Review Article

Symptom Clusters in People Living With HIV: A Systematic Review

Zheng Zhu, PhD, Rui Zhao, MSN, and Yan Hu, PhD

Fudan University School of Nursing (Z.Z., Y.H.), Shanghai; Fudan University Centre for Evidence-based Nursing: A Joanna Briggs Institute Centre of Excellence (Z.Z., Y.H.), Shanghai; and Children's Hospital of Fudan University (R.Z.), Shanghai, China

Abstract

Context. An increasing number of studies regarding symptom management have begun to shift their focus from managing a single symptom to multiple symptom clusters. However, there is a lack of consistency of compositions among different studies and even in two different analyses reported in a single study within the same population.

Objectives. The aim of this systematic review was to summarize the compositions, measures, and data analysis techniques of symptom clusters in people living with HIV (PLWH).

Methods. We conducted a comprehensive search to identify published studies about symptom clusters among PLWH. Databases including PubMed/MEDLINE, MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), Web of Science, and ProQuest Dissertations and Thesis were searched for studies published between January 2000 and December 2018.

Results. Thirteen articles were eligible for inclusion. Five most commonly reported symptom clusters were found: 1) sad/depressed/loss of interest and nervous/anxious/worrying; 2) difficulty sleeping, problems with having sex, and fatigue/loss of energy; 3) fever/chills/sweat, nausea/vomiting, and loss of appetite; 4) numbness, muscle aches, and joint pain; and 5) dizziness and headache.

Conclusion. This systematic review summarized the compositions, measures, and analytical techniques of symptom clusters for PLWH. Although this review found unstable results on the compositions of symptom clusters and it was difficult to reach a definitive conclusion, the results still implicate the necessity of developing a threshold to decide what symptoms should be included in the clusters and the use of multiple data analysis techniques to obtain stable results. J Pain Symptom Manage 2019;58:115–133. © *2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words

Symptom cluster, symptom management, HIV/AIDS, systematic review

Introduction

Since the successful advent of antiretroviral therapy (ART) in 1995, HIV infections have transformed from being a fatal infection to a chronic disease.[1] The main focus of health care staff has also shifted from life survival to the palliation of chronic symptoms.[2–4] People living with HIV (PLWH) may experience multiple symptoms caused by an HIV infection, the short- or long-term side effects of HIV medications, medical complications and comorbidities, and social factors.[5] Previous studies have shown that most PLWH face several somatic and psychological symptoms at the same time.[6,7]

Constellations of symptoms have been shown to negatively affect the quality of life, body functions, medication adherence, and social engagement of PLWH.[8–10] It is well established that advancing accurate symptom management is a fundamental strategy to help PLWH achieve an optimized quality of life. Previous studies highlighted the importance of better understanding the mechanisms among HIV-related symptoms to improve symptom management among PLWH.[2,4,11]

However, interventions that focus on only one or a few symptoms may not successfully tackle the distress that PLWH experience.[12] An increasing number of

Address correspondence to: Yan Hu, PhD, School of Nursing, Fudan University, Shanghai, China; and Director of Fudan University Centre for Evidence-based Nursing: A Joanna Briggs Institute Centre of Excellence, 305 Fenglin Rd, Shanghai 200032, China. E-mail: huyan@fudan.edu.cn

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studies regarding symptom management have begun to shift their focus from managing single symptoms to managing multiple symptoms that may co-occur. Previous studies found that the impact of multiple symptoms was greater than the sum of the individual symptoms.[13] Researchers incorporated the concept of clusters and defined a "symptom cluster" as three or more symptoms being related that may or may not have the same etiology.[14] Focusing on symptom clusters may better describe real-life situations because PLWH usually experience multiple symptoms at the same time.[15,16] Symptom clusters also provide health care staff with a better understanding of how PLWH experience symptoms and how symptoms affect patients from a first-person perspective, which further guides symptom management.[14]

Some HIV/AIDS symptom cluster studies have been conducted, especially in recent years. Wilson et al.[3] found two broad symptom clusters among 1945 PLWH in the U.S. Namisango et al.[7] identified five clusters among 302 PLWH in Uganda, including sensory/eating problems, psycho-gastrointestinal symptoms, pain and sensory disturbances, general symptoms, and mood-cognitive symptoms. Similarly, Moens et al.[6] found five clusters among 217 PLWH in South Africa and Uganda, including dermatological symptoms, generalized anxiety and elimination symptoms, social and image symptoms, symptoms that were persistently present, and gastrointestinal symptoms.

Nonetheless, in previous studies, there is a lack of consistency of symptom cluster compositions among different studies and even between two different analyses in a single study. Symptom cluster studies used various measures and analytical techniques to derive the clusters. The symptom clusters were not well described enough to serve as a grouping variable for demographic and clinical comparisons. Several studies have suggested that it is necessary to explore whether derived symptom clusters remain consistent across different measures and methodologies.[17,18] Therefore, we intentionally kept the focus of this systematic review on summarizing the findings of symptom clusters among PLWH. In addition, it is also crucial to identify how and why symptom clusters differ across studies. No previous review has systematically investigated the issues raised above.

Methods

Aims and Design

The aim of our systematic review was to summarize the compositions, measures, and analytical techniques of symptom clusters in PLWH. This review was in accordance with the guidelines of the Joanna Briggs Institute (JBI) Reviewers' Manual.[19] We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide the reporting of our study.[20]

Search Strategy

A comprehensive search was conducted to identify published studies. Keywords and derivatives of terms were captured from an initial limited search via PubMed/MEDLINE. This informed the development of the search strategy tailored for each information source. Databases including PubMed/MEDLINE, MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), Web of Science, and ProQuest Dissertations and Thesis were searched. This systematic review aims to identify studies conducted before and in the ART era, which may represent the full picture of symptom clusters in PLWH. Therefore, articles with no restriction on publication date were considered for inclusion. In MEDLINE (PubMed), we searched articles in English using MeSH terms ("Syndrome" AND ["HIV" OR "Acquired Immunodeficiency Syndrome"]) combined with title/abstract keywords (symptom* AND [cluster* OR multiple OR constellation* OR concurrent OR co-occurrence OR combination*] AND [HIV OR AIDS OR "acquired immunodeficiency syndrome"]). All search strategies are available on request. In addition, we hand-searched the references list of the included articles as a supplement of database searching.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) studies that aimed to identify symptom clusters or interrelationships between two or more symptoms in PLWH; 2) quantitative studies including, but not limited to, randomized controlled trials, quasi-experimental trials, and cross-sectional descriptive studies; and 3) studies published in English. Any type of settings including, but not limited to, outpatient and in-hospital palliative care was eligible for inclusion. Articles that included children and adolescents (less than 18 years) only were excluded.

Study Screening and Selection

Titles and abstracts were screened against the inclusion and exclusion criteria. All identified citations were imported into EndNote X8 (Clarivate Analytics, Philadelphia, PA), and duplicates were removed. Screening and selection were independently carried out by two reviewers (Z. Z. and R. Z.). Any conflicts were resolved by a third reviewer (Y. H.).

Quality Appraisal

Study quality was assessed using a set of criteria from the JBI Reviewers' Manual.[19] Assessment tools were selected in accordance with the study

designs encountered, which included randomized controlled trials, quasi-randomized controlled trials, case-control studies, prevalence studies, and cross-sectional descriptive studies. This process was independently performed by two reviewers (Z. Z. and R. Z.). Discrepancies were resolved by a joint discussion with the third reviewer (Y. H.) to obtain a consensus.

Data Extraction and Synthesis

Two reviewers (Z. Z. and R. Z.) independently extracted information from the included articles, including authors, year, location, study design, sample characteristics, aims, analytical methods, measures, symptom combinations, and main findings. In addition, other specific information relevant to the overarching aim of this study was also extracted. Discrepancies were solved through discussion between two reviewers. The third author (Y. H.) was engaged in the discussion if any disagreements arose. We were unable to synthesize outcomes in a meta-analysis because of the large heterogeneity in research designs, sample characteristics, and outcomes. Therefore, only a narrative synthesis of the findings was undertaken.

Results

Search Outcome

Figure 1 shows a flowchart of the article retrieval process. Searching six databases and additional sources yielded 10,506 articles. After removing duplicates, 5895 articles remained and were entered into the screening process. We excluded 5849 articles after reading the titles and abstracts and further excluded 33 articles based on the full-text review. Consequently, 13 articles were eligible for inclusion.[3,6,7,21–30]

Description of Studies

Design. Table 1 provides further details for each study. Ten of the 13 studies were cross-sectional. Three studies used a longitudinal design. Among these three studies, two used a cross-sectional sample.[22,26] The other study measured symptoms at four time points (baseline, month 1, month 3, and month 6).[28]

Sample Characteristics. The majority of studies took place in the U.S.,[3,22,24–26,28,30] followed by Uganda,[6,7] Mainland China and Taiwan,[27,29] South Africa,[6] France,[21] and Jamaica.[23] Two studies used secondary data that were collected before the ART era.[22,26] One study was conducted between 1994 and 1998.[24]

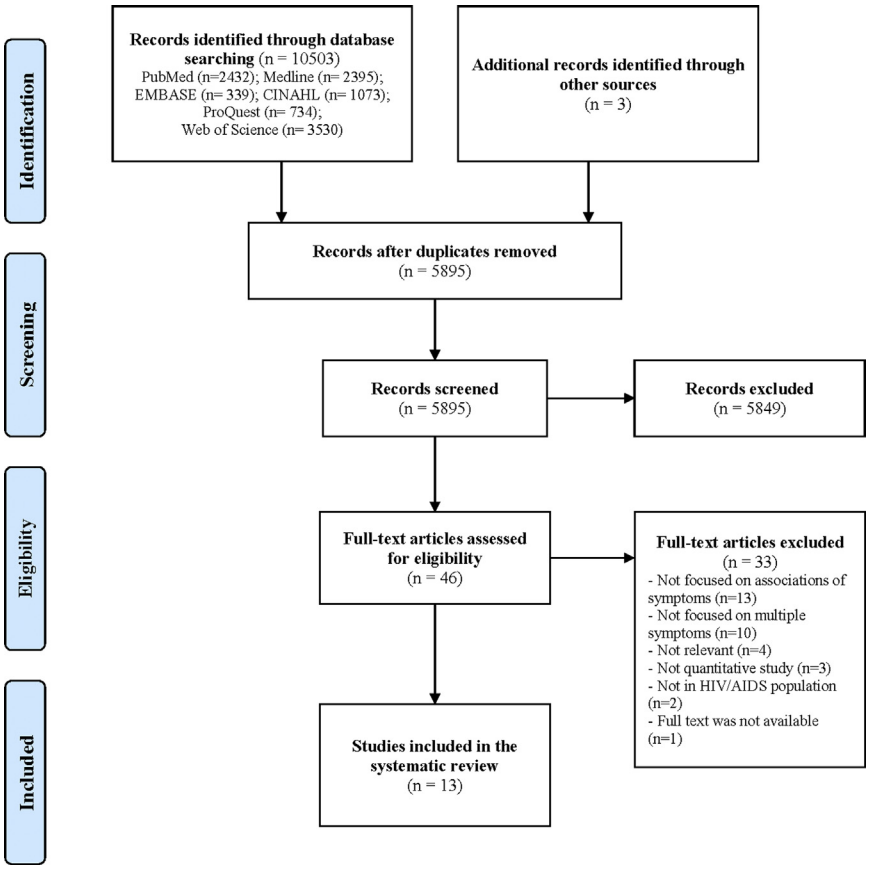

Fig. 1. PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1
Summary of the Included Studies

Author (year), Location	Design	Sample	Setting	Focus of Study	Analytical Technique	Symptom Assessment Tools	Key Findings
Boyer et al. (2017),[21] France	Cross sectional (between April 2011 and January 2012)	$N = 2505$ PLWH Age: not specified Male: 68% On ART: 90.7%−92.6% Years living with HIV: not specified CD4 count: not specified	73 French HIV/AIDS departments	1) Explore the types of bothersome symptoms reported by PLWH 2) Determine the associations between sociodemographic characteristics and SCs	Multiple correspondence analysis and hierarchical clustering	Author-developed symptom scale	Three clusters were reported: 1) Cluster A: all investigated symptoms. 2) Cluster B: psychological problems (nausea/vomiting, difficulty sleeping, nervous/anxious, sad/depressed, and trouble remembering), sexual problems (problems with having sex), and general symptoms (loss of appetite, coughing/trouble breathing, dizzy, fever/chills/sweat, and fatigue/loss of energy). 3) Cluster C: gastric problems (skin problems, bloating, and diarrhea), painful symptoms (problems when urinating, renal problems, muscle aches/joint pains, headache, and numbness), and physical appearance (hair loss, weight loss/wasting, and change in the way your body looks).
Cook et al. (2011),[22] U.S.	Longitudinal but cross-sectional sample (between January 1992 and October 1994)	$N = 246$ PLWH Age: 40.2 yrs Male: 100% On ART: 0% Living with HIV: 4.0 yrs CD4 count: 312.6	Not specified	Explore whether SCs are signs of HIV/AIDS progression and treatment failure	Multilevel modeling	SSC-HIV	1) Six clusters were discovered: malaise/fatigue, confusion/distress, fever/chills, gastrointestinal discomfort, shortness of breath, and nausea/vomiting.

							2) Malaise/fatigue and nausea/vomiting clusters may suggest HIV/AIDS progression. Other clusters may be related to comorbidities and aging.
Haye et al. (2010),[23] Jamaica	Cross sectional (not specified)	$N = 191$ PLWH Age: 40.5 yrs Male: 39% On ART: not specified Living with HIV: 5.5 yrs CD4 count: 6–2310	Three HIV clinics in Jamaica	Identify the level of depressive symptoms and patterns of depressive symptoms among PLWH	PCA (oblique rotation)	Beck Depression Inventory-II	Three clusters were reported: 1) Cognitive affective: loss of interest, agitation, suicidal thoughts, sadness, crying, past failure, irritability, pessimism, and loss of pleasure. 2) Negative cognition: self-dislike, self-criticalness, punishment feelings, and changes in sleeping. 3) Somatic symptoms: Loss of energy, tiredness or fatigue, worthlessness, concentration difficulty, changes in appetite, indecisiveness, and loss of interest in sex.
Holzemer et al. (1999),[24] U.S.	Cross sectional (Study 1: between 1994 and 1996; Study 2: between 1997 and 1998)	Study 1: $N = 247$ PLWH Age: 39.3 yrs Male: 88% On ART: 0% Living with HIV: 4.8 yrs CD4 count: 76 Study 2: $N = 686$ PLWH Age: 39.4 yrs Male: 77.2% On ART: not specified Living with HIV: 7.4 yrs CD4 count: 323	Study 1: Three area hospitals, one home care agency, and one nursing care facility Study 2: HIV/AIDS clinics, hospitals, day care facilities, community-based organizations, and home care	Examine the validation of an HIV/AIDS-related symptom assessment tool by using two samples.	Study 1: PCA (varimax rotation) and exploratory factor analysis Study 2: Confirmatory factor analysis	SSC-HIV	Six clusters were reported: 1) Malaise/weakness/fatigue (muscle aches, weakness, painful joints, fatigue, dry mouth, and thirsty). 2) Confusion/distress (difficulty in concentrating, depression, memory loss, fear, anxiety, and disorientation). 3) Fever/chills (fever, chills, day sweats, and night sweats).

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Table 1
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Author (year), Location	Design	Sample	Setting	Focus of Study	Analytical Technique	Symptom Assessment Tools	Key Findings
							4) Gastrointestinal discomfort (loose stools, diarrhea, gas/bloating, and abdominal pain). 5) Shortness of breath (shortness of breath at rest, wheezing, and shortness of breath with activity). 6) Nausea/vomiting (nausea, vomiting, and lack of appetite).
Holzemer et al. (2001),[25] U.S.	Cross sectional (not specified)	$N = 372$ PLWH Age: 40.0 yrs Male: 68.3% On ART: not specified Years living with HIV: not specified CD4 count: 521	One outpatient clinic in Texas, U.S.	Examine the construct validity and reliability of a revised symptom assessment tool (SSC-HIVrev)	PCA (varimax rotation)	SSC-HIVrev	Eleven SCs were reported including numbness, fear, gastrointestinal upset, bruising/bleeding, fatigue, headache, sore throat, rectal itch, shortness of breath, fever, body changes, and gynecological problems (women only).
Moens et al. (2015),[6] South Africa and Uganda	Cross sectional (not specified)	$N = 217$ PLWH Age: 36.5 yrs Male: 26.8% On ART: 49.1% Years living with HIV: not specified CD4 count: not specified	Four palliative care facilities in South Africa and one in Uganda	Identify SCs among PLWH attending palliative care facilities in South Africa and Uganda.	Hierarchical cluster analysis (Ward's method)	MSAS-SF 1) Physical Symptom Distress Index (MSAS-Phys) 2) Psychological Symptom Distress Index (MSAS-Psych) 3) Global Distress Index (MSAS-GDI)	Five SCs were reported: 1) Dermatological cluster: itching and changes in skin. 2) Generalized anxiety and elimination: feeling nervous, dizziness, shortness of breath, feeling bloated, difficulty concentrating, difficulty sleeping, problems urinating, and constipation. 3) Social and image: swelling of arms or legs, hair loss, mouth sores,

							problems with sexual interest/ activity, diarrhea, and difficulty swallowing. 4) Persistently present: numbness, pain, feeling irritable, cough, feeling tired, worrying, dry mouth, sweats, feeling sad, lack of energy, weight loss, and "I don't look like myself." 5) Gastrointestinal-related cluster: nausea, vomiting, lack of appetite, and changes in way food tastes.
Namisango et al. (2015),[7] Uganda	Cross sectional (not specified)	$N = 302$ ambulatory adult PLWH Age: not specified Male: 35.8% On ART: 74.2% Years living with HIV: not specified CD4 count: not specified	Two teaching hospitals in Uganda	Explore SCs among PLWH in Uganda and evaluate the clusters in regard to sociodemographic, health, and treatment characteristics	Hierarchical cluster analysis (Ward's method)	MSAS-SF	Five SCs were reported: 1) Cluster 1: pain, difficulty sleeping, difficulty swallowing, weight loss, swelling of arms or legs, feeling irritable, change in skin, lack of energy, and sweats. 2) Cluster 2: cough, dry mouth, feeling drowsy/tired, weight loss, and feeling irritable. 3) Cluster 3: pain, cough, numbness, difficulty urinating, shortness of breath, and lack of energy. 4) Cluster 4: difficulty concentrating, pain, lack of energy, changes in skin, dry mouth, numbness, difficulty sleeping, feeling bloated, vomiting, shortness of breath, mouth sores, lack of sexual interest, lack of

(*Continued*)

Table 1
Continued

Author (year), Location	Design	Sample	Setting	Focus of Study	Analytical Technique	Symptom Assessment Tools	Key Findings
							appetite, difficulty swallowing, changes in taste, weight loss, hair loss, swelling of arms or legs, and "I do not look like myself and feeling." 5) Cluster 5: difficulty concentrating, lack of energy, feeling bloated, feeling irritable, and feeling nervous.
Sousa et al. (2006),[26] U.S.	Longitudinal but cross-sectional sample (between January 1992 and October 1994)	$N = 917$ PLWH Age: 39.4 yrs Male: 100% On ART: 0% Living with HIV: 4.2 yrs CD4 count: not specified	Not specified	Evaluate symptom status based on the SSC-HIV and provide further the validity of the SSC-HIV	Structural equation modeling	SSC-HIV	Six clusters were reported: malaise/weakness/fatigue, confusion/distress, fever/chills, gastrointestinal discomfort, shortness of breath, and nausea/vomiting.
Tsai et al. (2003),[27] Taiwan	Cross sectional (not specified)	$N = 176$ PLWH Age: 34.8 yrs Male: 93.2% On ART: 86.4% Living with HIV: 3.3 yrs CD4 count: 318.7	Four hospitals, one clinic, and one community-based home visiting setting	Validate a Chinese version of the Sign and Symptom Checklist for Persons with HIV (SSC-HIV-C).	PCA (varimax rotation)	Chinese version of the Sign and Symptom Checklist for Persons with HIV (SSC-HIV-C)	Seven clusters were reported: confusion/distress, fever/chills, malaise/fatigue/weakness, nausea/vomiting, shortness of breath, gastrointestinal discomfort, and dry mouth/thirsty.
Wantland et al. (2011),[28] U.S.	Six-month longitudinal design (not specified)	$N = 240$ PLWH Age: 41.8 yrs Male: 65.4% On ART: 73.3% Living with HIV: 8.7 yrs CD4 count: not specified	Not specified	Determine the relationships between fatigue, neuropathic pain, and muscle aches and whether the SCs are maintained over time	Multilevel growth modeling and time-lagged effects linear growth modeling methods	SSC-HIVrev	The results showed a significant relationship between fatigue and muscle aches, and fatigue and numbness. Numbness and muscle aches explained 28% of the occurrence of fatigue.

Wilson et al. (2016),[3] U.S.	Cross sectional (between January and December 2011)	$N = 1945$ PLWH Age: 44 yrs Male: 78% On ART: 96% Years living with HIV: not specified CD4 count: not specified (51% of PLWH's CD4 count > 500)	One HIV clinic in Alabama, U.S.	Investigate the prevalence, burden, and patterns of symptoms in inpatient and outpatient PLWH	PCA (oblimin rotation)	HIV Symptom Index	Two clusters were reported: 1) Cluster 1: fatigue, muscle aches/joint pain, fever/chills/sweats, dizziness, numbness/pain in feet, nausea/vomiting, diarrhea, cough/shortness of breath, headache, loss of appetite, and bloating/abdominal pain. 2) Cluster 2: fatigue, muscle aches/joint pain, memory loss, sadness, nervous/anxious, poor sleep, and sex problems.
Zhu et al. (2018),[29] China	Cross sectional (between April and September 2017)	$N = 1116$ PLWH Age: 40.0 yrs Male: 77.7% On ART: 100% Living with HIV: 3.0 yrs CD4 count: 312	Four HIV/AIDS designated hospitals in China	Identify SCs among PLWH in China and examine sociodemographic and health factors related with the SCs	PCA (varimax rotation) and network analysis	Author-developed symptom scale	Five clusters were reported: 1) Cognitive dysfunction: having difficulty in concentrating, slow reaction, memory loss, having difficulty in reasoning, and becoming confusing. 2) Mood disturbance: uncontrollable worrying, feeling nervous, little interest in doing things, and feeling down. 3) Wasting syndrome: fever, appetite loss, diarrhea, nausea/vomiting, and weight loss. 4) Dizziness/headache: dizziness and headache. 5) Skin-muscle-joint disorder: rash, muscle/joint aches, hand/foot pain, and mouth ulcers.

(*Continued*)

Table 1
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Author (year), Location	Design	Sample	Setting	Focus of Study	Analytical Technique	Symptom Assessment Tools	Key Findings
Zuniga et al. (2017),[30] U.S.	Cross sectional (in 2015)	$N = 951$ PLWH with DM Age: 55.6 yrs Male: 79.8% On ART: not specified Years living with HIV: not specified CD4 count: not specified	Eight HIV clinics in U.S.	Describe symptom patterns for PLWH with DM	PCA (promax)	HIV Symptom Index	Three clusters were reported: 1) Neurological/ psychological cluster: sadness, anxious, poor sleep, fatigue, forgetful, sex problems, changes in body fat distribution, neuropathy, and aches. 2) Gastrointestinal/ flu-like cluster: nausea, dizziness, poor appetite, fever, cough, bloating, headache, and diarrhea. 3) Physical changes: weight loss, hair loss, and skin problems.

PLWH = people living with HIV; ART = antiretroviral therapy; SSC-HIV = Sign and Symptom Check-List for Persons with HIV disease; PCA = principal components analysis; SSC-HIVrev = revised Sign and Symptom Check-List for Persons with HIV disease; MSAS-SF = Memorial Symptom Assessment Scale Short Form; DM = diabetes mellitus; SCs = symptom clusters.

The sample sizes of the included studies varied from 176 to 2505. The average age of participants ranged from 34.8 to 55.6 years or was not specified. More than half of the studies ($n = 7$) evaluated whether participants were on ART medication.[3,6,7,21,27–29] Six studies reported an average CD4 count, which varied from 76 to 521.[3,22–25,27,29]

Settings. A majority of studies ($n = 8$) specified that they included PLWH from multiple sites, including HIV/AIDS hospitals,[7,21,23,27,29] clinics,[23,24,27,30] community-based nursing care or palliative care facilities,[6,24] or home care agencies.[24,27] Two studies recruited PLWH from a single HIV/AIDS clinic,[3,25] whereas three studies did not report detailed information about the settings.[22,26,28]

Analytical Technique. Principal components analysis (PCA) was the most common analytical technique used to derive symptom clusters, which was performed in seven studies.[3,23–25,27,29,30] Other methods included hierarchical cluster analysis (HCA),[6,7,21] exploratory factor analysis,[24] confirmatory factor analysis,[24] structural equation modeling,[26] and network analysis.[29] One study used multilevel growth modeling and time-lagged effects linear growth modeling methods to analyze the association between fatigue, muscle aches, and numbness in a longitudinal data set.[28]

Symptom Assessment Tools

Table 2 shows a summary of the measures used to assess symptoms. Two studies used the HIV Symptom Index.[3,30] The HIV Symptom Index includes 20 items that measured the degree of disturbance of symptoms, with 0 being symptom not present and 4 being "it bothers me a lot." Two studies used author-developed symptom scales that were developed based on the HIV Symptom Index.[21,29] Boyer's measure included 22 symptoms, among which 20 symptoms were derived from the HIV Symptom Index and two additional symptoms were added.[21] Zhu's measure included 27 symptoms, 18 of which were derived

Table 2
Summary of Measures

Study	Symptom Assessment Tool	Description	Dimension
Boyer et al. (2017)[21]	Author-developed symptom scale	22 items (20 symptoms were derived from the HIV Symptom Index and two additional symptoms were added). 0–1 scale, with 0 being no/little discomfort and 1 being moderate/great discomfort.	Distress
Cook et al. (2011)[22] Sousa et al. (2006)[26]	SSC-HIV (only using 23 items)	23 items derived from SSC-HIV. 0–1 scale was used to measure the occurrence of symptoms experienced on that day.	Occurrence
Haye et al. (2010)[23]	Beck Depression Inventory-II	21 items. A four-point scale (minimal, mild, moderate, and severe) was used to measure severity of depressive symptoms.	Severity
Holzemer et al. (1999)[24]	SSC-HIV	41 items. A four-point scale was used to measure the severity of symptoms experienced on that day.	Severity
Holzemer et al. (2001)[25]	SSC-HIVrev	72 items. A four-point scale was used to measure the severity of symptoms experienced on that day.	Severity
Moens et al. (2015)[6] Namisango et al. (2015)[7]	MSAS-SF	32 items. A Likert scale was used to measure the distress of symptoms during recent seven days on a range of 0 (least distressed) to 4 (most distressed).	Distress
Tsai et al. (2003)[27]	SSC-HIV (only using 26 and 28 items)	26 and 28 items. A four-point scale was used to measure the severity of symptoms experienced on that day.	Severity
Wantland et al. (2011)[28]	SSC-HIVrev (only using three items to measure fatigue, numbness, and muscle aches)	Three items. A four-point scale was used to measure the severity of symptoms experienced on that day.	Severity
Wilson et al. (2016)[3] Zuniga et al. (2017)[30]	HIV Symptom Index	20 items. A Likert scale, with 0 being symptom not present and 4 being "it bothers me a lot."	Distress
Zhu et al. (2018)[29]	Author-developed symptom scale	27 items (18 symptoms were derived from the HIV Symptom Index and nine additional symptoms were derived from the Patient Health Questionnaire 2, Generalized Anxiety Disorder 2-item Questionnaire, and cognition-related domain of the AIDS Health Assessment Questionnaire). A four-point scale was used to measure the severity of symptoms experienced in the past four weeks.	Severity

SSC-HIV = Sign and Symptom Check-List for Persons with HIV disease; SSC-HIVrev = revised Sign and Symptom Check-List for Persons with HIV disease; MSAS-SF = Memorial Symptom Assessment Scale Short Form.

from the HIV Symptom Index and nine additional symptoms were derived from the Patient Health Questionnaire 2, the Generalized Anxiety Disorder 2-item Questionnaire, and the cognition-related domain of the AIDS Health Assessment Questionnaire.[29]

Six studies used the Sign and Symptom Check-List for Persons with HIV disease (SSC-HIV) and a modified version to assess symptom severity. Holzemer developed the original version of the SSC-HIV, which included 41 symptoms, measuring the severity of symptoms, with 0 being symptom not present and 4 being "it bothers me a lot."[24] In 2001, Holzemer et al.[25] revised this measure (SSC-HIVrev) and included 72 HIV-related symptoms in total. Cook et al. and Sousa et al. used a modified 23-item version,[22,26] whereas Tsai et al.[27] used 26- and 28-item versions in one study. Wantland et al.[28] used three items from SSC-HIVrev to assess the severity of fatigue, muscle aches, and numbness.

Two studies used the Memorial Symptom Assessment Scale Short Form, which included 32 items, measuring the distress of symptoms during the last seven days on a range of 0 (least distressed) to 4 (most distressed).[6,7] The remaining study used the Beck Depression Inventory-II to assess depressive symptoms among PLWH, which included 21 items.[23]

Dimension. The majority of the studies ($n = 6$) measured the symptom dimension of severity.[23–25,27–29] Five studies evaluated symptom distress,[3,6,7,21,30] whereas two studies measured symptom occurrence only.[22,26]

Symptom Clusters

Five most commonly reported symptom clusters were found in 13 studies: 1) sad/depressed/loss of interest and nervous/anxious/worrying; 2) difficulty sleeping, problems with sex, and fatigue/loss of energy; 3) fever/chills/sweat, nausea/vomiting, and loss of appetite; 4) numbness, muscle aches, and joint pain; and 5) dizziness and headache. Further details are listed in Table 3.

The symptoms of sad/depressed/loss of interest and nervous/anxious/worrying co-occurred in eight studies.[3,21,22,24,26,27,29,30] Only one study found that the symptoms occurred independently.[29] Three studies reported additional symptom clusters co-occurring with sad/depressed/loss of interest and nervous/anxious/worrying.[3,21,30] Four studies reported that difficulty in concentrating, trouble remembering, confusion, fear, and disorientation were grouped in the same clusters.[22,24,26,27]

The symptoms of difficulty sleeping, problems with sex, and fatigue/loss of energy co-occurred in three studies. Only one study found that these symptoms co-occurred independently,[3] whereas two studies reported additional symptom clusters co-occurring with them.[21,30]

Fever/chills/sweat, nausea/vomiting, and loss of appetite was the most commonly reported symptom cluster in all included studies. Five studies reported that these symptoms were grouped in the same cluster,[3,6,21,29,30] whereas four studies divided three symptoms into two separate clusters that occurred independently.[22,24,26,27]

The symptom of numbness, muscle aches, and joint pain co-occurred in five studies,[3,6,21,29,30] but none of these five studies reported that these symptoms co-occurred independently.

The cluster of dizziness-headache was reported by four studies,[3,25,29,30] where only one study found it to occur independently.[29]

The results of symptom clusters were separated into five major classifications based on different symptom assessment tools and analytical techniques, defined as Group A: the study used the HIV Symptom Index or HIV Symptom Index–based symptom assessment tools[3,21,29,30]; Group B: the study used the Memorial Symptom Assessment Scale Short Form symptom assessment tools and HCA as the analytical technique[6,7]; Group C: the study used the SSC-HIVrev symptom assessment tools[25,28]; Group D: the study used the Beck Depression Inventory-II depressive symptom assessment tools[23]; and Group E: the study used the SSC-HIV symptom assessment tools and was conducted before the ART era.[22,24,26,27] All five classifications concluded that the consistency of the symptom clusters was unstable across different analytical techniques. The comparison between Group A and Group E revealed that using different symptom assessment tools also contributed to unstable results.

Risk of Bias

Table 4 provides the risk of bias of the included studies. We assigned ratings of yes, no, unclear, and not available to each criterion using the JBI Critical Appraisal Checklist. All included studies except that of Wantland et al.[28] used the JBI Critical Appraisal Checklist for Prevalence Studies to evaluate the risk of bias. Among 12 studies, nine studies lacked details regarding important population characteristics, including years living with HIV, years on ART, CD4 count, and other potentially influential factors.[3,6,7,21,23–26,30] Sampling methods were avoided in five studies,[21–23,25,26] whereas five studies lacked details regarding the description of settings and subjects.[21–24,26] We used the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies to evaluate the risk of bias in the study by Wantland et al.[28] This study presented a low risk of bias and failed to report specific information about settings due to secondary data analysis.

Table 3
Summary of Symptom Combinations

Study	Group[a]	Cluster 1: Sad/ Depressed/Loss of Interest and Nervous/ Anxious/Worrying	Cluster 2: Difficulty Sleeping, Problems With Having Sex, and Fatigue/ Loss of Energy	Cluster 3: Fever/Chills/ Sweat, Nausea/Vomiting, and Loss of Appetite	Cluster 4: Numbness, Muscle Aches, and Joint Pain	Cluster 5: Dizziness and Headache	Other Clusters
Boyer et al. (2017)[21]	A	1) Yes (see Cluster 3)	1) Yes (see Cluster 3)	1) Yes with dizziness, memory loss, coughing, and trouble breathing	2) Yes with headache, bloating, diarrhea, weight loss/wasting, skin problems, hair loss, renal problems, problems when urinating, and body changes		
Wilson et al. (2016)[3]	A	1) Yes (see Cluster 5)	2) Yes	1) Yes (see Cluster 5)	1) Yes (see Cluster 5)	3) Yes with bloating and pain in abdomen	
Zhu et al. (2018)[29]	A	1) Yes		2) Yes with diarrhea and weight loss/wasting	3) Yes with mouth ulcer and rash	4) Yes	5) Memory loss, having difficulty in concentrating, having difficulty in reasoning, becoming confusing, and slow reaction
Zuniga et al. (2017)[30]	A	1) Yes (see Cluster 4)	1) Yes (see Cluster 4)	2) Yes (see Cluster 5)	1) Yes with body change	2) Yes with coughing, bloating, and diarrhea	3) Weight loss/wasting, skin problems, and hair loss
Moens et al. (2015)[6]	B			1) Yes but without fever/ chills/sweat and with changes in way food tastes	2) Yes with feeling irritable, cough, feeling tired, worrying, dry mouth, sweats, feeling sad, lack of energy, weight loss, and "I don't look like myself"		3) Itching and changes in skin 4) Feeling nervous, dizziness, shortness of breath, feeling bloated, difficulty concentrating, difficulty sleeping, problems urinating, and constipation 5) Swelling of arms or legs, hair loss, mouth sores, problems with sexual interest/ activity, diarrhea, and difficulty swallowing
Namisango et al. (2015)[7]	B						1) Pain, difficulty sleeping, difficulty swallowing, weight loss, swelling of arms or legs, feeling irritable, change in skin, lack of energy, and sweats 2) Cough, dry mouth, feeling drowsy/tired, weight loss, and feeling irritable

(*Continued*)

Table 3
Continued

Study	Group[a]	Cluster 1: Sad/ Depressed/Loss of Interest and Nervous/ Anxious/Worrying	Cluster 2: Difficulty Sleeping, Problems With Having Sex, and Fatigue/ Loss of Energy	Cluster 3: Fever/Chills/ Sweat, Nausea/Vomiting, and Loss of Appetite	Cluster 4: Numbness, Muscle Aches, and Joint Pain	Cluster 5: Dizziness and Headache	Other Clusters
							3) Pain, cough, numbness, difficulty urinating, shortness of breath, and lack of energy 4) Difficulty concentrating, pain, lack of energy, changes in skin, dry mouth, numbness, difficulty sleeping, feeling bloated, vomiting, shortness of breath, mouth sores, lack of sexual interest, lack of appetite, difficulty swallowing, changes in taste, weight loss, hair loss, swelling of arms or legs, and "I do not look like myself and feeling" 5) Difficulty concentrating, lack of energy, feeling bloated, feeling irritable, and feeling nervous
Holzemer et al. (2001)[25]	C					1) Yes with heart racing and chest pain	2) Numbness; 3) fear; 4) gastrointestinal upset; 5) bruising/bleeding; 6) fatigue; 7) sore throat; 8) rectal itch; 9) shortness of breath; 10) fever; 11) body changes; and 12) gynecological problems (women only)
Wantland et al. (2011)[28]	C						1) Fatigue, muscle aches, and numbness
Haye et al. (2010)[23]	D						1) Loss of interest, agitation, suicidal thoughts, sadness, crying, past failure, irritability, pessimism, and loss of pleasure

				2) Self-dislike, self-criticalness, punishment feelings, and changes in sleeping 3) Loss of energy, tiredness or fatigue, worthlessness, concentration difficulty, changes in appetite, indecisiveness, and loss of interest in sex
Cook et al. (2011)[22]	E	1) Yes with difficulty in concentrating, trouble remembering, and confusion	2) Yes: fever/chills/sweat 3) Yes: nausea/vomiting and loss of appetite	4) Fatigue, muscle aches, weakness in muscles, joint pain, and dry mouth 5) Diarrhea, heartburn, and pain in abdomen 6) Dyspnea, dry cough, and asthma
Holzemer et al. (1999)[24]	E	1) Yes with difficulty in concentrating, memory loss, fear, and disorientation	2) Yes: fever/chills/sweat 3) Yes: nausea/vomiting and loss of appetite	4) Fatigue, muscle aches, weakness in muscles, joint pain, dry mouth, and thirsty 5) Diarrhea, loose stool, bloating, and pain in abdomen 6) Shortness of breath and wheezing
Sousa et al. (2006)[26]	E	1) Yes with difficulty in concentrating, trouble remembering, and confusion	2) Yes: fever/chills/sweat 3) Yes: nausea/vomiting and loss of appetite	4) Fatigue, muscle aches, weakness in muscles, joint pain, and dry mouth 5) Diarrhea, heartburn, and pain in abdomen 6) Dyspnea, dry cough, and asthma
Tsai et al. (2003)[27]	E	1) Yes with difficulty in concentrating, memory loss, fear, insomnia, and disorientation (only in 28-item scale)	2) Yes: fever/chills/sweat 3) Yes: nausea/vomiting and loss of appetite	4) Fatigue, muscle aches, weakness in muscles, joint pain, and headache (only in 28-item scale) 5) Diarrhea, loose stool, bloating, and pain in abdomen 6) Shortness of breath and wheezing 7) Dry mouth and thirsty

MSAS-SF = Memorial Symptom Assessment Scale Short Form; SSC-HIVrev = revised Sign and Symptom Check-List for Persons with HIV disease; SSC-HIV = Sign and Symptom Check-List for Persons with HIV disease; ART = antiretroviral therapy.

[a]Group A: Study used HIV Symptom Index or HIV Symptom Index–based symptom assessment tools. Group B: Study used MSAS-SF symptom assessment tools and hierarchical cluster analysis as an analytic technique. Group C: Study used SSC-HIVrev symptom assessment tools. Group D: Study used Beck Depression Inventory-II depressive symptom assessment tools. Group E: Study used SSC-HIV symptom assessment tools and was conducted before ART era.

Table 4
Risk of Bias

Study	C1[a]	C2	C3	C4	C5	C6	C7	C8	C9
Boyer et al. (2017)[21]	U	U	Y	U	Y	Y	Y	Y	Y
Cook et al. (2011)[22]	Y	U	Y	U	Y	Y	Y	Y	Y
Haye et al. (2010)[23]	U	U	Y	U	Y	Y	Y	Y	Y
Holzemer et al. (1999)[24]	U	Y	Y	U	Y	Y	Y	Y	Y
Holzemer et al. (2001)[25]	U	U	Y	Y	Y	Y	Y	Y	Y
Moens et al. (2015)[6]	U	Y	Y	Y	Y	Y	Y	Y	Y
Namisango et al. (2015)[7]	U	Y	Y	Y	Y	Y	Y	Y	Y
Sousa et al. (2006)[26]	U	U	Y	U	Y	Y	Y	Y	Y
Tsai et al. (2003)[27]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wantland et al. (2011)[28,b]	Y	U	Y	Y	Y	Y	Y	Y	
Wilson et al. (2016)[3]	U	Y	Y	Y	Y	Y	Y	Y	Y
Zhu et al. (2018)[29]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Zuniga et al. (2017)[30]	U	Y	Y	Y	Y	Y	Y	Y	Y

Y = yes; N = no; U = unclear; N/A = not available; JBI = Joanna Briggs Institute.
[a]All studies except Wantland et al. (2011) used the JBI Critical Appraisal Checklist for Prevalence Studies to evaluate the risk of bias. C1: Was the sample frame appropriate to address the target population? C2: Were study participants sampled in an appropriate way? C3: Was the sample size adequate? C4: Were the study subjects and the setting described in detail? C5: Was the data analysis conducted with sufficient coverage of the identified sample? C6: Were valid methods used for the identification of the condition? C7: Was the condition measured in a standard, reliable way for all participants? C8: Was there appropriate statistical analysis? C9: Was the response rate adequate, and if not, was the low response rate managed appropriately?
[b]This study used the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies to evaluate the risk of bias. C1: Were the criteria for inclusion in the sample clearly defined? C2: Were the study subjects and the setting described in detail? C3: Was the exposure measured in a valid and reliable way? C4: Were objective, standard criteria used for measurement of the condition? C5: Were confounding factors identified? C6: Were strategies to deal with confounding factors stated? C7: Were the outcomes measured in a valid and reliable way? C8: Was an appropriate statistical analysis used?

Discussion

In this review, we systematically summarized the compositions, measures, and analytical techniques of symptom clusters for PLWH. We reviewed 13 studies and found that symptom clusters varied considerably in combinations. Differences in methodology and symptom assessment tools were the central hindrance in reaching a generally consistent conclusion. The five most commonly reported symptom clusters included sad/depressed/loss of interest—nervous/anxious/worrying, difficulty sleeping—problems with having sex—fatigue/loss of energy, fever/chills/sweat—nausea/vomiting—loss of appetite, numbness, muscle aches—joint pain, and dizziness—headache.

The results showed that the sad/depressed/loss of interest and nervous/anxious/worrying combination appeared to be the most robust cluster across all included studies. The possible reason is that depression and anxiety are prevalent among PLWH. In this review, these symptoms represented a spectrum of psychological distress instead of the clinical definitions of "depression" and "anxiety." It is widely known that depression and anxiety are prevalent among PLWH,[31–33] particularly among younger and female patients. In addition, Zhu et al.[29] performed a network analysis and found that the combination of depression and anxiety was the most central cluster after cognitive dysfunction and was related to a board range of symptoms, including cognitive problems and other physical problems. Previous studies found that depression and anxiety may not only trigger or worsen somatic and other psychological symptoms but also deteriorate health conditions and quality of life.[34,35] Among all included studies, Haye et al.[23] identified subgroups of depressive symptoms among PLWH, which provided deeper insight into the classifications of HIV-related psychological distress.

We found that the fever/chills/sweat, nausea/vomiting, and loss of appetite combination was another robust cluster across studies. However, in the majority of the included studies, these symptoms did not co-occur independently. They occurred alongside a range of other symptoms, including diarrhea, bloating, coughing, pain in the chest or abdomen, and trouble breathing. The composition of this cluster and additional symptoms may vary with different characteristics of participants, such as types of comorbidities (especially opportunistic infections), CD4 levels, and ART regimens.[3,21,29] In addition, previous studies noted that the level of inflammation in PLWH may lead to fever, nausea, and a lack of appetite, especially in the advanced HIV stage.[36,37]

We also found insomnia problems with sex—fatigue combination, the numbness—muscle aches—joint pain combination, and the headache-dizziness combination that occurred only in recent studies that were conducted in the ART era. The results indicated that these symptom clusters were potential side effects of long-term ART. Previous studies found that all integrase strand transfer inhibitors, especially zidovudine and efavirenz, may cause muscle ache and sleeping problems, whereas numbness and other nerve problems were potentially related to older nucleoside reverse transcriptase inhibitors, including didanosine, stavudine, and zidovudine.[5,38] Tadesse et al.[39] reported that headache was one of the most frequently reported adverse drug reactions of ART and central nervous system symptoms, and peripheral neuropathy

was responsible for the majority of ART treatment regime changes. However, studies also noted that some of ART side effects, such as numbness, muscle aches, and joint pain, were often difficult to distinguish from HIV-induced comorbidities.[40,41]

The findings of the review should be interpreted with caution as various analytical techniques and symptom assessment tools were applied. The results indicated that symptom combinations varied according to the deriving methodology and measures performed. Our review revealed that symptom cluster findings using PCA were more similar to each other than to the results using HCA. However, some studies suggested that HCA is a more appropriate method than PCA to reduce dimensionality as HCA derives clusters based on the variance that had been removed from features with an error variance.[42] There still exists a disparity and lack of consensus in which statistical methodology is best for extracting symptom clusters.[43,44] This highlighted the notion that multiple methods should be performed within the same data set to extract symptom clusters to reach a more stable result across different methodologies. In our review, only three included studies reported that they performed another method to confirm the stability of the derived clusters.[21,24,29]

We found that symptom assessment tools were another crucial factor that affected the stability of the results. In this review, included studies assessed different ranges of symptoms by using 11 types of mature scales or author-developed checklists and finally contributed to five distinct groups of results. This highlighted the necessity to develop a threshold to decide what symptoms should be included in the clusters. Dong et al.[18] suggested that studies could set a symptom prevalence threshold ranging from 15% to 75% to achieve a more stable result of symptom clusters.

Limitations

Although this is the first study to summarize the symptom clusters among PLWH, there were several limitations. First, most of the included studies were cross-sectional studies or longitudinal studies using a cross-sectional sample. Only one study examined the longitudinal changes of one cluster.[28] As a result, the longitudinal stability of the derived clusters among PLWH is still unknown. Second, psychological symptoms were generally not well measured in all studies. The majority of studies used single items to measure depression and anxiety, which may not truly reflect clinically defined psychological symptoms. Third, there was little information about the predictors and impacts of symptom clusters on the outcomes of PLWH. Therefore, whether derived clusters add value to patient assessment and how the clusters would optimize clinical intervention are still unknown.

Conclusion

Overall, this systematic review summarized the compositions, measures, and analytical techniques of symptom clusters for PLWH. Although this review found unstable results on the compositions of symptom clusters and it was difficult to reach a definitive conclusion because of variations in study design, sample characteristics, measures, and analytical techniques, this review shows a great potential value for both clinicians and researchers. This systematic review recommends that health care staff be vigilant for multiple symptoms mentioned in this review. For researchers, this review suggests that future studies need to use standardized symptom measures and need to set a symptom prevalence threshold when choosing symptoms in PCA, HCA, or other analytical techniques. In addition, there is an urgent need to conduct a longitudinal design to evaluate the stability of symptom clusters over time. Future research can be guided by this review to address the instability and inconsistency of symptom clusters among PLWH.

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