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Health-related quality of life and virologic outcomes in an HIV clinic

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Abstract

Objective: The purpose of this study was to describe the relationship between viral load and health-related quality of life (HRQOL) in a cohort of persons with human immunodeficiency virus (HIV) infection. *Design*: We evaluated HRQOL measurements in a clinical cohort of HIV-positive patients recruited from a university-associated HIV primary care clinic. HRQOL instruments included the medical outcomes survey-short form-36(MOS-SF-36) from which mental and physical component summary scores (MCS and PCS) and subscale scores were calculated. *Results*: Significant negative associations were found between viral load and SF-36 PCS, physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), role-emotional (RE), and vitality (VT). Similar negative associations were found between CD4 cell count and SF-36 summary and subscale scores, with the notable exception of bodily pain. Multivariate analyses controlling for the effects of CD4 cell count and other clinical variables indicated viral load as an independent predictor of SF-36 PCS, RP, BP and VT scores. *Conclusions*: The relationship between viral load, a measure of HIV disease activity, and several dimensions of the SF-36, a patient-focused measure of HRQOL, appears to be strong and independent of CD4 cell count. These findings suggest that having a lower viral load positively impacts the quality of life of HIV-positive patients.

Key words: AIDS, Health-related quality of life, HIV, SF-36

Introduction

Clinical trials and intervention studies in human immunodeficiency virus (HIV) infection have focused on traditional clinical measures as outcomes. Primary outcome measures have included mortality, occurrence of opportunistic infections, progression to a clinical definition of acquired immunodeficiency syndrome (AIDS) and occurrence of adverse events. Biological markers have been used as surrogate outcome measures; traditionally in HIV, research has focused on changes in CD4 cell counts. Over the last few years, viral load has been shown to correlate with disease progression and prognosis, and thus, has become a frequently used outcome measure both in clinical practice and in investigation [1–7].

Protease inhibitors and the concept of highly active antiretroviral therapy (HAART) have changed the arena of HIV tremendously. The ability to monitor viral load has also contributed to the improved management of HIV. There have been significant decreases in traditional outcome events: there are fewer deaths, fewer opportunistic infections, fewer hospitalizations, and fewer persons progressing to AIDS [8–11]. With this decrease in more traditional outcomes, and with HIV infection becoming more of a chronic illness, there has been a shift in focus to other outcome measures, particularly those considered as

'patient-based' outcome measures. In HIV, attention has recently been directed at symptoms, health-related quality of life, adherence, and patient satisfaction. Many of these measures are now included routinely in clinical trials. These constructs are being evaluated both as direct outcome measures and as possible mediators or moderators of other outcomes.

Health-related quality of life measures (HRQOL) have been studied extensively in the HIV positive population. Initially there was a focus on establishing the validity and reliability of existing general HRQOL measures in the HIV population. These include multiple versions of the Medical Outcomes Survey (MOS) [12–20], the Sickness Impact Profile [21–23], the Spitzer Quality of Life Index [24], and the Quality of Well-being Scale [17, 25–28]. Investigators in this area then began developing disease-specific measures for the HIV infected and AIDS populations. Several measures have been developed and validated over the last 10 years. These include, but are not limited to, a disease specific modified version of the Medical Outcomes Survey (MOS-HIV) [19, 21, 25, 29–33], the HIV-QL31 [34], the HAT-QoL [35, 36], and the Functional Assessment of HIV Quality of Life Instrument (the FAHI) [37, 38].

Studies of both generic and disease-specific HRQOL measures in HIV infected populations have revealed several consistent observations. First, these measures appear to be associated with symptoms [14, 17, 19, 20, 31, 39–45]. Next, these measures appear to be responsive to adverse event occurrences. Finally, there is a correlation between HRQOL measures and most markers of disease severity [13, 14, 17, 19–21, 24, 31, 35–37, 39–42, 46]. Several indicators of disease severity have been evaluated, including symptom scores, CD4 cell counts, Center for Disease Control (CDC) clinical stage, and $B2$ microglobulin.

Notably, viral load has not been included as a marker of disease status in most of the prior studies. The association of both viral load and CD4 cell count with clinical progression of disease is well-established; and, although clinical practice has shifted to emphasize the monitoring of viral load in the management of HIV-infected patients, little research has been done to date in assessing the relationship of viral load to patient-based measures [4–7]. Viral load is a more direct measure of actual disease activity and, thus, fluctuates more rapidly than CD4 cell count, particularly in the settings of initiation of therapy or therapy failure. The relationship between viral load and HRQOL measures may not parallel the well-established relationship between CD4 cell counts and HRQOL. Indeed, the two papers that have been published examining these relationships specifically present conflicting results [47, 48]. Given the paucity of empirical findings and the conflicting outcomes, it is not clear whether viral load is related to HRQOL. Therefore, the purpose of the present study was to further characterize the relationship between viral load and HRQOL in an outpatient HIV clinic population. In this paper we present our current data on the association of viral load and HRQOL and compare it to relationships observed between CD4 cell count and HRQOL, using the MOS Short Form-36 (SF-36) as our measure of HRQOL.

Methods

Study subjects

Subjects were a cohort of HIV-positive, English-speaking individuals from whom clinical outcomes, adherence measures and quality of life measures could be obtained. The participants were drawn from the population of patients routinely followed at the HIV outpatient clinic associated with the University of Alabama at Birmingham (UAB). Eligibility criteria for inclusion in the cohort were a viral load measurement of $\geqslant 5000$ copies/ml RNA and plans by the primary care provider to either initiate or change antiretroviral therapy. Patients were excluded from study if they were unable or unwilling to complete either a paper or computerized questionnaire. Enrollment began on 1 March 1997 and continues at this time. The current analysis was based on data obtained through 1 January 1999. All subjects signed an informed consent prior to participation. The study was approved by the Institutional Review Board at UAB.

Data collection

Data collected at enrollment include sociodemographic information (date of birth, gender, race,

HIV risk factor, residence, insurance status), medication history, opportunistic infection history, and previous laboratory values including viral load values and CD4 cell counts. Historical information was obtained from the clinic's existing computerized clinical database, chart extraction and interview.

Clinical data, laboratory data (including viral load and CD4 cell count), interim history, medications and HRQOL measures were collected at the initial visit. Study visit interviews were face-to-face interviews conducted by one of three trained interviewers. HRQOL measures were self-administered in either paper or computerized form.

Clinical chart and database data were reviewed and verified by the interviewer. A random selection of 5% of the study charts was reviewed monthly (by SAC) to ensure accuracy of the data and to provide staff record abstraction retraining when needed.

Measures

HRQOL

Health-related quality of life was evaluated with the MOS-SF-36. The SF-36 is a 36-item general HRQOL measure that contains eight subscales that are scored independently. The subscales cover the following eight domains of health-related quality of life: general health perceptions, physical functioning, social functioning, role functioning (physical), role functioning (emotional), emotional well-being, pain and vitality. The SF-36 can also be scored to yield two summary scores: the physical component score (PCS) and the mental component score (MCS). Higher scores on all scales indicate better functioning.

The SF-36 has been used extensively and validated in a variety of populations and cultures. Studies of the SF-36 in the HIV/AIDS population have supported the reliability and construct validity of the measure in this population. The instrument can be administered in several forms, including both paper and computerized self-administered versions. The SF-36 takes an average of 10–15 min to complete [49–52].

Disease state

Disease states were classified by viral load and CD4 cell count strata based on clinically meaningful cut points as follows:

–Viral load subgroups: $\leqslant 5000$, 5001–20,000, 20,001–100,000, >100,000 copies/ml RNA. These cut points were used based on a consensus that these viral load levels indicate differing degrees of virologic control and are often used by clinicians to guide changes and initiation of therapy. (Notably, several individuals had HIV-1 RNA measurements less than 5000 copies/ml at their baseline visit, although at time of screening for inclusion the viral load was >5000 copies/ml). –CD4 cell count subgroups: <50, 50–200, >200 cells/mm^3.

Statistical analysis

The SF-36 was scored by the investigators using a SAS program (SAS Institute, Inc., Cary, NC) obtained from the Medical Outcomes Trust (MOT). Missing items were managed as recommended by the developers of the instrument [49, 51, 52]. Descriptive statistics included percentages, mean or median values, standard deviations and ranges for sociodemographic characteristics, baseline clinical characteristics, and baseline HRQOL scales. In addition, differences in HRQOL measures (both SF-36 summary score measures as well as each subscale measure) between subgroups of disease state were assessed by analysis of variance (ANOVA). When an overall *F*-test was significant, the Tukey method of multiple comparisons was used to identify statistically significant differences between the disease state subgroups [51]. To assess the robustness of the association between viral load and HRQOL, multivariate analyses were performed using CD4 cell count and demographic variables presented in Table 1 as covariates.

All statistical analyses were done using SAS V6.12 (SAS Institute, Inc., Cary, NC).

Results

Sample characteristics

A total of 259 patients were screened for eligibility for cohort enrollment. These potential patients were identified through the existing computerized clinical database. At the time of this analysis, 158 persons had enrolled in the cohort study. Of the remaining 101 patients, 62 were ineligible by

Table 1. Demographic and clinical characteristics of cohort

Variable	Median (range), Mean (SD) or Number (%)
Participants	158
Median follow-up (mo.)	17 (1, 23)
Mean age (years)	39 (8.6)
Male (%)	138 (87)
Caucasian (%)	101 (64)
Homosexual (%)	115 (73)
History intravenous drug use (%)	13 (8)
Median viral load (HIV RNA copies/ml)	69,542 (3489, 2,288,179)
Median CD4 cell count (cells/mm^3)	144 (1, 851)
CDC clinical definition AIDS (stage C or CD4 < 200/mm^3)	122 (77)
Median years HIV positive	3.9 (0, 13.4)
Antiretroviral therapy naïve (%)	40 (25)
Protease inhibitor experience (%)	84 (53)

criteria and 39 refused enrollment. Refusers were more likely to be female (23%), African American (64%), and less likely to be homosexual (43%). The median follow-up at the time of this analysis was 17 months. Sociodemographic, epidemiologic and baseline clinical characteristics of the 158 participants are presented in Table 1. The majority of patients were Caucasian (64%), male (87%), and identified homosexuality as a risk factor for HIV (73%). As noted in the table, 40 (25%) patients were naive to antiretroviral therapy at enrollment. The 118 antiretroviral-experienced patients had documented exposure to multiple regimens with 84 of 118 (71%) having experience with protease inhibitors prior to enrollment. Mean SF-36 summary scores for the cohort were 44.2 (SD = 11.9) for PCS and 43.9 (SD = 12.4) for MCS. Mean population age-appropriate norms from the MOT for comparison are 52.15 (SD = 7.75) for PCS and 49.91 (SD = 9.26) for MCS [49, 51, 52].

HRQOL and disease state

Viral load

Mean SF-36 PCS and subscale scores contributing to the PCS score are presented in Table 2a for each of the viral load subgroups. Significant differences between viral load subgroups were observed for the following scales: PCS, $p < 0.01$; PF, $p < 0.01$; RP, $p < 0.01$; BP, $p < 0.01$, and GH, $p < 0.05$. Tukey's pairwise multiple comparisons indicated

Table 2a. Mean (SD) SF-36 PCS and subscale scores contributing to the PCS by viral load subgroups

VL group	PCS**[ab]	PF**[ab]	RP**[b]	BP**[ab]	GH*[a]
>100,000 (n = 57)	39.84 (12.47)	60.99 (29.04)	38.16 (42.02)	59.46 (27.53)	48.81 (23.64)
20,001–100,000 (n = 55)	45.93 (10.48)	74.95 (23.94)	57.41 (43.88)	74.09 (24.48)	60.72 (20.16)
5001–20,000 (n = 30)	48.78 (10.15)	80.00 (24.28)	74.17 (29.71)	76.63 (24.34)	59.17 (21.09)
⩽5000 (n = 16)	45.15 (13.15)	72.40 (27.74)	60.94 (43.75)	70.60 (27.39)	61.07 (21.61)

PCS – Physical Component Summary; PF – Physical functioning; RP – Role-physical; BP – Bodily pain; GH – General health.

Table 2b. Mean (SD) SF-36 MCS and subscale scores contributing to the MCS by viral load subgroups

VL group	MCS	MH	RE*[ab]	SF	VT**[ab]
>100,000 (n = 57)	45.91 (13.22)	62.53 (20.07)	39.77 (42.46)	60.53 (28.42)	41.14 (25.04)
20,001–100,000 (n = 55)	45.26 (12.67)	68.74 (20.16)	62.96 (41.80)	69.21 (24.00)	55.80 (21.57)
5001–20,000 (n = 30)	45.60 (12.43)	67.00 (21.62)	66.67 (41.98)	73.75 (23.52)	58.50 (18.39)
⩽5000 (n = 16)	40.98 (11.87)	74.40 (19.82)	52.38 (42.80)	70.83 (27.82)	57.00 (27.37)

MCS – Mental Component Summary; VT – Vitality; SF – Social functioning; RE – Role-emotional; MH – Mental health.

* ANOVA significant; $p < 0.05$.

** ANOVA significant; $p < 0.01$.

[a] Significant pairwise difference by Tukey – VL > 100,000 vs. 20,001–100,000.

[b] Significant pairwise difference by Tukey – VL > 100,000 vs. 5001–20,000.

consistently lower mean physical summary and subscale scores for higher viral load subgroups.

Mean SF-36 MCS and subscale scores contributing to the MCS score are presented in Table 2b for each of the viral load subgroups. Significant differences between viral load subgroups were observed for the following subscale mean scores: RE, $p < 0.05$, and VT, $p < 0.01$. Notably, no significant differences between viral load subgroups were observed for the other two subscales contributing to the MCS or for the MCS itself. Tukey's pairwise multiple comparisons indicated consistently lower mean RE and VT subscale scores for higher viral load subgroups. In all of the viral load subgroup analyses, the mean SF-36 summary and subscale scores for the clinical subgroup with viral load $\leqslant 5000$ copies/ml RNA were not significantly different from the next subgroup. The small size of this subgroup relative to the three other viral load subgroups may have compromised the power of these analyses.

CD4 cell count

Mean SF-36 PCS and subscale scores contributing to the PCS score are presented in Table 3a for each of the CD4 cell count subgroups. Significant differences between CD4 cell count subgroups were observed for the following summary and subscale mean scores: PCS, $p < 0.01$; PF, $p < 0.01$; RP, $p < 0.01$, and GH, $p < 0.01$. Tukey's pairwise multiple comparisons indicated consistently lower mean physical summary and subscale scores for lower CD4 cell count subgroups. No significant differences between CD4 cell count subgroups were observed for BP subscale scores, $p > 0.05$.

Mean SF-36 MCS and subscale scores contributing to the MCS score are presented in Table 3b for each of the CD4 cell count subgroups. Significant differences between CD4 cell count subgroups were observed for the following subscale mean scores: SF, $p < 0.05$, and VT, $p < 0.01$. Again, similar to the viral load subgroup analysis, it is notable that there was no significant difference in MCS score between the CD4 cell count subgroups. Tukey's pairwise multiple comparisons indicated consistently lower mean SF and VT subscale scores for lower CD4 cell count subgroups.

Multivariate analyses

Multivariate models designed to control for the effect of CD4 cell count and other demographic and clinical variables from Table 1 indicated viral load to be a significant and independent predictor

Table 3a. Mean (SD) SF-36 PCS and subscale scores contributing to the PCS by CD4 cell count subgroups

CD4 group	PCS**[abc]	PF**[ab]	RP**[bc]	BP	GH**[b]
<50 (n = 39)	37.54 (10.24)	55.04 (25.85)	33.55 (39.11)	63.95 (26.39)	46.45 (21.38)
50–200 (n = 58)	43.55 (11.64)	70.40 (26.84)	48.28 (42.37)	67.62 (27.15)	56.21 (22.63)
>200 (n = 60)	49.30 (23.20)	81.29 (23.20)	73.33 (37.07)	74.14 (25.48)	62.37 (20.78)

PCS – Physical Component Summary; PF – Physical functioning; RP – Role-physical; BP – Bodily pain; GH – General health.

Table 3b. Mean SF-36 MCS and subscale scores contributing to the MCS by CD4 cell count subgroups

CD4 group	MCS	MH	RE	SF*[b]	VT**[b]
<50 (n = 39)	43.78 (13.00)	65.79 (22.33)	50.88 (43.66)	58.55 (28.93)	41.97 (22.91)
50–200 (n = 58)	43.63 (12.23)	67.86 (19.99)	43.63 (42.78)	67.46 (26.17)	49.28 (24.18)
>200 (n = 60)	44.28 (12.48)	66.34 (20.21)	44.28 (43.40)	72.88 (22.88)	58.73 (22.56)

MCS – Mental Component Summary; VT – Vitality; SF – Social functioning; RE – Role-emotional; MH – Mental health.

* ANOVA significant; $p < 0.05$.

** ANOVA significant; $p < 0.01$.

[a] Significant pairwise difference by Tukey – CD4 <50 vs. CD4 50–200.

[b] Significant pairwise difference by Tukey – CD4 <50 vs. CD4 > 200.

[c] Significant pairwise difference by Tukey – CD4 50–200 vs. CD4 > 200.

of SF-36 PCS score, $p = 0.05$, as well as of the subscale scores RP, $p < 0.05$; BP, $p < 0.05$, and VT, $p < 0.05$. CD4 cell count was also a significant and independent predictor of the SF-36 PCS score, $p < 0.01$ as well as of the following subscales scores: PF, $p < 0.01$; RP, $p < 0.01$; GH, $p < 0.05$; VT, $p < 0.05$. None of the clinical or demographic variables listed in Table 1 were independent predictors of either of the summary scale scores in the adjusted analyses. In addition, none were independent predictors of more than one subscale score, although homosexuality was independently associated with PF, $p < 0.03$ and protease inhibitor experience was associated with GH, $p < 0.02$.

Discussion

The current goals of therapy for HIV-infected individuals focus on the traditional outcomes of increased life expectancy, decreased disease-associated mortality, and decreased occurrence of opportunistic infections. However, as we shift toward a new paradigm in the treatment of HIV infection, focusing on the long-term management of a chronic illness, emphasis must be placed on patient-based outcomes. This study assessed the relationship between HIV viral load, a traditional biological marker of disease state, and health-related quality of life, a patient-focused measure. While prior studies have examined the relationship of other clinical parameters of HIV disease and HRQOL, few studies have focused on the more direct measure of viral activity, viral load.

In our cohort of ambulatory HIV-positive individuals, we demonstrated a consistent association between viral load measures and HRQOL measures. Specifically, we found a consistent association between viral load and the PCS of the SF-36, as well as six of the eight SF-36 subscale scores: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), role-emotional (RE), and vitality (VT). No such association was identified for the MCS of the SF-36 or the MH (mental health) or SF (social functioning) subscale scores.

In addition, we were able to reproduce the previously documented association between CD4 cell counts and HRQOL measures. A consistent association was found between CD4 cell count and the PCS of the SF-36, as well as five of the eight SF-36 subscale scores: PF, RP, GH, SF, and VT. It is important to note that the associations between viral load and the BP and RE subscale scores of the SF-36 were not found for CD4 cell count. Multivariate models revealed CD4 cell count to be a significant and independent predictor of PCS, PF, RP, GH, and VT.

Notably, the relationships identified between CD4 cell count and the individual HRQOL scales appear to be monotonic; persons with higher CD4 cell counts have higher scores. In contrast, the relationships between viral load and the individual HRQOL scales appear to be monotonic only for the higher viral load subgroups; the patients in the lowest viral load subgroup actually have subscale scores that are generally lower than the next viral load subgroup. This is unexpected, as persons with lower viral load measurements are, in general, considered the healthier group. One possible interpretation of this observed pattern is that persons in the lowest viral load group are more adherent to their medications or are taking more aggressive medical regimens (thus resulting in their lower viral loads). This might make this group more likely to suffer from adverse effects of the medications and result in a decreased quality of life.

Finally, we were able to demonstrate the robustness of the negative association between viral load and HRQOL by controlling for the effect of CD4 cell count and other demographic and clinical variables. Viral load was found to be an independent predictor of PCS score, as well as RP, BP, and VT subscale scores.

Associations with physical dimensions, but not mental or cognitive dimensions, have been shown in a variety of studies assessing HRQOL and CD4 cell counts [25, 38, 40, 45, 53] as well as in studies assessing HRQOL and CDC stage [17, 21, 25, 38, 39, 53–55]. Similarly, our study demonstrated associations with primarily physical dimensions of HRQOL for both CD4 cell count and viral load. Interestingly, the one mental subscale associated with both disease state markers was vitality. Vitality is assessed in the SF-36 questionnaire with questions about feeling full of pep, having energy, feeling tired and feeling worn out; these questions focus on the physical feeling of having energy, perhaps explaining why the associations with

disease state parallel those of the more physical dimensions of HRQOL. Among previous studies with instruments derived from the MOS, associations between the clinical variables and HRQOL have been the strongest with the role physical and bodily pain subscales [17, 21, 25, 45, 53]. Notably we were able to reproduce these associations in our current study, particularly between viral load and both the RP and BP subscales; CD4 cell count, however, showed an association for the RP, but not the BP subscale.

Recently published studies assessing the relationship between viral load and HRQOL have presented conflicting results [47, 48]. Weinfurt et al. conducted a study examining the relationship between change in surrogate markers of disease state (viral load and CD4 cell count) and change in HRQOL (MOS-HIV) in a cohort of over one thousand HIV-infected individuals enrolled in a randomized trial of antiretroviral therapy [47]. They noted an association between baseline viral load and subsequent change in HRQOL over time as well as an association between change in viral load and change in HRQOL over time. Notably, unlike in our study, this association was present, and of similar degree, for both the mental and physical summary scores of the MOS-HIV. This population was similar to ours in demographics and disease state, but all subjects did receive anti-retroviral therapy in a randomized fashion during the time of evaluation.

Contrary to these and our findings, a recent study by Badia et al. found no statistically significant association between viral load and any summary or subscale score of two HRQOL measures, the MOS-HIV and the MQOL-HIV, in a cohort of 558 HIV-infected patients [48]. Again, no difference was seen between physical and mental dimensions of HRQOL. Notably, they also did not note an association between CD4 cell count and HRQOL in this population.

Several limitations must be considered in interpreting the results of our study. The study population is small in size, and thus restricted our ability to perform further stratified or adjusted analyses. This was a particular limitation in assessing the viral load subgroup of < 5000 copies/ml HIV-1 RNA. The majority of the participants were Caucasian homosexual males with fairly advanced disease. The cohort consisted of few women, few minorities and few intravenous drug users; findings in these populations may differ from the results found in this population of individuals. In addition, we would be interested in assessing whether adherence or adverse effects of medications had an impact on HRQOL in this cohort; we did not have data on these factors at baseline but will consider such analyses in follow up.

The SF-36 was used as the HRQOL measure for this analysis. As several authors have noted, this instrument may not capture all HIV-specific dimensions of HRQOL. In addition, it is a general HRQOL measure and does not take patient preference into account. Further analyses are planned involving preference-based measures of HRQOL in this cohort.

The paradigm of HIV infection is shifting toward that of a chronic illness. With this shift, we must focus not only on increasing the quantity of life but also on maintaining and maximizing the quality of that life. Thus, the relationships between traditional measures of disease states and patient-focused measures of health-related quality of life become increasingly important. Strong evidence supports the fact that suppression of viral replication decreases both morbidity and mortality in HIV-infected persons. Our study suggests that, in addition to the known biological benefits, suppression of viral replication may have patient-focused benefits, particularly the maintenance of several dimensions of HRQOL.

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