>Factor loadings  $\geq 0.4$  are in **bold**. Items were allowed to load on more than one 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,<sup>38,39</sup> allowed for the identification of four distinct symptom clusters.

Consistent with a previous report of PLWH,<sup>4</sup> 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,<sup>21</sup> 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<sup>21</sup> years) and race/ethnicity (24.4% vs. 37% Black<sup>21</sup>) of the patients that are characteristics that are known to influence symptom burden.<sup>40,41</sup>

Consistent with previous reports in oncology patients,<sup>25,37,42,43</sup> 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<sup>24,43,44</sup> and HIV<sup>17-19,21</sup> 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<sup>17-19</sup> of the four<sup>21</sup> 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,<sup>45</sup> the decrease in CD4<sup>+</sup> cells,<sup>46</sup> and changes in the diversity of the gut microbiota contribute to the development of gastrointestinal symptoms.<sup>47-51</sup> In addition, ongoing dysbiosis in the gastrointestinal tract leads to chronic immune activation and systemic inflammation.<sup>52</sup> 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.<sup>53,54</sup>

#### *Psychological Symptom Cluster*

A psychological symptom cluster was identified in previous studies that used the HIV Symptom Index.<sup>4,21</sup> 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.<sup>4,21</sup> 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.<sup>55-59</sup>

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

#### *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%.<sup>70</sup> 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,<sup>71</sup> 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,<sup>72</sup> 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	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,<sup>21</sup> 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).<sup>73,74</sup> 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.<sup>75</sup> 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.<sup>76</sup>

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.<sup>77,78</sup> Another symptom that can effect a person's perception of their body image is hair loss. While age-related changes can result in alopecia,<sup>79</sup> some antiretroviral drugs can produce alopecia.<sup>80</sup>

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,<sup>81</sup> 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,<sup>82,83</sup> researchers need to develop interventions to address the various symptom clusters that PLWH experience.

### Disclosures and Acknowledgments

The authors have no conflicts of interest to declare. This study was funded by grants from the National Institute of Allergy and Infectious Diseases [3R24AI067039-14S1](#) and the University of Alabama at Birmingham Center for AIDS Research (CFAR) [[AI027767](#)]. This publication was made possible with help from the UCSF-Gladstone CFAR, an NIH-funded program [[P30 AI027763](#)]. Dr. Wilson would like to acknowledge the people living with HIV infection who are burdened by and report HIV symptoms who have not been acknowledged for their lived experience. Thank you for sending me to do this work.

### References

- Johnson MO, Stallworth T, Neilands TB. The drugs or the disease? Causal attributions of symptoms held by HIV-positive adults on HAART. *AIDS Behav* 2003;7:109–117.
- Johnson MO, Folkman S. Side effect and disease related symptom representations among HIV+ adults on antiretroviral therapy. *Psychol Health Med* 2004;9:139–148.
- Swan H, McDannold S, McInnes DK, et al. Symptom bothersomeness and symptom attribution in adults on HIV medications. In: 9th International Conference on HIV Treatment and Prevention Adherence, Miami, FL: 2014.
- Wilson NL, Azuero A, Vance DE, et al. Identifying symptom patterns in people living with HIV disease. *J Assoc Nurses AIDS Care* 2016;27:121–132.
- Gay C, Portillo CJ, Kelly R, et al. Self-reported medication adherence and symptom experience in adults with HIV. *J Assoc Nurses AIDS Care* 2011;22:257–268.
- Miaskowski C, Barsevick A, Berger A, et al. Advancing symptom science through symptom cluster research: expert panel proceedings and recommendations. *J Natl Cancer Inst* 2017;109:djw253.
- Kim HJ, McGuire DB, Tulman L, Barsevick AM. Symptom clusters: concept analysis and clinical implications for cancer nursing. *Cancer Nurs* 2005;28:270–282.
- Dodd M, Janson S, Facione N, et al. Advancing the science of symptom management. *J Adv Nurs* 2001;33:668–676.
- Zhu Z, Zhao R, Hu Y. Symptom clusters in people living with HIV: a systematic review. *J Pain Symptom Manage* 2019;58:115–133.
- Cook PF, Sousa KH, Matthews EE, Meek PM, Kwong J. Patterns of change in symptom clusters with HIV disease progression. *J Pain Symptom Manage* 2011;42:12–23.
- Sousa KH, Tann SS, Kwok OM. Reconsidering the assessment of symptom status in HIV/AIDS care. *J Assoc Nurses AIDS Care* 2006;17:36–46.
- De La Haye W, Clarke TR, Lipps G, et al. Patterns of depressive symptoms among patients with HIV infection. *West Indian Med J* 2010;59:380–385.
- Wantland DJ, Mullan JP, Holzemer WL, et al. Additive effects of numbness and muscle aches on fatigue occurrence in individuals with HIV/AIDS who are taking antiretroviral therapy. *J Pain Symptom Manage* 2011;41:469–477.
- Namisango E, Harding R, Katabira ET, et al. A novel symptom cluster analysis among ambulatory HIV/AIDS patients in Uganda. *AIDS Care* 2015;27:954–963.
- Boyer V, Vilotitch A, Marcellin F, et al. Self-reported bothersome symptoms across different socioepidemiological groups of people living with HIV attending French hospitals: results from the ANRS-VESPA2 survey. *J Pain Symptom Manage* 2017;54:110–119.
- Moens K, Siegert RJ, Taylor S, et al. Symptom clusters in people living with HIV attending five palliative care facilities in two Sub-Saharan African countries: a hierarchical cluster analysis. *PLoS One* 2015;10:e0126554.
- Holzemer WL, Henry SB, Nokes KM, et al. Validation of the sign and symptom check-list for persons with HIV disease (SSC-HIV). *J Adv Nurs* 1999;30:1041–1049.
- Holzemer WL, Hudson A, Kirksey KM, Hamilton MJ, Bakken S. The revised sign and symptom check-list for HIV (SSC-HIVrev). *J Assoc Nurses AIDS Care* 2001;12:60–70.
- Tsai YF, Hsiung PC, Holzemer WL. Validation of a Chinese version of the sign and symptom checklist for persons with HIV diseases. *J Pain Symptom Manage* 2003;25:363–368.
- Zhu Z, Hu Y, Xing W, et al. Identifying symptom clusters among people living with HIV on antiretroviral therapy in China: a network analysis. *J Pain Symptom Manage* 2019;57:617–626.
- Zuniga JA, Bose E, Park J, Lapiz-Bluhm MD, García AA. Diabetes changes symptoms cluster patterns in persons living with HIV. *J Assoc Nurses AIDS Care* 2017;28:888–896.

22. Skerman HM, Yates PM, Battistutta D. Multivariate methods to identify cancer-related symptom clusters. *Res Nurs Health* 2009;32:345–360.
23. Russell J, Wong ML, Mackin L, et al. Stability of symptom clusters in patients with lung cancer receiving chemotherapy. *J Pain Symptom Manage* 2019;57:909–922.
24. Han CJ, Reding K, Cooper BA, et al. Stability of symptom clusters in patients with gastrointestinal cancers receiving chemotherapy. *J Pain Symptom Manage* 2019;58:989–1001.
25. Sullivan CW, Leutwyler H, Dunn LB, et al. Stability of symptom clusters in patients with breast cancer receiving chemotherapy. *J Pain Symptom Manage* 2018;55:39–55.
26. Kitahata MM, Rodriguez B, Haubrich R, et al. Cohort profile: the centers for AIDS research network of integrated clinical systems. *Int J Epidemiol* 2008;37:948–955.
27. Justice AC, Holmes W, Gifford AL, et al. Development and validation of a self-completed HIV symptom index. *J Clin Epidemiol* 2001;54(Suppl 1):S77–S90.
28. R Development Core Team. R: A language and environment for statistical computing. In: Vienna, Austria: R Foundation for Statistical Computing, 2014.
29. Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. *J Natl Cancer Inst Monographs* 2004;32:17–21.
30. Brown TA. Confirmatory factor analysis for applied research. 2nd ed. New York; London: The Guilford Press; 2015.
31. Browne MW. An overview of analytic rotation in exploratory factor analysis. *Multivar Behav Res* 2001;36:111–150.
32. Muthen LK, Muthen BO. Mplus user's guide. 7th ed Los Angeles, CA: Muthén & Muthén; 1998.
33. Fox J. Polycor: Polychoric and Polyserial Correlations. In: R package version 0.7-10, 2019.
34. Revelle W. Psych: Procedures for psychological, psychometric, and personality research. Evanston, Illinois: Northwestern University; 2020 R package version 1.9.2 ed..
35. Fabrigar LR, Wegener DT. Exploratory factor analysis. Oxford; New York: Oxford University Press; 2012.
36. Kirkova J, Walsh D. Cancer symptom clusters—a dynamic construct. *Support Care Cancer* 2007;15:1011–1013.
37. Russell J, Wong ML, Mackin L, et al. Stability of symptom clusters in patients with lung cancer receiving chemotherapy. *J Pain Symptom Manage* 2019;57:909–922.
38. Sainani KL. Introduction to principal components analysis. *PM & R* 2014;6:275–278.
39. Costello AB, Osborne J. Best practices in exploratory factor analysis: four recommendations for getting the most from your analysis. *Pract Assess Res Evaluation* 2005;10:1–9.
40. Schnall R, Siegel K, Jia H, Olender S, Hirshfield S. Racial and socioeconomic disparities in the symptom reporting of persons living with HIV. *AIDS Care* 2018;30:774–783.
41. Eckerblad J, Theander K, Ekdahl AW, Jaarsma T. Symptom trajectory and symptom burden in older people with multimorbidity, secondary outcome from the RCT AGE-FIT study. *J Adv Nurs* 2016;72:2773–2783.
42. Wong ML, Cooper BA, Paul SM, et al. Differences in symptom clusters identified using ratings of symptom occurrence vs. severity in lung cancer patients receiving chemotherapy. *J Pain Symptom Manage* 2017;54:194–203.
43. Ward Sullivan C, Leutwyler H, Dunn LB, et al. Differences in symptom clusters identified using symptom occurrence rates versus severity ratings in patients with breast cancer undergoing chemotherapy. *Eur J Oncol Nurs* 2017;28:122–132.
44. Han CJ, Reding K, Cooper BA, et al. Symptom clusters in patients with gastrointestinal cancers using different dimensions of the symptom experience. *J Pain Symptom Manage* 2019;58:224–234.
45. Thompson CG, Gay CL, Kashuba ADM. HIV persistence in gut-associated lymphoid tissues: pharmacological challenges and opportunities. *AIDS Res Hum Retroviruses* 2017;33:513–523.
46. Brenchley JM, Schacker TW, Ruff LE, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med* 2004;200:749–759.
47. Somsouk M, Estes JD, Deleage C, et al. Gut epithelial barrier and systemic inflammation during chronic HIV infection. *AIDS* 2015;29:43–51.
48. Vujkovic-Cvijin I, Dunham RM, Iwai S, et al. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. *Sci Transl Med* 2013;5:193ra91.
49. Brenchley JM, Douek DC. The mucosal barrier and immune activation in HIV pathogenesis. *Curr Opin HIV AIDS* 2008;3:356–361.
50. Klatt NR, Funderburg NT, Brenchley JM. Microbial translocation, immune activation, and HIV disease. *Trends Microbiol* 2013;21:6–13.
51. Wilson NL, Vance DE, Moneyham LD, et al. Connecting the dots: could microbial translocation explain commonly reported symptoms in HIV disease? *J Assoc Nurses AIDS Care* 2014;25:483–495.
52. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 2006;12:1365–1371.
53. Murrell DE, Cluck DB, Moorman JP, et al. HIV integrase inhibitor pharmacogenetics: an exploratory study. *Clin Drug Investig* 2019;39:285–299.
54. Kolakowska A, Maresca AF, Collins IJ, Cailhol J. Update on adverse effects of HIV integrase inhibitors. *Curr Treat Options Infect Dis* 2019;11:372–387.
55. Brandt C, Zvolensky MJ, Woods SP, et al. Anxiety symptoms and disorders among adults living with HIV and AIDS: a critical review and integrative synthesis of the empirical literature. *Clin Psychol Rev* 2017;51:164–184.
56. Koegler E, Kennedy CE. A scoping review of the associations between mental health and factors related to HIV acquisition and disease progression in conflict-affected populations. *Confl Health* 2018;12. 20.
57. Low Y, Goforth H, Preud'homme X, Edinger J, Krystal A. Insomnia in HIV-infected patients: pathophysiologic implications. *AIDS Rev* 2014;16:3–13.
58. Hoffmann C, Llibre JM. Neuropsychiatric adverse events with dolutegravir and other integrase strand transfer inhibitors. *AIDS Rev* 2019;21:4–10.
59. Treisman GJ, Soudry O. Neuropsychiatric effects of HIV antiviral medications. *Drug Saf* 2016;39:945–957.
60. Nicolaidis NC, Kino T, Chrousos G. AIDS and HPA Axis. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *Endotext*,

- South Dartmouth (MA): MDText.com, Inc. Copyright © 2000-2021, MDText.com, Inc., 2000.
61. Ayano G, Duko B, Bedaso A. The prevalence of post-traumatic stress disorder among people living with HIV/AIDS: a systematic review and meta-analysis. *Psychiatr Q* 2020;91:1317–1332.
  62. Nyblade L, Mingkwan P, Stockton MA. Stigma reduction: an essential ingredient to ending AIDS by 2030. *Lancet HIV* 2021;8:e106–e113.
  63. Sowell RL. Stigma and discrimination: threats to living positively with human immunodeficiency virus. *Nurs Clin North Am* 2018;53:111–121.
  64. Yuvaraj A, Mahendra VS, Chakrapani V, et al. HIV and stigma in the healthcare setting. *Oral Dis* 2020;26(Suppl 1):103–111.
  65. Appleton J. The gut-brain axis: Influence of microbiota on mood and mental health. *Integr Med* 2018;17:28–32.
  66. Liu L, Zhu G. Gut-brain axis and mood disorder. *Front Psychiatry* 2018;9:223.
  67. Li Y, Hao Y, Fan F, Zhang B. The role of microbiome in insomnia, circadian disturbance and depression. *Front Psychiatry* 2018;9:669.
  68. Cernackova A, Durackova Z, Trebaticka J, Mravec B. Neuroinflammation and depressive disorder: the role of the hypothalamus. *J Clin Neurosci* 2020;75:5–10.
  69. Yang S, Chu S, Gao Y, et al. A narrative review of cancer-related fatigue (CRF) and its possible pathogenesis. *Cells* 2019;8.
  70. Merlin JS, Bulls HW, Vucovich LA, Edelman EJ, Starrels JL. Pharmacologic and non-pharmacologic treatments for chronic pain in individuals with HIV: a systematic review. *AIDS Care* 2016;28:1506–1515.
  71. Aziz-Donnelly A, Harrison TB. Update of HIV-associated sensory neuropathies. *Curr Treat Options Neurol* 2017;19:36.
  72. Walker-Bone K, Doherty E, Sanyal K, Churchill D. Assessment and management of musculoskeletal disorders among patients living with HIV. *Rheumatology (Oxford)* 2017;56:1648–1661.
  73. Raggio GA, Looby SE, Robbins GK, et al. Psychosocial correlates of body image and lipodystrophy in women aging with HIV. *J Assoc Nurses AIDS Care* 2020;31:157–166.
  74. Finkelstein JL, Gala P, Rochford R, Glesby MJ, Mehta S. HIV/AIDS and lipodystrophy: implications for clinical management in resource-limited settings. *J Int AIDS Soc*. 2015;18:19033.
  75. Koethe JR, Lagathu C, Lake JE, et al. HIV and antiretroviral therapy-related fat alterations. *Nat Rev Dis Primers* 2020;6:48.
  76. Guzman N, Vijayan V. HIV-associated lipodystrophy. In: *StatPearls*, Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC., 2021.
  77. Koethe JR, Heimburger DC, PrayGod G, Filteau S. From wasting to obesity: the contribution of nutritional status to immune activation in HIV infection. *J Infect Dis* 2016;214 Suppl 2:S75-82.
  78. Mankal PK, Kotler DP. From wasting to obesity, changes in nutritional concerns in HIV/AIDS. *Endocrinol Metab Clin North Am* 2014;43:647–663.
  79. Katzer T, Leite Junior A, Beck R, da Silva C. Physiopathology and current treatments of androgenetic alopecia: going beyond androgens and anti-androgens. *Dermatol Ther* 2019;32:e13059.
  80. Woods EA, Foisy MM. Antiretroviral-related alopecia in HIV-infected patients. *Ann Pharmacother* 2014;48:1187–1193.
  81. Blashill AJ, Goshe BM, Robbins GK, Mayer KH, Safren SA. Body image disturbance and health behaviors among sexual minority men living with HIV. *Health Psychol* 2014;33:677–680.
  82. Kwekkeboom KL, Abbott-Anderson K, Cherwin C, et al. Pilot randomized controlled trial of a patient-controlled cognitive-behavioral intervention for the pain, fatigue, and sleep disturbance symptom cluster in cancer. *J Pain Symptom Manage* 2012;44:810–822.
  83. Kwekkeboom KL, Cherwin CH, Lee JW, Wanta B. Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. *J Pain Symptom Manage* 2010;39:126–138.