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Changes in symptoms and health-related quality of life in a nationally representative sample of adults in treatment for HIV

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Abstract

Patient-centered measures of functioning and well-being are needed to monitor and improve health for HIV-infected persons. We estimated the associations between HRQOL and symptoms over time in HIV-infected persons, adjusting for demographic and clinical characteristics using a longitudinal study of a nationally representative cohort of 2267 patients in care for HIV infection surveyed in 1996 and again in 1998. We used two global measures of HRQOL (overall health and overall quality of life) scored to have a mean of 50 and standard deviation of 10 in the sample. The total number of symptoms decreased (−1.29, $p < 0.001$ for the difference), and overall health (1.09, $p < 0.001$ for the difference) and overall quality of life (1.31, $p < 0.001$ for the difference) improved over the period. Controlling for baseline symptoms and HRQOL, each additional symptom at follow-up ($B = -1.14$, $p < 0.001$) was associated with worsened overall health and worsened overall quality of life ($B = -0.95$, $p < 0.001$). The association of two additional symptoms with lower global HRQOL was similar in magnitude to the effect of having significant depressive symptoms or the diagnosis of AIDS. In conclusion, among HIV-infected patients, symptoms are significantly related to HRQOL over time. The functioning and well-being of patients with HIV is inextricably linked to the symptoms they experience.

Key words: Health, Longitudinal studies, Quality of life, Symptoms

Background

Commonly used measures (e.g. mortality, clinical parameters) of assessing health may not capture many important aspects of individual functioning and well-being. Health related quality of life (HRQOL) offers a comprehensive patient-defined outcome, and has proven useful to characterize health disparities, track population trends, and monitor progress in achieving national health objectives [1, 2]. One important consideration in the use of HRQOL for evaluating health is the extent to which change in such measures may be related to clinically meaningful outcomes. We have previously described the cross-sectional relationship between HRQOL and clinical measures in a nationally representative sample [3–6]. In the case of HIV, few studies have examined these relationships longitudinally, particularly in representative samples.

There are two important reasons to examine the longitudinal association of symptoms and HRQOL. First, the finding that symptom improvement is associated with HRQOL improvement would strengthen our understanding of the clinical relevance of HRQOL as a measure of change. In addition, such an association would demonstrate that HRQOL is sensitive to changes in symptoms, reinforcing the importance of addressing symptoms as an important aim of care. In this study, we examine this longitudinal relationship over 18 months in a national probability sample of adults receiving care for HIV infection. We examine changes in total number of symptoms and changes in global perceptions of two aspects of HRQOL – current health and overall quality of life. We discuss the implications of these findings for the use of symptom and HRQOL measures along with other clinical services provided to HIV-infected persons.

Methods

Study design

We evaluated the responses of 2267 participants in the HIV Cost and Services Utilization Study (HCSUS) who completed a baseline and a follow-up survey approximately 18 months later. These study participants constituted a national random sample of patients with HIV infection. Participants were selected using a multi-stage sampling approach that accounted for the likelihood of residing in a particular geographic area, being cared for by a particular healthcare provider, and the likelihood of selection from the universe of that provider's patients. Of the 2864 patients who participated in baseline interviews between January 1996 and April 1997, 2267 patients also participated in the follow-up between August 1997 and January 1998. The study was conducted under the oversight of participating institutions and with informed consent of all participants. Further details of the study design and sampling approach are available [7, 8].

Variables: HRQOL and symptoms

For this analysis, we use two HRQOL global rating items that were administered using a 0–10 response scale (0 represents worst possible and 10 best possible) and a four weeks recall interval: (1) "How would you rate your current health, overall?" (2) "How would you rate your quality of life, overall?" We selected these HRQOL items because they do not include symptoms. Both global items were scored to have a mean of 50 and standard deviation of 10 for the overall sample at baseline of the study [9]. Change in HRQOL was determined by subtracting the second follow-up score from the baseline score.

In addition to the symptom of vaginal discharge which was only assessed in women, both men and women were asked about 13 symptoms including headache; fever, sweats, or chills; pain in the mouth, lips, or gums; white patches in the mouth; dry mouth; genital rashes or sores; nausea or loss of appetite; trouble with eyes; sinus infection, pain, or discharge; pain, numbness, or tingling of hands or feet; persistent cough, difficulty breathing, or difficulty catching one's breath for more than 1 week; diarrhea or loose or watery stools; and weight loss. The recall interval at baseline was 6 months; at the 18-month follow-up patients were queried about symptoms since their last study contact, an interval that averaged 6 months. We counted the number of symptoms (0–14 range) at baseline and the follow-up and computed the change in symptoms by subtracting the follow-up score from the baseline score. To account for gender differences in the different number of symptom items, we averaged the baseline and follow-up means for the additional symptom asked of women and added it to the count of men at each interval.

Other patient demographic, clinical, and treatment characteristics included age in years (18–29, 30–34, 35–39, 40–44, 45–49, $\geqslant 50$), gender (male, female), race/ethnicity (white, African-American, Hispanic, other), education (elementary, some high school, high school graduate, some college, associate degree, bachelor's degree, graduate degree), HIV exposure group (e.g., mutually exclusive categories of intravenous drug abuse, heterosexual, other risk group, and homosexual exposure), baseline clinical stage (asymptomatic HIV infection, symptomatic HIV infection, AIDS), baseline report of lowest ever CD4 count (< 50, 50–199, 200–499, or $\geqslant 500$), and the intensity of baseline antiretroviral therapy (single drug, multi-drug, and 'highly active' therapy). Antiretroviral therapy was defined by querying the patient in detail about a list of drugs available when the survey was conducted. We used a hot deck approach to replace the less than 5 percent of essential missing values [10, 11]. Further descriptions of these variables and the conceptual and empiric basis for these models are available elsewhere [3–6].

Analysis

We first examined bivariate changes in HRQOL and symptoms in all patient demographic and clinical subgroups. Then we examined the magnitude of changes in HRQOL in patients in whom the number of symptoms decreased, stayed the same, or increased from baseline to follow-up. Using multivariate linear regression, we modeled the change in both of the HRQOL measures (global ratings of current health and overall quality of life). Each model was adjusted for either baseline current health or baseline overall quality of life in addition to baseline and the change in total symptoms, accounting for other patient characteristics. We also explored the interaction between global perceptions of current health and overall quality of life at baseline and change in symptoms to examine whether the associations we found were consistent among patients with lower and higher initial values of HRQOL. We only emphasize findings that were strongly and consistently significant. All analyses were performed using Stata 8.0.

Results

Participants experienced significant improvements in number of symptoms, overall health, and overall quality of life during the course of the study (Table 1). Participants reported a mean of 4.80 symptoms at baseline versus 3.51 symptoms at the follow-up interview ($p < 0.001$ for the difference). These differences were consistent and significant across all demographic subgroups we examined. Participants reported a mean current health score of 50.75 at baseline, compared with 51.84 at second follow-up ($p < 0.001$ for the difference). Participants reported a mean overall quality of life score of 50.53 at baseline and 51.84 at second follow-up ($p < 0.001$ for the difference). (Baseline mean scores are not exactly 50 because the analytic cohort represents a subset of the complete HCSUS cohort.)

Part of the reason that symptoms improved more markedly than HRQOL for the entire cohort is that the improvement in HRQOL among patients whose symptoms improved was accompanied by a decrease in HRQOL in patients whose symptoms were unchanged or worsened (Table 2). Most patients ($n = 1348$) experienced a decrease in symptoms, although 403 patients noted no change, and 516 patients noted a worsening of their symptoms. Standardized comparison of the change in symptoms and HRQOL (e.g., change in a quantity/its own standard deviation) indicate that the 1348 patients whose symptoms improved (standardized change in symptoms $= -1.53$) experienced improvement in HRQOL (standardized change in overall health $= 0.24$; standardized

Table 1. Description of the sample

Sample characteristics	*N*	%
Gender		
Male	1603	70.71
Female	664	29.29
Age of respondent (years)		
18–29	289	12.75
30–34	477	21.04
35–39	562	24.79
40–44	427	18.84
45–49	289	12.75
⩾50	223	9.84
Race/ethnicity		
White	1158	51.08
African-American	707	31.19
Hispanic	326	14.38
Other race	76	3.35
Education		
Elementary	130	5.73
Some high school	417	18.39
High school degree	627	27.66
Some college	414	18.26
Associate degree	244	10.76
Batchelor's degree	306	13.50
Graduate degree	129	5.69
Exposure category		
Intravenous drug use	531	23.42
Homosexual	1071	47.24
Heterosexual	474	20.91
Other	191	8.43
Clinical stage		
Asymptomatic HIV	198	8.73
Symptomatic HIV	1229	54.21
AIDS	840	37.05
Lowest reported CD4 count		
⩾500	200	8.82
200–499	908	40.05
50–199	710	31.32
0–49	449	19.81

change in overall quality of life = 0.23); whereas, 516 patients with worsened symptoms (standardized change in symptoms = 1.57) experienced a decrement of HRQOL (standardized change in overall health = –0.14; standardized change in overall quality of life = –0.06).

We examined the independent association of demographic and clinical characteristics including symptoms with changes in HRQOL. As expected, baseline total symptoms ($b = -1.09$, $p < 0.001$) and baseline overall health ($b = 0.23$, $p < 0.001$) were associated with overall health at second follow-up; baseline total symptoms ($b = -0.88$, $p < 0.001$) and baseline overall quality of life ($b = 0.33$, $p < 0.001$) were associated with overall quality of life at second follow-up. Importantly, worsening total symptoms was consistently associated with decreased overall health ($b = -1.14$, $p < 0.001$) and overall quality of life ($b = -0.95$, $p < 0.001$) (Table 3). Lowest CD4 count ⩾500 ($b = 2.42$, $p = 0.001$), and lowest CD4 count 200–499 ($b = 1.97$, $p < 0.001$) were associated with improved overall health as was highly effective antiretroviral therapy ($b = 1.08$, $p = 0.042$), Hispanic ethnicity ($b = 1.83$, $p < 0.001$) and an elementary as compared with a high school education ($b = 1.73$, $p = 0.023$). AIDS was associated with worse overall quality of life ($b = -0.97$, $p = 0.018$).

Table 2. The relationship between change in symptoms and change in health-related quality of life

Symptom subgroup[a]	Change in HRQOL (Followup 2 – baseline HRQOL value[b])
Improved ($n = 1348$)	
Overall health	2.47, 10.20
Overall quality of life	2.29, 9.95
Unchanged ($n = 403$)	
Overall health	–0.23, 9.07
Overall quality of life	0.49, 9.76
Worsened ($n = 516$)	
Overall health	–1.48, 10.38
Overall quality of life	–0.60, 10.09

[a] Patients in the improved subgroup had a change in their total symptom score of ⩾1 (mean improvement of 2.96 symptoms). Patients in the unchanged group had no change in their total symptom score, and patients in the worsened group had an increase in their total symptom score of ⩾1 (mean worsening of 2.06 symptoms).

[b] Mean and standard deviation are shown.

We evaluated the association of changes in individual symptoms with changes in overall health and overall quality of life. We found that worsening fever ($b = -1.36$, $p = 0.014$), patches in the mouth ($b = -1.06$, $p = 0.003$), nausea ($b = -0.87$, $p = 0.005$), and weight loss ($b = -1.65$, $p < 0.001$) were associated with worse overall health. With the exception of fever, these same symptoms (patches in the mouth, $b = -0.88$, $p = 0.012$; nausea, $b = -1.14$, $p < 0.001$; weight loss, $b = -1.64$; $p = 0.002$) as well as Kaposi's sarcoma ($b = -1.81$; $p = 0.041$) and persistent cough ($b = -1.07$, $p = 0.001$) were associated with worsened quality of life.

Discussion

In a prospective, longitudinal, nationally representative study of patients in care for HIV infection, we found that changes in HRQOL were strongly and consistently associated with changes in symptoms. Both total symptoms and global ratings of current health and quality of life improved significantly over about 18 months. Although the change in total number of symptoms was associated with the change in HRQOL, the improvement in HRQOL among patients whose symptoms improved was matched by deterioration in HRQOL among patients whose symptoms were unchanged or worsened. In addition to baseline symptoms and baseline HRQOL, the change in symptoms was a consistent and important determinant of subsequent HRQOL.

In order to better illustrate the impact of symptoms on HRQOL, we compared the association of symptoms to HRQOL with the impact of a having significant depressive symptoms on the SF-36 5-item mental health scale (MHI-5) and with the impact of a diagnosis of AIDS. The MHI-5 is a useful tool for screening for mental health disorders in patients with HIV as well as the general population [12, 13]. To put in perspective the impact of additional symptoms on a patient's HRQOL, a score on the MHI-5 consistent with a depressive diagnosis was associated with a decrement in overall quality of life (−2.25) approximating the impact of two additional symptoms at baseline (−2.18) or follow-up (−2.28). A diagnosis of AIDS was associated with a decrement in overall quality of life (−0.97) comparable to that of

Table 3. Independent association of demographic factors, treatment, and symptoms to change in health-related quality of life

Variable	Overall health (Coefficient, SE)	*p*-Value	Overall quality of life (Coefficient, SE)	*p*-Value
Baseline symptoms	*−1.09 (0.12)*	*<0.001*	*−0.88 (0.10)*	*<0.001*
Change in symptoms	*−1.14 (0.10)*	*<0.001*	*−0.95 (0.09)*	*<0.001*
Baseline HRQOL[b]	*0.23 (0.02)*	*<0.001*	*0.33 (0.02)*	*<0.001*
Antiretroviral therapy intensity				
None[a]	N/A	N/A	N/A	N/A
Low	0.16 (0.67)	0.813	0.11 (0.80)	0.892
Medium	0.74 (0.62)	0.233	0.87 (0.46)	0.063
High	1.08 (0.52)	0.042	1.01 (0.53)	0.062
Gender				
Female	−0.64 (0.44)	0.152	0.46 (0.44)	0.302
Male[a]	N/A	N/A	N/A	N/A
Age				
18–29	0.33 (0.58)	0.573	−0.46 (0.55)	0.406
30–34	0.68 (0.36)	0.063	−0.07 (0.48)	0.881
35–39[a]	N/A	N/A	N/A	N/A
40–44	0.06 (0.50)	0.910	−0.36 (0.56)	0.529
45–49	−0.36 (0.79)	0.655	−0.53 (0.64)	0.411
>50	−1.02 (0.76)	0.182	−1.15 (0.65)	0.085
Race/ethnicity				
Black	0.72 (0.42)	0.065	0.29 (0.40)	0.468
Hispanic	*1.83 (0.45)*	*<0.001*	0.64 (0.47)	0.182
White[a]	N/A	N/A	N/A	N/A
Other	0.80 (1.29)	0.537	1.61 (0.92)	0.085
Education				
Elementary	*1.73 (0.74)*	*0.021*	−0.59 (0.71)	0.411
Some high school	0.26 (0.60)	0.420	0.17 (0.56)	0.764
High school degree[a]	N/A	N/A	N/A	N/A
Some college	0.49 (0.60)	0.420	−0.35 (0.55)	0.526
Associate degree	0.43 (0.78)	0.580	0.29 (0.77)	0.710
Batchelor's degree	0.11 (0.69)	0.874	0.40 (0.54)	0.458
Graduate degree	1.27 (0.78)	0.109	0.22 (0.62)	0.720
Exposure category				
IVDU	−0.29 (0.60)	0.730	−0.15 (0.59)	0.805
Heterosexual	0.31 (0.68)	0.591	0.14 (0.69)	0.839
Homosexual[a]	N/A	N/A	N/A	N/A
Other	0.44 (0.90)	0.471	0.76 (0.78)	0.338
Clinical stage				
Aysymptomatic HIV	−0.21 (0.53)	0.693	−1.12 (0.78)	0.158
Symptomatic HIV[a]	N/A	N/A	N/A	N/A
AIDS	−0.21 (0.43)	0.583	*-0.97 (0.40)*	*0.018*
Lowest reported CD4 count				
⩾500	*2.45 (0.72)*	*0.001*	−0.01 (0.93)	0.995
200–499	*1.94 (0.51)*	*0.000*	0.78 (0.47)	0.099
50–199	0.47 (0.51)	0.365	0.00 (0.55)	0.938
0–49[a]	N/A	N/A	N/A	N/A

[a] Omitted category.

[b] Model of change in overall health used baseline overall health as HRQOL measure. Model of change in overall quality of life used baseline overall quality of life as HRQOL measure.

one additional symptom at baseline (−1.09) or follow-up (−1.14).

The linkage we demonstrated between change in symptoms and HRQOL illustrates the potential contribution of HRQOL as a longitudinal outcome measure for populations. Like depression, other symptoms are subjective indicators of patients' distress that are sometimes discounted in health encounters. Yet depression, pain, and other symptoms are often clinically remediable. Patient-centered measures such as HRQOL thus capture important information about health unaccounted for by other commonly used measures of disease impact. Such measures have found application in monitoring the health of the United States population [1, 2], and our analysis suggests that because of their clinical relevance, they should be considered routinely for monitoring patients and populations with HIV.

Our findings also underscore the responsibility that providers and healthcare organizations caring for HIV infected patients share in targeting symptom reduction as an intervention. Indeed, symptoms are the primary reason that patients seek health care and symptoms have an important underlying relationship to well-being. Patients are subject to debilitating symptoms as a direct result of HIV, but also as a result of difficult treatments [14–16]. The burden of treatment may become a greater consideration as HIV-infected patients live longer and co-morbid illness becomes more prevalent. Providers may neglect symptoms even when their importance to patients is clear [17, 18] Our findings underscore the relevance of healthcare organizations' efforts to improve routine symptom assessment and management [19, 20].

We found that some individual symptoms had particularly noteworthy associations, and such symptoms may reflect either the severity of an individual's illness or the side effects of common HIV medications. Some of the symptoms with the most notable impact such as oral disease are also important because they may not be routinely addressed in office assessments. However, all of these symptoms point to interventions that can either address underlying disease through augmenting effective treatment, ameliorate side effects of drug therapy through changes in specific medications, or institute palliative modalities that address the symptoms themselves as the primary goal.

One limitation of our study is the time interval averaged only 18 months, and we don't know much about the impact of different chronological intervals on the relationship between symptoms and HRQOL. We were unable to address the impact of different time periods on this relationship, although it is an important subject for future study. The symptom list that we used was developed through literature review, opinions of experts in the field of symptoms and quality of life measurement, and with community representatives; however, we recognize that the symptoms we included may not reflect the full spectrum of symptoms that are important to HIV-infected patients, and that there may be limitations in generalizing our findings to sub-populations in which symptom reports differ [21]. Because they would be strongly related to HRQOL, we decided not to simultaneously account for symptom bother, functional impairment, or disability in these analyses, although we acknowledge these are also important considerations for understanding symptom impact.

Additional research would be helpful to examine a larger spectrum of symptoms and their relationship to HRQOL. It would be useful to know which attributes of symptoms (e.g., intermittently severe vs. average level) are most strongly associated with HRQOL, as these distinctions may have therapeutic importance. The role of other factors in mitigating symptoms such as social support, treatments, and other factors needs to be elucidated. In conclusion, one important measure of progress in the treatment of HIV is our ability to improve functioning and well-being in individuals and the population. HRQOL provides a meaningful measure of disease impact, and providers and healthcare organizations must attend directly to symptoms in addressing the clinical needs of patients confronting the long-term consequences of HIV infection and therapies.

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