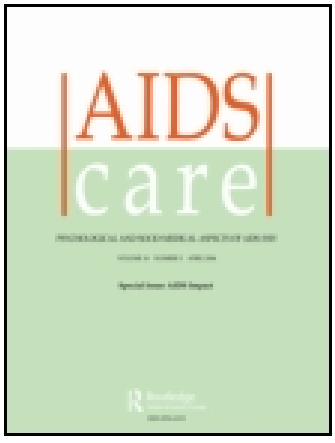

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A novel symptom cluster analysis among ambulatory HIV/AIDS patients in Uganda

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Symptom clusters are gaining importance given HIV/AIDS patients experience multiple, concurrent symptoms. This study aimed to: determine clusters of patients with similar symptom combinations; describe symptom combinations distinguishing the clusters; and evaluate the clusters regarding patient socio-demographic, disease and treatment characteristics, quality of life (QOL) and functional performance. This was a cross-sectional study of 302 adult HIV/AIDS outpatients consecutively recruited at two teaching and referral hospitals in Uganda. Socio-demographic and seven-day period symptom prevalence and distress data were self-reported using the Memorial Symptom Assessment Schedule. QOL was assessed using the Medical Outcome Scale and functional performance using the Karnofsky Performance Scale. Symptom clusters were established using hierarchical cluster analysis with squared Euclidean distances using Ward's clustering methods based on symptom occurrence. Analysis of variance compared clusters on mean QOL and functional performance scores. Patient subgroups were categorised based on symptom occurrence rates. Five symptom occurrence clusters were identified: Cluster 1 (n = 107), *high–low* for sensory discomfort and eating difficulties symptoms; Cluster 2 (n = 47), *high–low* for psycho-gastrointestinal symptoms; Cluster 3 (n = 71), *high* for pain and sensory disturbance symptoms; Cluster 4 (n = 35), *all high* for general HIV/AIDS symptoms; and Cluster 5 (n = 48), *all low* for mood-cognitive symptoms. The *all high* occurrence cluster was associated with worst functional status, poorest QOL scores and highest symptom-associated distress. Use of antiretroviral therapy was associated with *all high* symptom occurrence rate (Fisher's exact = 4, $P < 0.001$). CD4 count group below 200 was associated with the *all high* occurrence rate symptom cluster (Fisher's exact = 41, $P < 0.001$). Symptom clusters have a differential, affect HIV/AIDS patients' self-reported outcomes, with the subgroup experiencing high-symptom occurrence rates having a higher risk of poorer outcomes. Identification of symptom clusters could provide insights into commonly co-occurring symptoms that should be jointly targeted for management in patients with multiple complaints.

Keywords: symptom clusters; ambulatory HIV/AIDS patients; Africa

Background

With lives extended by antiretroviral therapy (ART), HIV patients can experience more medical comorbidities associated with ageing, and complications from HIV disease processes, treatment side effects, drug interactions and long-term sequela (Deeks & Phillips, 2009; Justice et al., 2009). Symptoms of these comorbidities are defined as subjective health-related experiences described by their intensity, duration, interference with daily activities or degree of change over time (Miaskowski, Aouizerat, Dodd, & Cooper, 2007).

Current key priorities of the HIV/AIDS global programme include minimising medicinal side effects and improving patient adherence (Joint United Nations Programme on HIV/AIDS, 2013). Effective symptom management is therefore a critical pillar for HIV/AIDS care and treatment (World Health Organization [WHO], 2013). Several reports have described the prevalence of such symptoms in isolation (Harding, Clucas, et al., 2012; Makoae et al., 2005; Wakeham et al., 2010). There has, however, been increasing interest in transitioning away from a model of symptom research focusing only on single symptoms to the promotion of multiple symptom models that give a broader insight into symptomatology, recognising that HIV/AIDS patients experience multiple concurrent symptoms. Studies conducted among cancer patients have shown multiple symptoms are additive in their impact, significantly affecting patient function (Cleeland, 2007; Dodd, Miaskowski, & Paul, 2001; Valentine & Myeres, 2001) and

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likely to better predict patient outcomes [e.g., behaviour, function or quality of life (QOL)] than a single symptom (Dodd, Cho, Cooper, & Miaskwoski, 2010).

To date only three studies exist of symptom clusters in HIV populations. In the first, six clusters were identified in a population of people with HIV-associated illness: malaise/fatigue, confusion/distress, fevers/chills, gastrointestinal discomfort, shortness of breath and nausea/vomiting (Sousa, Tann, & Kwok, 2006). Using these clusters, the second studied their change with HIV progression and noted the occurrence of the symptom clusters malaise/fatigue and nausea/vomiting appeared to relate specifically to disease progression rather than participants' overall health (Cook, Sousa, Matthews, Meek, & Kwong, 2011). However, this study was conducted in a retrospective (1992–1994) cohort of 246 people living with HIV before the advent of highly efficacious ART and may no longer be relevant. In the third study, Voss, Portillo, Holzemer, and Dodd (2007) investigated the conceptually distinct differences between fatigue and depression and noted that with increasing depression patients become more fatigued, supporting the conclusion that both symptoms should be evaluated jointly. Importantly, all three studies were conducted in high-income countries; there is a dearth of evidence on symptom clusters in sub-Saharan Africa, where the burden of HIV/AIDS is highest.

Dodd et al. (2001) noted symptom clusters have an adverse effect on patient outcomes, resulting in a strong clinical argument for focusing on clusters than individual symptoms to improve HIV care and treatment. Kurtz, Kurtz, Given, and Given (2007) found a symptom cluster approach to symptom management among cancer patients effective in reducing severities of a pain, fatigue and insomnia cluster. This evidence suggests that, based on symptom experience clusters, different groups of patients may warrant different treatment types or more targeted symptom management interventions to improve their outcomes (Gwede, Small, Munster, Andrykowski, & Jacobsen, 2008; Miaskowski et al., 2006; Pud et al., 2008).

This study therefore aimed to: identify clusters of patients with similar symptom experiences; describe symptom combinations distinguishing the clusters; and evaluate the clusters in regard to patient socio-demographic, disease and treatment characteristics, QOL and functional performance.

Methods

Participants

Ambulatory HIV/AIDS patients were consecutively recruited from Mbarara and Mulago teaching and referral hospitals in Uganda, with the inclusion criteria being: a documented HIV diagnosis; patients being aware of their diagnosis; at least 18 years of age; and able to give informed consent. Patients either too ill to complete the questionnaires or with cognitive impairment were excluded.

Procedures and variables

Patient outcome data on QOL, symptoms and socio-demographic variables were self-reported, whilst data on clinical characteristics (e.g., time of HIV diagnosis, use of ART, CD4 T-cell count) were obtained from the most recent laboratory report in the patients' medical record. Patients were staged for the WHO clinical stage by health workers on the day of the survey.

Data on symptoms were collected using the Memorial Symptom Assessment Schedule – Short Form (MSAS-SF), functional performance was rated by trained health workers using the Karnofsky Performance Scale (KPS), whilst QOL was measured using the Medical Outcomes Study (MOS-HIV). All tools were forward and back translated into the two most commonly used languages (Luganda and Runyankore-Rukiga) by a university clinical psychologist and a researcher conversant with the subject matter.

Measures

Memorial Symptom Assessment Schedule

The MSAS-SF is a patient-rated symptom assessment tool commonly used in HIV-infected populations (Makoae et al., 2005) that records the presence and burden of 28 physical symptoms and 4 psychological symptoms in the 7 days prior to the assessment (Harding, Molloy, Easterbrook, Frame, & Higginson, 2006; Harding, Clucas, et al., 2012; Wakeham et al., 2010). Each physical symptom experienced by the patient was scored for the level of distress it caused on a 5-point (0–4) Likert scale (not at all, a little bit, somewhat, quite a bit, and very much). Subscale indices of global distress, physical symptoms distress and psychological distress were calculated from the mean burden ratings (Chang, Hwang, Thaler, Kasimis, & Portenoy, 2004).

The Karnofsky Performance Scale

This is an observer-rated scale used to report a patient's level of physical functioning ability. Patients are rated on a scale of 0–100, with 0 corresponding to no functioning ability (i.e., death) and 100 corresponding to complete, independent functioning (Karnofsky & Burchenal, 1949). In this study, health workers were trained to use the KPS and rated patients' functional performance using its definitions rating (%) criteria (Karnofsky & Burchenal, 1949).

The MOS-HIV

The MOS-HIV was developed in the USA (Wu, Hays, Kelly, Malitz, & Bozette, 1997) and has been adapted and validated in Uganda and found to be a valid and reliable QOL measure in HIV patients ($\alpha > 0.7$) for all domains, indicating high internal inconsistency (Mast et al., 2004; Streiner & Norman, 1985). Mental, physical health and general well-being subscales were computed and used as the main outcome measures of interest (Revicki, Sorensen, & Wu, 1998).

Ethics

Approval to conduct the study was obtained from Mulago Hospital Research Committee and Mbarara University Faculty of Medicine Research Ethics Committee.

Data analysis

Descriptive analysis was performed to profile the sample by socio-demographic characteristics and clinical and symptom characteristics. Means and standard deviations were calculated for continuous variables and percentages for categorical variables. Data are presented by gender.

Cluster analysis was undertaken to identify groups of patients that are internally homogenous but clearly different in some respect from other clusters (i.e., with maximal homogeneity within the groups but maximal heterogeneity between the groups). Participants were placed into clusters via hierarchical (agglomerative) clustering using Ward's method based on squared Euclidean distances on the identified symptom types. Given the optimal number of clusters identified, the Duda and Hart Je(2)/Je(1) index was used to select the final number of clusters (Milligan & Cooper, 1985). Distinct clustering is generally considered to be indicated by large values of the Duda and Hart Index and small values of the Duda and Hart Pseudo T-squared. The clusters to be fitted included all identified variables. Clusters were characterised as having unusually high or low prevalence (compared to other clusters) on the original 32 identified symptoms, and there were 160 tests based on them (32 × 5). To retain a 95% confidence level on the overall results, statistical significance was set at a Bonferroni-corrected level of $p < 0.0003$ for each test, corresponding to a chi-squared statistic of >13. At the bivariate level, symptom clusters were compared regarding to patient socio-demographic, disease and treatment characteristics using the chi-square test and Fisher's exact test where expected cell counts were less than 5.

Naming of clusters

Subgroups of patients were categorised based on symptom occurrence rates as *all high* where *all* symptoms in a cluster had a high occurrence rate, *high–low* where a symptom cluster had *equal counts* for high and low occurrence symptom rates, *all low* where *all* symptoms in a cluster had a low occurrence rate and *high* occurrence where only *one* symptom in the cluster had a low occurrence rate. This conceptual approach allows for the identification of patient subgroups that are at greater risk for more severe symptom experiences (Miaskowski et al., 2007).

Analysis of variance was used to assess for differences between the clusters on demographic, disease, treatment characteristics, symptom scores, mental and physical health subscales, the general well-being item of the MOS-HIV and functional performance. Independent variables entered in univariate analysis were gender (female versus male), age (categorised as ≤35 and >35 years), use and non-use of ART (yes/no) and WHO clinical stages 1 and 2, 3 or 4 (WHO clinical stages 1 and 2 were combined due to their small numbers). CD4 T-cell count categories of ≤200, 201–499 and 500 and above were used, as were ≤70 and >70 categories for the KPS (where a score of 70 indicates the patient is able to care for their self but unable to carry on normal activity or do active work, while a score below 70 indicates an inability to care for their self without assistance; Potter, Hami, Bryan, & Quigley, 2003). A more stringent *P* value cut-off of <0.005 was adopted for confirming statistical significance, given the multiple tests conducted.

Results

Sample characteristics

We approached 343 patients and 302 (88%) participated. Of these, 110 were recruited from Mulago hospital and 192 from Mbarara hospital, with a greater proportion being female ($n = 194$; 64.2%), married ($n = 142$; 47%), Anglican ($n = 166$; 55%) and educated to either primary or secondary levels ($n = 217$; 71.8%). The majority ($n = 264$, 87.4%) of respondents had KPS scores above 70%, the majority ($n = 217$, 71.8) belonged to WHO clinical stages 3 and 4, 224 (74.2%) were on ART (first line treatment) at the time of data abstraction (Table 1).

All 32 symptoms of the MSAS-SF – except nausea, problems urinating, diarrhoea, dizziness, feeling sad and worrying – were critical for differentiating patient symptom experience. The Duda and Hart [a large Je (2)/Je(1)] index and its associated small pseudo T-squared value identified five clusters as the most appropriate number for the data. The summary of the cluster characteristics is provided in Table 2.

Cluster 1 ($n = 107$): *high–low* occurrence cluster was characterised by low occurrence for the symptoms of pain, difficulty sleeping, difficult swallowing, weight loss, swelling of arms or legs, feeling irritable, and

Table 1. Socio-demographic characteristics of the study sample.

	Female (194, 64.2%)	Male (108, 35.7%)	Over all (302)
	n (%)	*n* (%)	*n* (%)
On ART (yes)	140 (62.5%)	84 (37.5)	224 (74.2)
WHO clinical stage			
1 and 2	57 (67.1)	28 (32.9)	85 (28.1)
3	111 (67.7)	53 (32.3)	164 (54.3)
4	26 (49.1)	27 (50.9)	53 (17.5)
CD4 count group[a]			
≤200	42 (56.0)	33 (44.0)	75 (26.9)
201–499	92 (62.6)	55 (37.4)	147 (52.7)
500+	42 (73.7)	15 (26.3)	57 (20.4)
Karnofsky performance score			
≤70	16 (42.1)	22 (57.8)	38 (12.3)
>70	178 (67.4)	86 (32.6)	264 (87.7)
	Mean (SD)		
Mean number of symptoms	12.2 (5.0)	13.1 (7.2)	12.5 (5.87)
Global distress	1.25 (0.57)	1.40 (0.85)	1.29 (0.68)
Physical symptom distress	0.71 (0.50)	0.81 (0.80)	0.74 (0.62)
Psychological symptom distress	1.21 (0.71)	1.44 (0.95)	1.29 (0.81)
	n (%)		
Age group (years)			
≤35	99 (77.4)	34 (25.6)	133 (44.0)
>35	95 (56.2)	74 (43.8)	169 (56.0)
Highest level of education			
None	28 (78.3)	9 (24.3)	37 (12.2)
Primary	74 (63.2)	43 (36.7)	117 (38.7)
Secondary	65 (65.0)	35 (35.0)	100 (33.1)
Diploma plus	27 (56.2)	21 (43.8)	48 (15.9)
Religion			
Anglican	116 (69.8)	50 (30.1)	166 (55.0)
Catholic	43 (57.3)	32 (42.7)	75 (24.8)
Muslim	21 (55.3)	17 (44.7)	38 (12.6)
Traditionalist	14 (60.9)	9 (39.1)	23 (7.6)
Marital status			
Single	20 (66.7)	10 (33.3)	30 (9.9)
Married	70 (49.2)	72 (50.7)	142 (47.0)
Widowed	61 (87.1)	9 (3.0)	70 (23.2)
Separated/divorced	43 (71.7)	17 (28.3)	60 (19.9)

[a]23 missing values.

changes in skin and a high occurrence rate for lack of energy and sweats. Cluster 2 (n = 47): *high–low* occurrence cluster was characterised by a low occurrence rate for cough, dry mouth and feeling drowsy or tired and a high occurrence rate for weight loss and feeling irritable. These symptoms are typically psycho-gastro-intestinal in nature.

Cluster 3 (n = 71): *high occurrence cluster* was characterised by a high occurrence rate for pain, cough, numbness/tingling in hands/feet, problems urinating, shortness of breath and low occurrence rate for lack of energy, and it was named pain/lack of energy symptom cluster. Cluster 4 (n = 35): characterised by an *all high* occurrence rate for the symptoms of difficulty concentrating, pain, lack of energy, difficulty concentrating, changes in skin, dry mouth, numbness/tingling in hands or feet, difficulty sleeping, feeling bloated, vomiting, shortness of breath, mouth sores, problems with sexual interest, lack of appetite, difficulty swallowing, changes in taste, weight loss, hair loss, swelling of arms or legs, I do not look like myself and feeling irritable. The symptoms are generally general HIV symptoms. Cluster 5 (n = 48): *all low* occurrence cluster was characterised by low occurrence of all difficulty concentrating, lack of energy, feeling bloated, feeling irritable and feeling nervous. These symptoms were typically cognitive-mood in nature.

Table 2. Clustering of patient symptom experiences (n = 302).

	Prevalence of symptom in cluster						Decision				
Symptoms	*Cluster 1*	*Cluster 2*	*Cluster 3*	*Cluster 4*	*Cluster 5*	*Overall*	*Cluster 1*	*Cluster 2*	*Cluster 3*	*Cluster 4*	*Cluster 5*
Difficulty concentrating	44	30	20	35	7	136				High	Low
Pain	20	29	54	35	17	155	Low		High	High	
Lack of energy	77	28	28	33	16	182	High		Low	High	Low
Cough	21	3	35	17	18	94		Low	High		
Changes in skin	6	19	7	29	6	67	Low			High	
Dry mouth	38	2	31	23	12	106		Low		High	
Nausea	19	11	21	13	5	69					
Feeling drowsy/tired	72	11	53	29	22	187		Low			
Numbness/tingling in hands or feet	5	5	21	14	3	48	Low		High	High	
Difficulty sleeping	18	13	28	34	11	104	Low			High	
Feeling bloated	27	8	24	24	1	84				High	Low
Problems urinating	1	3	11	3	1	19			High		
Vomiting	5	4	7	10	4	30				High	
Shortness of breath	1	6	2	17	1	27				High	
Diarrhoea	4	9	18	1	5	37			High		
Sweats	50	10	18	1	5	84	High				
Mouth sores	3	5	10	16	6	40	Low			High	
Problems with sexual interest/activity	17	14	10	30	15	86				High	
Itching	15	10	22	21	14	82				High	
Lack of appetite	31	25	25	34	11	126				High	
Dizziness	30	9	26	20	7	92				High	
Difficulty swallowing	1	4	6	20	2	33	Low			High	
Changes in way food tastes	12	5	14	33	3	67				High	
Weight loss	11	29	12	31	5	88	Low	High		High	
Hair loss	3	3	1	24	0	31				High	
Constipation	19	9	15	9	11	63					
Swelling of arms or legs	2	5	5	18	3	33				High	
I don't look like myself	14	11	12	31	7	75				High	
Feeling sad	93	44	69	32	39	277					
Worrying	91	44	71	35	44	285					
Feeling irritable	25	41	26	34	8	134	Low	High		High	Low
Feeling nervous	88	37	63	35	4	227				High	Low
Number of subjects	101	47	71	35	48	302					

Table 3. Variation of socio-demographic and clinical characterises by symptom experience.

Symptom clusters		Cluster 1 (n = 107) high–low	Cluster 2 (n = 47) high–low	Cluster 3 (n = 71) high	Cluster 4 (n = 35) all high	Cluster 5 (n = 48) all low
Variables	Statistic, P value					
Age group	(X^2 = 3.07, P = 0.545)					
≤35 years		39	24	30	18	22
>35 years		62	23	41	17	26
Gender	(X^2 = 6.33, P = 0.176)					
Male		33	21	20	17	17
Female		68	26	51	18	31
WHO clinical stage	(Fisher's exact test = 53, P < 0.001)*					
1 and 2		28	15	24	4	14
3		63	23	40	9	29
4		10	9	7	22	5
CD4 category +	(Fisher's exact test = 41, P < 0.001)*					
≤200		24	8	12	22	9
201–499		52	25	36	6	28
500+		22	5	21	1	8
Use of ART	(Fisher's exact test = 4, P = 0.001)*					
Yes		77	37	41	33	36
No		24	10	30	2	12
Karnofsky performance score	(Fisher's exact = 16, P < 0.001)*					
>70		98	43	69	7	47
≤70		3	4	2	27	2

*Statistically significant p values; +23 missing values.

The following symptoms were overlapping across clusters: pain, lack of energy, difficulty swallowing, changes in skin, weight loss, feeling irritable, difficulty concentrating and difficulty sleeping.

Differences in demographic, disease and treatment characteristics

Female patients were more likely to experience cluster 1 symptoms, although the association was not statistically significant, while use of ART was associated with the *all high* occurrence rate symptom cluster (Cluster 4; Fisher's exact test = 9.88, P = 0.042; (Table 3).

Differences in symptom experience in the whole sample and subsamples

Patients in Cluster 4 *all high* occurrence rate for general symptoms experienced also reported the highest global symptom distress, the highest physical and psychological symptoms and the highest mean number of symptoms compared to other clusters ($P \leq 0.001$ in all instances; Table 4). The Cluster 4 *all high* occurrence rate for the general symptoms group of patients reported significantly lower scores on all QOL domains compared to patients in other symptom clusters (Table 5).

Discussion

This study demonstrates that ambulatory HIV/AIDS patients can be grouped based on their symptom experience and demonstrate the associations between symptom clusters and patient self-reported outcomes.

The differentiation in symptom experience was towards severity of occurrence. Symptom cluster 1 – the sensory discomfort and eating difficulties cluster shows an overlap between neurologic and psychiatric/psychological symptoms, highlighting the need for integrating mental health services into routine HIV care for improved patient outcomes.

Cluster 2 – the psycho-gastrointestinal symptoms cluster shows an overlap between gastrointestinal symptoms and psychological distress. Previous studies have found a positive correlation between gastrointestinal symptoms and psychological distress, with high psychological morbidity possibly influencing perceptions of

Table 4. Symptom experience variation across symptom occurrence clusters.

		Cluster 1 (n = 107) high–low	Cluster 2 (n = 47) high–low	Cluster 3 (n = 71) High	Cluster 4 (n = 35) all high	Cluster 5 (n = 48) all low	General mean
MSAS-SF subscale	F statistic, P value			Mean (SD)			
GDI	(F = 99.3, P < 0.001)*	1.17 (0.43)	1.22 (0.49)	1.21 (0.37)	2.65 (0.69)	0.75 (0.30)	1.29 (0.68)
MSAS physical	(F = 170.0, P < 0.001)*	0.61 (0.32)	0.57 (0.37)	0.64 (0.29)	2.11 (0.68)	0.37 (0.25)	0.74 (0.63)
MSAS psychological	(F = 130.1, P < 0.001)*	1.03 (0.44)	1.43 (0.55)	1.20 (0.43)	2.96 (0.78)	0.65 (0.34)	1.29 (0.81)
Total number of symptoms	(F = 178.4.0, P < 0.001)*	10.0 (2.75)	12.21 (4.13)	12.76 (3.62)	25.4 (3.26)	8.21 (2.66)	12.5 (5.6)

*Statistically significant p values.

Table 5. Differences in symptom experience and QOL scores.

		Symptom clusters					
		Cluster 1 (n = 107) high–low	Cluster 2 (n = 47) high–low	Cluster 3 (n = 71) high	Cluster 4 (n = 35) all high	Cluster 5 (n = 48) all low	General mean score
Quality of life domains)	F, P values			Mean (SD)			
General QOL	F = 26, P < 0.001*	54.7 (16.5)	53.7 (15.6)	52.1 (13.2)	25.7 (17.7)	60.42 (20.5)	51.5 (19.1)
Physical health summary	F = 133, P < 0.001*	54.1 (5.2)	49.8 (7.3)	51.5 (5.2)	28.1 (8.9)	54.7 (4.6)	50.0 (10.0)
Mental health summary	F = 133, P < 0.001*	54.1 (5.2)	49.8 (7.3)	51.5 (5.2)	28.1 (8.9)	54.7 (4.6)	50.0 (10.0)

*Statistically significant P values.

symptoms like weight loss, feeling drowsy/tired and dry mouth (Jarrett, Heitkemper, Cain, Burr, & Hertig, 2000).

Cluster 3 is a typical pain and sensory discomfort symptom cluster. The symptom cluster of pain and lack of energy is very common and has been widely studied in cancer patients with findings showing a tendency of the two to reinforce each other. Targeting these two symptoms jointly could lead to better care outcomes.

Cluster 4 – the general HIV/AIDS symptom cluster with all high occurrence rate might be representative of that group of patients who self-report numerous bodily symptoms (Levy et al., 2006). This finding has important implications for care as it suggests that symptom assessments in unselected patients may underestimate the symptom burden and associated distress, as well as impact on patient subgroups (Molassiotis, Wengdtrom, & Kearney, 2010). Most symptoms in this cluster are typical of depressive symptoms and, if not managed well, could result in poor patient outcomes. This cluster was also associated with use of ART, as countries adopt the 2013 WHO guidelines on HIV treatment (WHO, 2013) in which fostering adherence and reducing treatment-associated side effects are pivotal, the need for innovative approaches to effective symptom management strategies should be prioritised (Harding et al., 2010; Lampe et al., 2010; Sherr et al., 2008).

The *low* occurrence rate of mood-cognitive symptoms cluster presents a set of symptoms increasingly being recognised as a challenge in HIV/AIDS. These symptoms are commonly neglected yet they negatively affect adherence to medication (Sherr et al., 2008) and negatively impact on patients' QOL.

Symptoms of pain, lack of energy, weight loss, numbness and tingling in hands and feet and feeling irritable seemed to overlap across clusters and these have been found to occur almost universally. This symptoms set has also been shown to be highly prevalent in other samples (Harding et al., 2010; Karus et al., 2005; Vogl et al., 1999; Wakeham et al., 2010). Studies have shown that depression and anxiety-related symptoms are associated with pain, palpitations, dizziness and nausea and support the notion that physical and mental problems are intertwined (Koenig, Cohen, Blazer, Krishnan, & Sibert, 1993; Kroenke et al., 1994; Mulsant, Ganguli, & Seaberg, 1997) and concur with our findings. The presence of overlapping symptoms is also clinically important, as it demonstrates the need to equip care providers with the appropriate skills to manage co-occurring symptoms.

Symptom cluster experience and differences in impact on patient-reported outcomes

The cluster of patients reporting an *all high* occurrence rate for general symptoms reported poorer QOL scores and impaired functional performance, demonstrating the differential impact of symptom experience on patient-reported outcomes. High symptom occurrence rate and distress impact on patient's survival and ability or willingness to adhere to treatment regimens, compromising their well-being. Similar findings have been reported in oncology symptom cluster research, where severity of cancer clustered symptoms has predicted functional disability (Dodd et al., 2001) and QOL impairments (Dodd et al., 2010).

There were significant differences in the frequency, severity and distress from symptoms between those patients presenting with an *all high* occurrence rate for symptoms in a cluster and the whole sample, suggesting that the experience of symptoms is higher in those patients who have co-occurring symptoms. This group of patients also reported higher symptom severity and distress, further demonstrating the potential impact of experiencing multiple symptom occurrence. Managing a patient with a high number of symptoms can be very complex and more costly (Kurtz, Kurtz, Given, & Given, 2007) and calls for advanced skills in HIV care as it may require clinical assessment and review, polypharmacy assessment of drug and symptom interactions and the potential for compound side effects (Karus et al., 2005).

Conclusion

This study did not examine symptom clustering by ARV regimen and as such the aetiology of symptom clusters was not explored. Findings suggest the presence of symptom clusters in ambulatory HIV/AIDS patients. For better care outcomes, there is need for joint evaluation of the proposed symptoms in the; mood-cognitive, pain and sensory discomfort, psycho-gastrointestinal, sensory discomfort and eating difficulties and general symptom clusters in ambulatory HIV/AIDS patients with multiple complaints.

Notably, symptom clusters have a differential, adverse effect on HIV/AIDS patients' self-reported outcomes. This makes identifying high-risk groups that can be targeted for early interventions to improve patient self-reported outcomes critical in care.

Future research on symptom cluster underlying dimensions and aetiology is needed to further the development of symptom cluster based approaches to symptom assessment and management.

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