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HIV-related symptoms and patient clusters among Chileans living with HIV

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Identifying both Human immunodeficiency virus (HIV)-related and co-morbid symptoms experienced by people living with HIV (PLWH) who are receiving antiretroviral therapy (ART) treatment is a major challenge for healthcare providers globally. Yet, little research to date has examined the symptoms of illness experienced by PLWH including patients living in Central and South American. To address this gap, this study was designed to identify symptoms of HIV by socio-demographic and/or clinical characteristics among Chilean patients living with the virus. A convenience sample of 209 Chilean PLWH was recruited from an outpatient clinic in Santiago, Chile. A structured interview was used to elicit socio-demographic information and HIV symptoms status. Additional clinical information was obtained through a review of the participants' medical records. Results show that patients' most commonly reported HIV-related symptoms were fear/worries (66%), anxiety (52%), gas/bloating (50%), and thirst (50%). Multivariate analysis revealed a positive association between the number of reported HIV-related symptoms and number of years living with HIV. Having completed college was negatively associated with number of symptoms. Latent class analysis indicated that PLWH in the sample who had completed college were two times more likely to experience a mild intensity of HIV-related symptoms than their lesser educated counterparts. Similarly, logistic regression revealed that college-educated PLWH were twice as likely to be classified in the subgroup reporting mild intensity of symptoms than those who lacked a college degree. Overall, the study's results reveal that many Chilean PLWH, even those with high CD4 counts and low or undetectable viral loads, are not symptom free. The findings point to the need for clinicians to tailor a plan of care for individuals living with HIV that is based on their symptomatology.

Keywords: symptoms; HIV infections; people living with HIV; clusters analysis; quantitative method

Introduction

Human immunodeficiency virus (HIV) is now considered a chronic disease because the availability of highly active antiretroviral therapy has led to long-term survival (Corless, Nicholas, Davis, Dolan, & McGibbon, 2005; Hudson, Kirksey, & Holzemer, 2004; Reynolds et al., 2009; Tsai, Hsiung, & Holzemer, 2002). As with other chronic illnesses, HIV-related symptoms are of major concern for those who have the disease. The frequency and intensity with which they experience such symptoms have been identified as motivators in seeking healthcare (Chou, 2004; Wu et al., 2004) and starting self-care behaviors (Robinson & Rempel, 2006).

The HIV-related symptoms experienced by people living with HIV (PLWH), including individuals receiving antiretroviral therapy (ART), remain under-explored scientifically despite their importance to successful clinical care. Also most research on HIV symptoms has been conducted in non-South American countries, and no published studies of symptoms among Chilean PLWH exist. This research uses multiple regression and Latent class analysis (LCA) to examine the HIV-related symptoms experienced by subgroups of PLWH attending an HIV clinic in Chile. Its intent is to determine those clusters (groups) of socio-demographic characteristics and clinical conditions (if any) that are associated with differences in the frequency and intensity of HIV-reported symptoms.

HIV-related symptoms among PLWH

Regardless of their ART status (Willard et al., 2009), PLWH experience a constellation of concurrent symptoms across different levels of HIV-disease markers including CD4 count. The actual etiology of an HIV-related symptom is difficult to determine because symptoms can arise from the HIV illness itself, from ART's side effects, from opportunistic infections, and from comorbidities. Comorbidity

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influences HIV-related symptoms by adding symptoms from other diseases that may have a direct effect on their current HIV-related symptoms.

Symptoms often do not occur in isolation; instead, they occur in a cluster or pattern (Pennebaker, Gonder-Frederick, Stewart, Elfman, & Skelton, 1982). Moreover, groups of symptoms can be found clustered among patients with certain sociodemographic and clinical conditions. The number and intensity of symptoms experienced also have been found to vary by race/ethnicity (Corless et al., 2008; Israelski et al., 2007; Johnson et al., 2005; Silverberg, Jacobson, French, Witt, & Gange, 2009; Voss, 2005). Being able to recognize subgroups of patients who tend to experience similar symptoms could help to improve the accuracy of symptom assessment and also the effectiveness of symptom management.

How people with HIV experience disease-related symptoms can influence their psychosocial well-being and healthcare outcomes. For example, having a high number of HIV-related symptoms has been associated with poor quality of life (QOL) (Corless et al., 2000; Silverberg et al., 2009; Tangkawanich, Yunibhand, Thanasilp, & Magilvy, 2008; Yang, Chen, Kuo, & Wang, 2003), poorer adherence to medication (Corless et al., 2002; Sousa, Tann, & Kwok, 2006; Tsai et al., 2002), an AIDS diagnosis (Silverberg et al., 2009), lower CD4 counts (Lee et al., 2009; Wu et al., 2004), low initial viral set point level (Kelley, Barbour, & Hecht, 2007), and taking ART (Lee et al., 2009; Rivero-Mendez, Portillo, Solis-Baez, Wantland, & Holzemer, 2009). Meanwhile, having a high intensity of HIV-related symptoms has been associated with poor QOL (Corless et al., 2002; Hudson et al., 2004) and poor adherence to ART (Chou, 2004; Corless et al., 2005).

Chilean context of HIV

Chile's first case of HIV was diagnosed in 1984. Since then, an increasing number of cases have been observed. From January 1984 to December 2008, over 20,000 cases of HIV/AIDS were registered and 6102 deaths (MINSAL, 2009). In 2007, three times more men than women were living with HIV, and the number of men living with AIDS outnumbered women by almost six to one (Martínez, Olea, & Chiu, 2006). Most HIV in Chile occurs among individuals 20–49 years of age. Transmission most often occurs through sexual behavior, especially among men who have sex with men (MSM) and also between these men and their female partners (Pérez et al., 1999).

Since 2003, the Ministry of Health of Chile has provided free access to ART (CONASIDA, 2003; Wolff et al., 2005) and also therapeutic care using international standards (Wolff, Cortes, Shepherd, & Beltran, 2010). This coverage includes routine visits every three months for patients receiving ART and every four to six months for patients without ART. In addition, laboratory testing (CD4, viral load, and HIV genotypic resistance), access to medication to treat side effects of ART, and health expenses for treating opportunistic infections also are covered (Wolff et al., 2010).

The provision of ART in Chile has decreased mortality and also reduced major HIV-related complications and hospitalizations among the country's PLWA (CONASIDA, 2003; Wolff et al., 2001). Viral resistance to the ART also has been low (Afani et al., 2007). In 2008, Chilean patients' probability of survival at one and five years on ART was 0.95 and 0.89, respectively, with a mortality rate of 2.55 per 100 patient-years at 6-year follow-up (Wolff et al., 2010). This study examines the HIV-related symptoms that can accompany this survival.

Methods

Study design and sampling

Data for this cross-sectional study are drawn from a convenience sample of 209 PLWH recruited between December 2009 and March 2010 from an outpatient clinic in Santiago, Chile. Eligible participants were 18 years of age and older who were diagnosed with HIV and had not been hospitalized in the last 30 days or been diagnosed with dementia or other serious mental impairments. Those PLWH who were taking ART had to have been on the medication for at least three weeks to avoid reports of symptoms related to initial but temporary side effects.

All study procedures were approved by the Institutional Review Boards at the Pontificia Universidad Católica de Chile at Santiago, Chile and at the University of Illinois at Chicago, IL, USA. Patients were informed about the study by physicians or nurses at the clinic during their routine medical appointments. PLWH who were interested in participating were referred to the principal investigator to check eligibility criteria and to obtain informed consent to participate. During their office visits at the clinic, participants completed a face-to-face structured interview in Spanish administered by trained interviewers. The interview elicited socio-demographics and HIV-related symptom information. Each participant received $10 USD as compensation for their time spent in being interviewed. Following their visits, participants' medical records were reviewed to obtain information about their clinical conditions.

Measures

HIV-related symptoms

The revised Signs and Symptoms Checklist for Persons with HIV Disease (SSC-HIVrev) was used to assess HIV-related symptoms (Holzemer, Hudson, Kirksey, Hamilton, & Bakken, 2001). Originally created in English, a Spanish-language version of the scale was developed for the study following the translation/back translation method (Guthery & Lowe, 1992). Three Chilean HIV care providers assessed the content validity of the SSC-HIVrev Spanish version for item clarity and coherence; it was then pre-tested with 10 Chileans of unknown HIV status.

The SSC-HIVrev has three parts. Part 1 consists of 45 items related to HIV-related symptoms that cluster into 11 factors. Part 2 consists of 19 HIV-related symptoms that do not cluster. Together, parts 1 and 2 form 64 items. Participants were asked to report on how often and with what intensity they experienced each of the 64 items (symptoms) in the last four weeks. Intensity in this study refers to the strength of a specific HIV-related symptom. Response categories per item ranged from "0" (not present) to "3" (severe) and were based on each participant's personal perception of intensity. Possible overall scoring for each participant ranged from 0 to 64 for total number of symptoms and from 0 to 192 for symptom intensity. The SSC-HIVrev's internal consistency combining parts 1 and 2 was 0.92. Part 3 of the SSC-HIVrev was not included in the study's data collection because it focuses on gynecological symptoms. Most PLWH in Chile, including participants in our sample, are male and part 3's items would have limited applicability.

Socio-demographic

Information was collected for age, gender (female or male), sexual orientation (MSM/bisexual or heterosexual), marital status (single, married, separate, or widow/widower), number of children, if any, having employment (yes or no), level of education (completed college level or less than college level), living with spouse/partner (yes or no), and number of friends/relatives.

Clinical conditions

Clinical information extracted from the participants' medical records included age at HIV diagnosis, length of time since HIV diagnosis, age when started ART, taking ART (yes or no), type of ART used, latest CD4 counts, latest viral load, stage of illness based on the 1993 CDC classification (HIV or AIDS). In addition, an interview item asked, "Do you have any other illness/disease besides HIV and if yes, which one?" Responses subsequently were coded for analysis as either "0" for none or "1" if one or more co-morbid conditions were reported.

Statistical analysis

Descriptive statistics were used to assess HIV symptom status, socio-demographics, and clinical condition. Means and standard deviations were calculated for continuous variables, and percentages for categorical variables. Pearson or Spearman correlations were calculated between the number of HIV-related symptoms and socio-demographics and the clinical characteristics. Then, significant correlated variables were selected for inclusion in a multiple regression model. Categorical variables that were incorporated in the correlation and multivariate analysis were dummy coded. The dependent variable was the total number of HIV-related symptoms. Medium effect size ($R^2 = 0.15$), a power of 0.95, and a significance level of 0.05 was set for this study. SPSS for Windows Version 19.0 and Latent Gold program 4.5 were used.

LCA is used to identify groups within multivariate categorical data predicting class membership. In this study it was used to determine non-overlapping subgroups (clusters) of PLWH who experienced similar type of HIV-related symptoms. Chi-square for categorical variables and *t*-test for continuous variables analysis tested whether or not the observed differences between subgroups were statistically significant. Logistic regression analysis was used to determine variables related to each subgroup membership.

Results

Table 1 reports the socio-demographics and clinical condition of the sample.

Participants ranged in age from 18 to 76 years with a mean of 41 years. Of the total sample, more than a third (38%) lived with a spouse or partner, and 28% reported having between one to five children. The time interval since first diagnosed with HIV ranged from 1 to 26 years with a mean of about four years. Of the total sample, 78.5% were receiving ART. About 27% of the sample reported experiencing at least one co-morbid condition (mean = 1.4). Diabetes mellitus, hypertensive diseases, hypertriglyceridemia, and hypothyroidism were the most frequently reported.

Table 1. Socio-demographic and clinical characteristics of participants ($N = 209$).

Characteristics	M (SD)	Percentage
Age at time of interview	41.0 (11.0)	
Male		90
Men who have sex with men/ bisexual		74.9
Marital status		
Single		78.5
Married		6.2
Separate		12.9
Widow/widower		2.4
Having children		28
Mean number of children	2.2 (1.2)	
Highest level of education completed		
Elementary school		3.8
High school		23.4
Technical school		26.3
College		46.4
Employment status		
Full-time		70.2
Part-time		8.2
Unemployed		21.6
Health insurance		
Public		60.8
Private		39.2
Number of HIV-related symptoms		
0–7		23.4
8–13		22.5
14–19		23.0
20 or more		31.1
Intensity of HIV-related symptoms	21.7 (16.5)	
Length of time since diagnosis (years)	4.1 (4.5)	
HIV CDC classification at the time of diagnosis		47.8
Taking ART		78.5
Years living under ART	4.6 (6.0)	
CD 4 count: ≥ 350 cell/mm^3		60.8
Undetectable viral load level (≤ 80 copies/mL)		68.9
Frequency of HIV-related symptoms	15.2 (9.6)	
Having comorbidities		27.3
Mean of comorbidities	1.4 (0.7)	

HIV-related symptom characteristics

On average, study participants experienced 15 of the 64 symptoms listed in the SSC-HIVrev with an overall reported range of between 0 and 53. HIV-related symptoms characteristics for each group are presented in Table 2.

The four most commonly reported symptoms consisted of fear/worries (66%), anxiety (52%), gas/bloating (50%), and thirst (50%). The three least reported were breast pain (2%), blood present in saliva and/or sputum (3%), and sores or lumps on genitals (5%).

Table 2. Number and percentage of participants with the most frequent HIV-related symptoms of the study sample from the SSC-HIV Scale ($N = 209$).

HIV-related symptoms	Frequency and percentage of PLWH
Fear and/or worries	136 (65)
Anxiety	109 (52)
Gas and/or bloating	102 (49)
Thirst	102 (49)
Fat deposit in the abdomen	100 (48)
Depression	96 (46)
Weakness	96 (46)
Difficulty concentrating	94 (45)
Muscle aches	92 (44)
Memory loss	88 (42)
Insomnia	86 (41)
Headaches	79 (38)
Fatigue	77 (37)
Shortness of breath with activity	75 (36)
Dry mouth	75 (36)
Itchy skin	69 (33)
Skinny arms and legs	69 (33)
Painful joints	67 (32)
Prominent leg veins	67 (32)
Concern over weight gain	65 (31)

Note: PLWH, People living with HIV.

Bivariate analysis examined the possible association between reported symptoms and the study's demographic and clinical variables (not shown in a table). Only two factors, years living with HIV ($r = 0.152$, $p < 0.05$) and having completed a college-level education ($\rho = -0.178$, $p < 0.01$), correlated with reporting a high number of HIV-related symptoms. Contrary to expectation, no association was found between number of reported HIV-related symptoms and the following socio-demographic characteristics: age, being male, being MSM/bisexual, employment status, having co-morbidities, living with spouse/partner, having children, or number of close friends/relatives. Also, none of the following clinical characteristics was found to be significant: stage of illness at diagnosis, taking ART, CD4 count, and viral load. Multiple regression analysis subsequently was used to regress the number of reported HIV-related symptoms on years living with HIV and having completed college. Both variables remained statistically significant, accounting for 5.7% of the variance in number of HIV-related symptom, $F(2, 203) = 6.1$, $p = 0.003$.

Sub-group analysis

LCA revealed three clusters (subgroups) of patients (see Table 3). Cluster 1 included PLWH with moderate symptom intensity ($n = 110$), cluster 2 included those with mild symptom intensity ($n = 89$), and cluster 3 included those with severe symptom intensity ($n = 10$). Cluster 3 was excluded from the inferential statistics analysis due to its small cell sizes. Socio-demographic and clinical characteristics for each group are presented in Table 3.

For PLWH with mild symptom intensity, HIV-related symptoms with the highest prevalence were: fear/worries (42%), fat deposit in the abdomen (37%), and skinny arms/legs (28%). For PLWH experiencing moderate symptom intensity, the most prevalent symptoms were fear/worries (81%), anxiety (69%), and gas/bloating. Socio-demographics and clinical condition were included in a binary logistic regression analysis to identify possible variables related to cluster groups. Differences in level of education were found between clusters of patients. Fifty-five percent of the sample reporting mild symptom intensity had completed a college education in contrast to only 40% of Chilean PLWH with moderate symptom intensity ($\chi^2 = 4.48$, $p = 0.034$). No other significant differences in other demographics and clinical characteristics were found among subgroups.

Univariate logistic regression was used to regress the three clusters (group analysis) on all socio-demographic and clinical measures for participants. Only gender and educational level were significantly related to group membership. A simplified model with these two variables subsequently was conducted. The second model significantly explained 2.8% of clusters variance ($\chi^2 = 5.66$, $df = 2$, $N = 199$, $p = 0.05$). PLWH with a completed college education were twice as likely to be classified in the subgroup with mild intensity of symptoms as PLWH with less than a college-level education (OR = 1.83, $p = 0.037$).

Discussion

This may well be the first study to describe the frequency and intensity of HIV-related symptoms and also their relationship to socio-demographics and clinical conditions among a sample of Chilean PLWH. Findings show that symptoms vary according to the patient's demographic characteristics. Completing college had a negative relationship with the intensity of HIV-related symptoms. Participants who had completed college were more likely than their lesser educated counterparts to report experiencing mild HIV-related symptoms as opposed to reporting moderate symptoms. This result is consistent with findings from other studies (Atkins et al., 2010; Kemppainen et al., 2003). One possible explanation is that better educated persons have greater access to informational resources to deal with their chronic illness and therefore fewer symptoms than persons with lower levels of education. Higher levels of education also tend to be associated with higher socioeconomic status and therefore less social

Table 3. Socio-demographic and clinical characteristics of participants and group differences by chi-square and *t*-test ($N = 209$).

	HIV symptom intensity		
Variable (categorical)	Mild ($n = 89$) (%)	Moderate ($n = 110$) (%)	Severe ($n = 10$) *N* (%)
Male	92.1	87.3	100.0
Heterosexual	24.7	22.7	20.0
Completed college	55.1*	40.0*	40.0
Unemployed	25.8	17.3	30.0
Having children	30.3	27.3	10.0
Living with spouse or partner	40.4	36.4	20.0
Having AIDS at diagnosis	52.8	50.9	40.0
In treatment with ART	80.9	76.4	80.0
Currently detectable viral load	22.5	29.1	20.0
Having comorbidity	28.1	24.5	50.0
Variable (continuous)	Mean	Mean	Mean
Age (years)	42.1 (11.5)	40.1 (11.5)	41.7 (10.1)
Number of close relatives/friends	5.4 (8.1)	5.9 (7.7)	3.1 (4.0)
Length of time being HIV infected	3.8 (4.1)	4.5 (4.5)	5.8 (7.0)
Current $CD4^+$ T cell count	436.2 (216.2)	430.78 (234.1)	432.4 (211.4)
Numbers of HIV-related symptom	6.8 (3.7)**	18.7 (5.0)**	36.8 (7.6)

*$p < 0.05$, **$p < 0.001$

vulnerability and better access to medical care and other benefits (Atkins et al., 2010).

Length of years since, HIV diagnosis was positively associated with an increased number of HIV-related symptoms. One possible explanation is that the symptoms of HIV, and perhaps the secondary effects of ART, accumulate over time. Surprisingly, this study found no correlation between HIV-related symptoms and typical HIV disease markers such as stage of illness, CD4 counts, and viral load. Perhaps traditional HIV disease markers may be less representative of symptoms related to the psychological aspects of HIV illness. Another possible reason is that the study site was a model clinic known for providing high-quality HIV care to patients. Most of the participants had their disease under good control as evidenced by an adequate control of HIV disease markers: CD4 counts and viral load. Thus, commonly reported HIV biomarkers may not play a major role in their symptomatology.

This sample of Chilean PLWH, all of whom were receiving high quality care and free ART, had lower numbers of HIV-related symptoms than reported for other populations such as Puerto Rico, Colombia, Southern Africa, USA, Taiwan, and Norway (Makoae et al., 2005; Portillo et al., 2005; Valencia, Canaval, Rizo, Correa, & Marín, 2007). However, they were not symptom free. Moreover, their symptoms were not related to the standard markers of HIV disease control, viral load and CD4 counts. Previous researchers have found that even a low number of HIV-related symptoms can cause significant problems among patients under ART (Lampe et al., 2010). Fear, worries, and anxiety were the most frequent symptoms reported by more than 50% of Chilean PLWH, which is consistent with other studies from South Africa, London, Puerto Rico, and Colombia (Kagee & Martin, 2010; Lampe et al., 2010; Rivero-Mendez et al., 2009; Valencia et al., 2007). Those psychological symptoms may represent an emotional response to a perceived threat. HIV disease progression is uncertain, and this ambiguity can contribute to higher levels of anxiety (Gifford & Sengupta, 1999; Valencia et al., 2007). Consistent with the literature (Kemppainen et al., 2003), fear of death and also of the future was the most frequent cause for anxiety reported by the study's sample.

One limitation of this study is that HIV-related symptoms are a dynamic phenomenon, and therefore longitudinal studies are needed to examine patterns and predictors of these patterns predictors over time. Also, the sample included a disproportionate number of men, and, thus, generalizability of the findings to women remains tentative. Indeed, women's gender roles, such as being spouse/partner, having children, and taking care of others, may play a role in HIV-related symptom status. Further research is needed to measure and discern the effects of gender role differences on the symptoms of both women and men living with HIV. Likewise ART adherence was not measured in this study; PLWH could have less HIV-related symptom frequency and intensity that their counterparts elsewhere because of strict adherence to treatment. Finally, patients recruited from one outpatient clinic may not be representative of the total population of HIV-infected persons in Chile. The patients in this study were seen for HIV care on average from three to four times a year, and may well-constitute a select group when compared to other Chilean PLWH who receive lesser medical attention.

Conclusion and implications for practice

The results of this study underscore the fact that this sample of Chilean PLWH with an adequate CD4 counts and low or undetectable viral loads were not symptom free. The results show that our study participants experienced multiple HIV-related symptoms. In addition, years living with HIV and having completed a college-level education correlated with reporting a high number of HIV-related symptoms. Even though those variables are not modifiable, clinicians can concentrate their effort in provide education at the begging of the HIV diagnosis and to less educated PLWH in order to contribute to decrease the numbers of HIV-related symptoms.

The etiology of HIV-related symptoms is complex (Silverberg et al., 2004, 2009) and can vary according to a patient's socio-demographic characteristics. HIV care providers largely have focused mostly on symptoms related to HIV and its treatment (Willard et al., 2009), which needs to change, as PLWH also experience symptoms related to their co-morbidities. Healthcare providers should recognize the whole spectrum of symptoms among those who are HIV infected to enhance QOL and reduce ART non-adherence and virologic rebound (Lampe et al., 2010).

Symptom assessment, as part of a routine of HIV clinical care, is a challenging procedure in which self-report symptom instruments can play an important role. Patients' self-reports are clinically meaningful because they relate to survival rates and also the risk of hospitalization regardless of levels of CD4 counts and viral load (Justice, Chang, Rabeneck, & Zackin, 2001). Healthcare providers tend to underestimate prevalence and the intensity of symptoms (Justice et al., 2001). Using self-report instruments for symptom assessment may address this problem by helping clinicians to identify current HIV-related symptoms and to use this

information to individually tailor a plan of care to PLWH based on their symptomatology.

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