

Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence

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Abstract *This study assesses changes in quality of life (QoL) over time among HIV-infected individuals receiving antiretroviral therapy (ART) and evaluates how this relates to ART adherence. Prospective, longitudinal data were examined from 1050 participants in two large, randomized, multi-centre antiretroviral clinical trials. QoL was assessed by the SF-12; adherence by the Terry Beinr Community Programs for Clinical Research on AIDS Antiretroviral Medication Self-report. Participants included 20% women, 53% African Americans, 16% Latinos; mean age was 39 years; mean baseline CD4+ cell count 230 cells/mm³; 89% were ART-naïve at entry. Baseline physical and mental health summary QoL scores were 45.4 and 42.9, comparable to scores reported in other advanced HIV populations. Significant improvements in mean QoL scores were seen for the group as a whole after 1 to 4 months on new ART regimens, and persisted for 12 months. Participants reporting 100% ART adherence achieved significantly higher QoL scores at 12 months compared to those with poorer adherence, particularly if 100% adherence was consistent ($p < 0.001$). Those with at least 80% ART adherence had smaller gains in QoL at 12 months when compared to baseline, while those with <80% adherence had worsening of QoL. In this analysis, ART adherence was associated with improved QoL, particularly if adherence was sustained.*

Introduction

Adherence is a critical component for therapeutic success in HIV infection, while improved quality of life (QoL) has been recognized as an important outcome from the treatment of HIV

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(Cohen *et al.*, 1998; Franchi & Wenzel, 1998; Wu, 2000). Adherence to antiretroviral therapy (ART) has been shown to be a major determinant of biological outcome measures in HIV, including HIV ribonucleic acid (RNA) level, CD4 lymphocyte count, and genotypic resistance (Hecht *et al.*, 1998; Montaner *et al.*, 1998; Haubrich *et al.*, 1999; Bangsberg *et al.*, 2000; Gifford *et al.*, 2000; Montessori *et al.*, 2000; Paterson *et al.*, 2000; Knobel *et al.*, 2001; Bangsberg *et al.*, 2002; Mannheimer *et al.*, 2002; Raboud *et al.*, 2002). Adherence has also been found to predict clinical outcome measures in HIV, including mortality, AIDS progression, and hospitalization (Bangsberg *et al.*, 2001; Hogg *et al.*, 2001; Garcia de Olalla *et al.*, 2002).

The relationship between QoL and adherence has not been well studied. ART adherence is known to contribute to improved HIV clinical outcomes, which could result in a better QoL. QoL may also influence adherence, as persons with better QoL may have a greater ability to adhere to their ART regimens. Studies have shown that adherence and QoL share some determinants. Both QoL and adherence have been associated with HIV RNA levels, HIV disease stage, and symptoms. QoL and adherence both share an inverse relationship with HIV RNA: lower adherence rates predict higher HIV RNA levels (Hecht *et al.*, 1998; Montaner *et al.*, 1998; Haubrich *et al.*, 1999; Bangsberg *et al.*, 2000; Gifford *et al.*, 2000; Montessori *et al.*, 2000; Paterson *et al.*, 2000; Mannheimer *et al.*, 2002), and this virological failure has been associated with lower QoL scores (Nieuwkerk *et al.*, 2000a). In addition, having an AIDS diagnosis and disease-related symptoms have both been associated with lower QoL scores (Cunningham *et al.*, 1998; Vogl *et al.*, 1999; Bing *et al.*, 2000; Hays *et al.*, 2000; Nieuwkerk *et al.*, 2000b; Lorenz *et al.*, 2001; Nicholas *et al.*, 2002) and higher adherence levels (Samet *et al.*, 1992; Besch, 1995; Singh *et al.*, 1996). These relationships could change, however, when symptoms are related to the HIV therapy. Symptoms related to side-effects from therapy have been associated with lower QoL scores (Zinkernagel *et al.*, 1999; Orlando *et al.*, 2002; Sipes *et al.*, 2002) and poorer adherence (Crespo-Fierro, 1997; Chesney, 2000).

QoL has also been shown to improve with ART (Nieuwkerk *et al.*, 2001; Fumaz *et al.*, 2002), though the effect may differ depending on the person's baseline QoL (Nieuwkerk *et al.*, 2002). Persons with advanced HIV disease and low QoL scores have demonstrated significant improvements in QoL with ART (Cohen *et al.*, 1998; Revicki *et al.*, 1999a; Nieuwkerk *et al.*, 2002), while those with asymptomatic HIV and higher QoL scores have shown short-term impairment of QoL related to medication side-effects (Zinkernagel *et al.*, 1999). While some aspects of QoL have been shown to impact on ART adherence (Holzemer *et al.*, 1999), little is known about the effect of ART adherence on QoL. Limited data suggest that adherence affects QoL (Swindells *et al.*, 1999), but it is not known what degree of adherence is required to achieve QoL benefits.

To gain a better understanding of QoL in the setting of HIV clinical trials and the relationship between QoL and ART adherence, we examined QoL and self-reported adherence among ART-naïve and -experienced participants in two large, multi-centre antiretroviral clinical trials.

Methods

QoL and adherence were measured in all participants in two US antiretroviral clinical trials conducted by the Terry Beinr Community Programs for Clinical Research on AIDS (CPCRA). The CPCRA, sponsored by the United States National Institutes of Health (NIH), is a clinical trials network that conducts community-based HIV/AIDS research. The CPCRA consists of 15 sites throughout the USA that seek to enrol persons of colour, women,

and injection drug users. The two trials, CPCRA 057 and 058 (MacArthur *et al.*, 2001), evaluate ART strategies among antiretroviral-experienced and antiretroviral-naïve patients, respectively. CPCRA 057 was designed to compare salvage ART strategies for persons failing their first protease inhibitor- (PI-) containing regimen. CPCRA 058 compares three different strategies for ART-naïve patients: (1) PI-containing regimens; (2) non-nucleoside reverse transcriptase inhibitor- (NNRTI-) containing regimens; and (3) regimens including both a PI and an NNRTI; all arms also included concomitant nucleoside analogues. CPCRA 057 opened in October 1998 and closed in June 2000, while CPCRA 058 opened in January 1999 and was ongoing when this analysis was conducted. In both studies, participants were randomized at baseline to begin new antiretroviral regimens.

Data collection

Data collection from participants in both studies was carried out at baseline and at 1 and 4 months after randomization, and then every 4 months for the duration of the studies. Data gathered included participant demographics, HIV transmission risk category, CD4+ cell count, HIV RNA level (using RT-PCR, ultrasensitive Roche Amplicor HIV assays, Alameda, CA), history of AIDS-defining illnesses, symptom severity, and QoL. Adherence measurements were collected beginning at 1 and 4 months of follow-up and every 4 months thereafter for the duration of the studies.

QoL was measured using the SF-12[®] Health Survey instrument (© 1995, John E. Ware, Jr). Items in the short-form 12-item health status SF-12 instrument are a subset of those in the short-form health survey SF-36 (McHorney *et al.*, 1993; Jenkinson *et al.*, 1994; McHorney *et al.*, 1994). The SF-12 is widely used because it has demonstrated construct, criteria, and predictive validity (Kodraliu *et al.*, 2001), and because it assesses depressed mental health functioning in a manner that is relatively unrelated to physical health (Wu *et al.*, 1997). This measure is one of the shortest instruments available for the assessment of health-related quality of life (Wu *et al.*, 1997). The two summary scores also have high test–retest reliability ($r=0.89$) and are able to discriminate between mental and physical health conditions (Ware *et al.*, 1996). This discriminatory power is particularly important when dealing with an HIV-infected population that may suffer diminished physical health due to symptoms of HIV disease and side-effects of therapy. In addition to being a reliable measure of QoL in the general US population (Ware *et al.*, 1996) and in patients with rheumatoid arthritis (Hurst *et al.*, 1998), the reliability of the SF-12 has also been recently demonstrated among persons with advanced HIV infection (Han *et al.*, 2002). Han *et al.* (2002) suggested that the SF-12 was an effective substitute for the SF-39 (the SF-39 is essentially identical to the widely used MOS HIV questionnaire), and that the SF-12 reduced redundancy and the burden of data requirements (Wu *et al.*, 1991; Han *et al.*, 2002). The SF-12 has also been shown to be a useful instrument for longitudinal survey assessments (Kodraliu *et al.*, 2001).

Participants' responses to the SF-12 are aggregated into eight QoL dimensions: general health perceptions (question 1), physical functioning (2 and 3), pain (8), mental health (9 and 11), role—physical health (4 and 5), role—emotional health (6 and 7), energy/fatigue (10), and social functioning (12). Participants who responded to every QoL question were considered to have complete QoL data. Methods for calculating summary scores reflecting mental and physical health are described below. These standardized summary scores can be compared to national norms.

Adherence was measured using the CPCRA Antiretroviral Medication Self-report (Form 646, available at <http://sdmc.cpcra.org/CRFormsIndex.html#module>). This instrument for assessing self-reported ART adherence was previously validated among over 1,000

HIV-infected participants in CPCRA clinical trials. Adherence measured using this instrument (categorized as 100%, 80–99%, and <80%) was shown to be significantly associated with virological and immunological outcome while on ART (Mannheimer *et al.*, 2002). The questionnaire employs a global 7-day recall. For each medication prescribed, patients were asked to record whether they took ‘all, most, about half, very few, none’ of their pills in the past 7 days. Study participants filled out the questionnaire and submitted it in a sealed envelope directly to the CPCRA Statistical and Data Monitoring Center. Staff assistance for completing the patient portion of the questionnaire was provided only when needed or requested by the participant.

Statistical analysis

For the current cross-protocol analysis, data were combined from the CPCRA 057 and CPCRA 058 study participants enrolled between the openings of the two studies, in October 1998 and January 1999, respectively, and May 2001. Data were included for all participants with at least 1 month of follow-up, including at least the 1-month adherence measure, as of May 2001. Up to 12 months of adherence and QoL follow-up data were reviewed.

QoL scores for each dimension were obtained by rescaling the eight SF-12 dimensions from 0 to 100, with 100 being most favourable (e.g. for item 1, responses of 1, 2, 3, 4, or 5 were converted to 100, 75, 50, 25, or 0, respectively). QoL physical component summary (PCS) and mental component summary (MCS) scores are standardized scores calculated to have means of 50 and standard deviations of 10 in the general US population. These were calculated using standard methods for participants with complete QoL data (Ware *et al.*, 1998). Each point on these scores represents one-tenth of a standard deviation. For PCS and MCS scores, differences of 3–5 points are considered clinically meaningful (Ware *et al.*, 1998).

An adherence score was calculated, based on the mean of the combined total of each medication reported taken during the previous week. In order to convert participant responses into a numerical scale for calculation of an adherence score, responses for ART pills taken were assigned the following values: ‘all’ = 100%, ‘most’ = 80%, ‘about half’ = 50%, ‘few’ = 20%, ‘none’ = 0%; no numerical values were listed on the questionnaire. Adherence levels for each participant’s ART regimen were then classified as 100%, 80–99%, and <80% to be consistent with previously reported data (Mannheimer *et al.*, 2002).

Chi-square tests and Fisher’s exact tests were used to compare categorical data. Analysis of variance was used to evaluate the relationship of QoL with adherence. To test the hypothesis that QoL influences ART adherence, analysis of variance (ANOVA) was conducted to examine for an association between baseline QoL scores and future adherence self-report levels (at months 1, 4, 8, and 12 of follow-up). Baseline adherence data were not available as most participants were antiretroviral-naïve at study enrolment. To test the hypothesis that ART adherence may result in improved QoL, we examined the relationship between adherence self-report at 1 month of follow-up and future QoL measurements (at months 4, 8, and 12 of follow-up) and also between adherence data over the 12-month study period and QoL outcome at 12 months. Each time point was examined separately for the entire group of participants, as well as for the cohort of participants who had completed 12 months of follow-up. Repeated measures analyses were performed to assess variables associated with follow-up summary QoL measures. These were adjusted for the baseline summary QoL measure. The relationship between QoL and HIV RNA was estimated using an ANOVA. Analyses adjusted for adherence were performed by adding adherence as a covariate. Similar analyses were conducted to examine the relationship between QoL and CD4.

Results

Participant characteristics

Adherence was evaluated among all CPCRA 057 and CPCRA 058 participants who had completed at least 1 month of follow-up and the 1-month adherence self-report questionnaire as of May 2001. Among the 1,095 participants with at least 1 month of follow-up, complete 1-month QoL data were available for 1,050 (95.8%). Participants included 20% women, 53% African Americans, 16% Latinos, and 16% with injection drug use risk category; mean age was 39 years. Participants' mean baseline CD4+ lymphocyte cell count was 230 cells/mm³, mean baseline HIV RNA was 4.95 log₁₀ copies/ml, and 29% of participants had a prior history of an AIDS-defining illness. At baseline, 936 participants (89%) were ART-naïve and 114 were ART-experienced. Among participants who completed 12 months of study follow-up, complete QoL data were available for 514.

QoL

The 1,050 participants had baseline PCS and MCS QoL scores of 45.4 and 42.9, respectively. The QoL scores are comparable to those reported in other studies of persons with advanced HIV disease (Cohen *et al.*, 1998; Revicki *et al.*, 1999a, b; Hays *et al.*, 2000). ART-experienced participants scored significantly higher in the general health and energy QoL domains at baseline compared to the ART-naïve participants.

All QoL domains and both summary QoL scores improved significantly over time among participants in the HIV antiretroviral clinical trials who had completed 12 months of follow-up (Table 1 and Figure 1). The characteristics of the 12-month cohort were similar to those of the entire group of participants. Significant increases in QoL, when compared to baseline QoL, were seen beginning after 1 to 4 months from enrolment into the clinical trials. The improvements in QoL persisted during the 12-month follow-up period in the clinical trial. No significant differences were seen between antiretroviral-naïve and -experienced participants in terms of baseline or follow-up PCS and MCS scores; both groups of participants experienced improvements in QoL over time. ART-naïve participants achieved significantly higher gains in the health QoL domain at all follow-up time points examined when compared to the ART-experienced group.

By repeated measures analysis, male gender ($p=0.028$) and not having a history of injection drug use ($p < 0.001$) were associated with improved PCS scores, while older age was associated with lower PCS scores ($p < 0.001$). Participants with lower baseline CD4 counts

Table 1. *Baseline and follow-up QoL scores in 12-month cohort (N=514)*

QoL category	Mean baseline QoL score	Mean 12-month QoL score	Standard error	<i>p</i> value
General health	52.9	62.0	1.23	<0.001
Mental health	63.7	68.2	1.06	<0.001
Role-physical	57.3	70.2	2.30	<0.001
Role-emotional	65.3	72.5	2.21	0.002
Pain	76.7	82.1	1.33	<0.001
Physical functioning	71.6	75.6	1.43	0.004
Energy	52.8	60.2	1.36	<0.001
Social functioning	71.2	81.0	1.48	<0.001
PCS	45.5	48.0	0.50	<0.001
MCS	43.3	44.7	0.46	<0.001

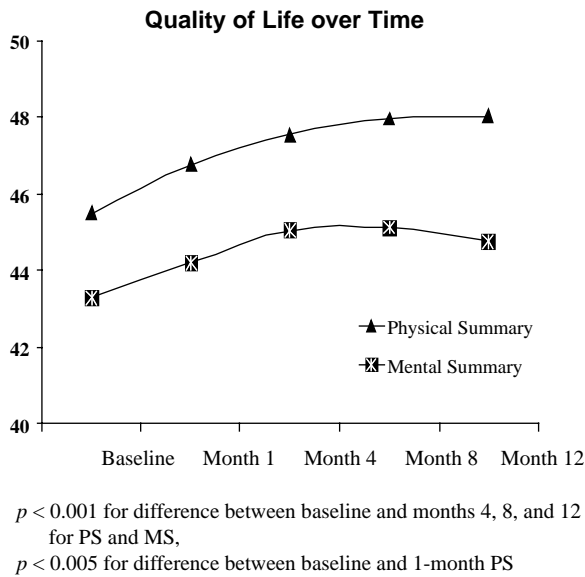


FIG. 1. *Physical Component Summary (PCS) and Mental Component Summary (MCS) Quality of Life scores over time for the 12-month cohort (N = 514).*

had the greatest improvements in their MCS scores ($p = 0.024$). Race/ethnicity, having an AIDS diagnosis, and baseline HIV RNA levels were not significantly associated with PCS or MCS scores.

Adherence

Using the CPCRA Antiretroviral Medication Self-report, participants' mean self-reported adherence scores were 89%, 86%, 85%, and 85% at 1, 4, 8, and 12 months of follow-up, respectively. Among the cohort of participants who completed 12 months of study follow-up, 100% adherence was reported by 76%, 66%, 66%, and 67% of the cohort after 1, 4, 8, and 12 months, respectively. This represented a significant decrease in adherence after 1 month (Mannheimer *et al.*, 2002). Adherence scores of 80–99% were reported by 19% of participants at 12 months, with most of those having scores between 80% and 85% (15%). The remaining 14% had scores of 0–79% at 12 months, with 8% having scores of 0. Adherence measured with the CPCRA self-report has been shown to correlate strongly with virological and immunological outcomes of HIV therapy (Mannheimer *et al.*, 2002), with 70%, 46%, and 19% of subjects reporting 100%, 80–99%, and 0–79% adherence, respectively, achieving non-detectable HIV RNA levels (< 50 copies/ml) at 12 months ($p < 0.001$). Among the same three groups, the CD4+ lymphocyte count increased by 152, 175, and 41 cells/mm³, respectively, at 12 months ($p = 0.005$).

Relationship between QoL and adherence

Participants' QoL was significantly associated with their concurrent self-reported antiretroviral adherence level for the two QoL summary scores and for each of the eight QoL dimensions at 12 months of follow-up and also at the majority of other time points. Persons reporting higher levels of adherence also reported higher QoL scores. Patients reporting 100%

adherence had significantly higher PCS and MCS scores at all four follow-up time points (months 1, 4, 8, and 12) than patients reporting 80–99% or <80% adherence. Participants reporting 100% adherence at 12 months, for example, had 12-month PCS and MCS scores of 48.7 and 45.8, respectively, compared to 43.9 and 42.0, respectively, for those reported <80% adherence ($p < 0.001$). The greatest gains in QoL over time occurred among participants reporting better adherence. At 12 months, significant differences in the change in physical (PCS) and mental (MCS) components of QoL from baseline were seen among participants reporting different levels of ART adherence ($p < 0.03$ and $p < 0.005$ for PCS and MCS, respectively) (see Figures 2 and 3), with the greatest gains occurring for those reporting 100% ART adherence. Participants reporting 80–99% ART adherence had smaller increases in QoL scores and those reporting <80% ART adherence had decreases in QoL at 12 months. Greater improvements in PCS and MCS QoL scores were also seen at 4 and 8 months for those with at least 80% adherence, though only reaching statistical significance for MCS at 4 months ($p < 0.001$) (see Figure 3). Similar improvements in all QoL dimensions at 12 months were seen for those with at least 80% adherence, reaching statistical significance for seven of the eight dimensions (except for pain). For example, general health perception scores improved by an average of 11.8 for those with 100% adherence, 7.8 for those with 80–99% adherence, and decreased by 1.4 for those with <80% adherence ($p = 0.001$).

The consistency of ART adherence during the 12-month study period was also predictive of QoL outcomes. Among the 514 participants with complete QoL data at 12 months of follow-up in the two antiretroviral clinical trials (the 12-month cohort), 318 reported 100% adherence at 3 or 4 of the total of 4 follow-up study visits (at months 1, 4, 8, and 12 after enrolment) in that 12-month time period (adherent group), while 196 participants reported 100% adherence at either 0, 1, or 2 of the 4 follow-up study visits (non-adherent group). When compared to the non-adherent group, the adherent patients had significantly higher QoL scores at 12 months for the two summary scores as well as for all of the eight domains (see Figure 4). At 12 months, adherent participants had a higher mean PCS score (49.20 vs. 46.15, $p < 0.001$) and a higher mean MCS score (45.87 vs. 42.93, $p < 0.001$), compared to those in the non-adherent group. Adherent participants also achieved significantly higher increases in their QoL scores from their baseline when compared to non-adherent participants.

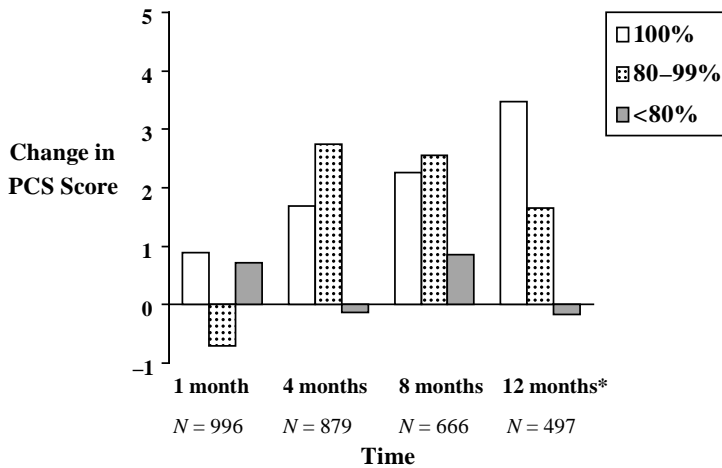


FIG. 2. Change in Physical Component Summary (PCS) Quality of Life Score from Baseline by Adherence Level: * $p < 0.05$.

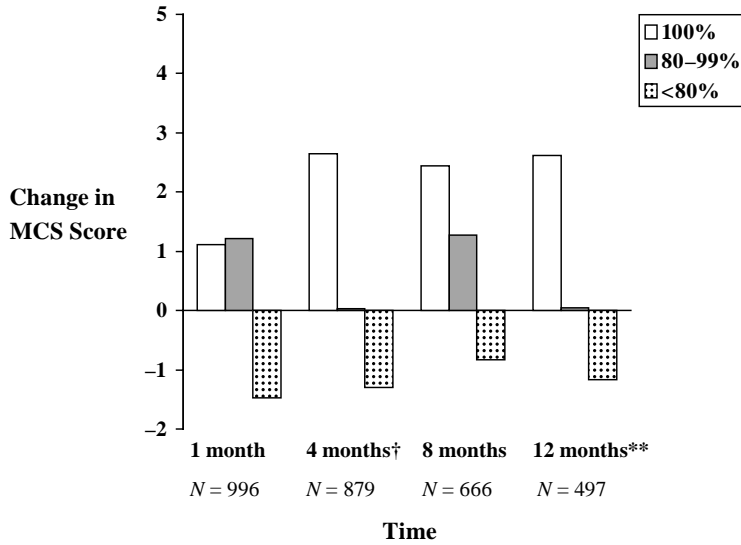


FIG. 3. Change in Mental Component Summary (MCS) Quality of Life Score from Baseline by Adherence Level: ** $p < 0.005$; † $p < 0.001$.

Participants' 1-month adherence data were also associated with future gains in some QoL categories, with significant improvements seen in energy and mental summary QoL scores ($p = 0.021$ and 0.034 , respectively, for change in QoL from baseline to month 12). Baseline QoL scores (for the two summary scores as well as for each of the eight QoL domains), however, were not predictive of future adherence levels over the duration of the study.

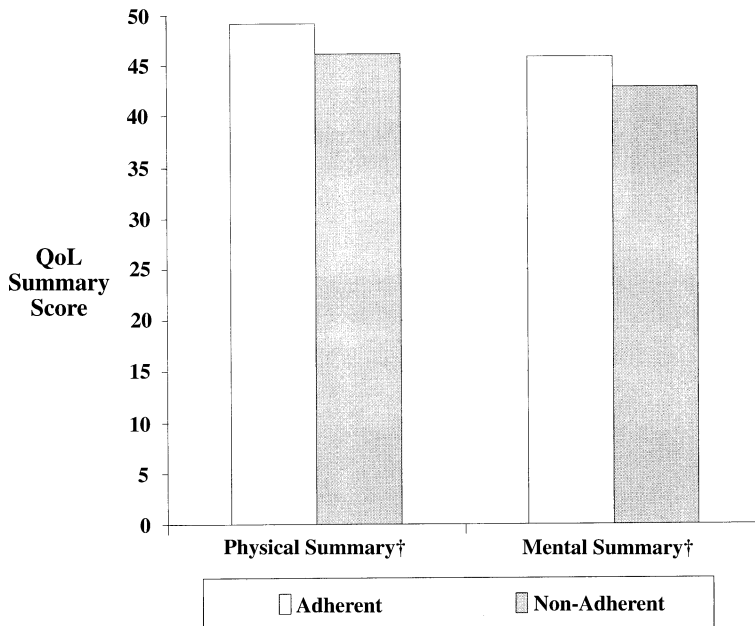


FIG. 4. QoL Physical and Mental Component Summary Scores Among Adherent (N=318) and Nonadherent (N=196) HIV-Infected Patients at 12 months after enrollment into 2 CPCRA HIV Antiretroviral Clinical Trials: † $p < 0.001$.

Virological and immunological outcomes

When examined at each time point, high PCS and MCS scores were significantly associated with improved virological outcome at the 4-, 8-, and 12-month follow-up visits (for PCS, $p < 0.001$ for change from baseline in log HIV RNA at 4 and 8 months, $p < 0.005$ for virological change at 12 months; for MCS, $p < 0.05$ for change from baseline in log HIV RNA at 4 and 8 months, $p < 0.01$ for virological change at 12 months). Adherence at each time point also was significantly associated with HIV RNA level ($p < 0.001$ for 1, 4, 8, and 12 months) and with virological suppression (HIV RNA < 50 copies) ($p < 0.001$ for months 4, 8, and 12) (Mannheimer *et al.*, 2002). After adjustment for adherence level, however, only the 4- and 8-month PCS scores remained associated with change in HIV RNA from baseline ($p = 0.009$ and 0.012 , respectively).

QoL improvements were also associated with improvements in CD4 lymphocyte counts. Improved immunological outcome was associated with higher PCS scores at months 4, 8, and 12 and with higher MCS scores at month 12. After adjusting for adherence level, however, only PCS at month 8 remained significantly associated with improved immunological outcome ($p < 0.018$).

Discussion

This longitudinal study demonstrated that the QoL improved over time for HIV-infected individuals receiving ART. This improvement was demonstrated among over 1,000 HIV-infected participants in two large multi-centre antiretroviral clinical trials following the initiation of new highly active antiretroviral therapy (HAART) regimens. Significant improvements in QoL were noted as early as 1 month after initiating the HAART regimens for the physical (PCS) and 4 months for the mental (MCS) component of QoL. The improved QoL was sustained over the 12-month study period. The improvements in QoL were most striking among those with the highest adherence levels. In a cross-sectional analysis at 4, 8, and 12 months after initiation of new ART regimens, significant differences were seen at 4 months for MCS and at 12 months for both MCS and PCS summary scores and in seven of the eight QoL domains. In each case, those reporting 100% adherence had the greatest gains, those with 80–99% adherence levels had smaller benefits, and those with $< 80\%$ adherence had lower QoL scores than at baseline. Longitudinal data showed that participants reporting 100% adherence at either 3 or 4 of the total of 4 study follow-up visits over the 12 months achieved the best QoL outcomes, highlighting the importance of consistent adherence.

This is the first analysis in the setting of a large clinical trial to demonstrate this relationship between QoL and adherence. Those with the highest adherence levels achieved the greatest virological and immunological gains from therapy (as demonstrated in previous studies), and presumably the improvements in HIV status led to the improved QoL. However, causality could not be definitively determined in this study, as baseline QoL did not predict future adherence, and baseline adherence data were not available. Adherence levels reported at 1 month, however, were associated with future gains in QoL. In addition, the significant association between consistently high self-reported adherence levels over a 12-month period and the resulting QoL level at the end of the 12-month period suggests that adherence may be an important contributing factor leading to the significant increases in QoL from baseline.

Male gender was also found to be associated with improved PCS scores in this study. This was not related to differences in access to treatment as all patients were receiving medications in HIV antiretroviral trials. The underlying cause for this gender difference

remains unclear and would require further exploration in another study. Participants with lower baseline CD4 lymphocyte count had the greatest improvement in MCS. Factors associated with poorer PCS outcomes in this study included injection drug use and older age.

In this study, as in previous studies, both QoL and adherence were associated with virological and immunological outcome. Antiretroviral adherence, however, was found to be the strongest predictor of HIV RNA level and CD4 lymphocyte count, as reported previously (Mannheimer *et al.*, 2002). The significant decrease in adherence levels over time may be related to pill fatigue and/or side-effects.

The strengths of this study include the large sample size and the longitudinal follow-up. Limitations include the subjective nature of the self-reported adherence and QoL measures. Despite concerns that self-report may overestimate adherence (Cramer *et al.*, 1989; Waterhouse *et al.*, 1993; Arnsten *et al.*, 2001; Liu *et al.*, 2001), several studies have demonstrated a strong association between self-reported adherence and both virological and immunological outcomes in HIV (Hecht *et al.*, 1998; Nieuwkerk *et al.*, 2001; Fischl *et al.*, 2002; Cahn *et al.*, 2004; Mannheimer *et al.*, 2002; Mellors *et al.*, 2002; Fletcher *et al.*, 2003). Self-reported adherence has also been shown to correlate with plasma concentrations of antiretroviral medications (Nieuwkerk *et al.*, 2001). The scoring of the CPCRA adherence instrument is also a potential limitation, as the adherence categories (taking 'all, most, about half, very few, none' of the ART pills in the prior 7 days) were later converted into corresponding percentages (100%, 80%, 50%, 20%, and 0). The grouping of adherence scores into the three categories of 100%, 80–99%, and 0–79% was based on previous work with this validated instrument. While the 80–99% category represents a broad range of adherence behaviour, the majority in this group had adherence scores <85%. Because of the nature of this cross-protocol analysis, the population studied represents a diverse group of patients, including ART-naïve and -experienced individuals at baseline. The majority of participants were ART-naïve at baseline, so no definite conclusions can be inferred for ART-experienced individuals.

This report confirms the utility of the SF-12 instrument in measuring QoL in HIV and highlights the value of self-reported adherence. Baseline QoL scores in this study were comparable to those reported in other advanced HIV/AIDS populations. This study also identified improved QoL as another benefit associated with adherence to ART. Participants reporting 100% ART adherence had the best QoL outcomes, though those with at least 80% ART adherence still achieved gains in QoL from baseline. Those reporting adherence levels below 80% had worsening of QoL over time. While previous data have suggested a requirement of at least 95% adherence for the best virological outcomes (Paterson *et al.*, 2000), clinical benefits such as improved QoL may occur at lower adherence levels.

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References

- ARNSTEN, J., DEMAS, P., FARZADEGAN, H., GRANT, R., GOUREVITCH, M., CHANG, C., BUONO, D., ECKHOLDT, H., HOWARD, A. & SCHOENBAUM, E. (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clinical Infectious Diseases*, 33, 1417–1423.

- BANGSBERG, D.R., HECHT, F.M., CHARLEBOIS, E.D., ZOLOPA, A.R., HOLODNIY, M., SHEINER, L., BAMBERGER, J.D., CHESNEY, M.A. & MOSS, A. (2000). Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*, *14*, 357–366.
- BANGSBERG, D., PERRY, S., CHARLEBOIS, E., CLARK, R., ZOLOPA, A. & MOSS, A. (2001). Adherence to HAART predicts progression to AIDS. Poster presented at the Eighth Conference on Retroviruses and Opportunistic Infections, Chicago, IL, February 4–8.
- BANGSBERG, D., CHARLEBOIS, E., GRANT, R., HOLODNIY, M., PERRY, S., CONROY, K.N., GUZMAN, D., ZOLOPA, A. & MOSS, A. (2002). Low levels of adherence do not increase risk of HIV drug resistance. Poster presented at the Ninth Conference on Retroviruses and Opportunistic Infections, Seattle, WA, February 24–28, p. 256.
- BESCH, C.L. (1995). Compliance in clinical trials. *AIDS*, *9*, 1–10.
- BING, E.G., HAYS, R.D., JACOBSON, L.P., CHEN, B., GANGE, S.J., KASS, N.E., CHMIEL, J.S. & ZUCCONI, S.L. (2000). Health-related quality of life among people with HIV disease: results from the Multicenter AIDS Cohort Study. *Quality of Life Research*, *9*, 55–63.
- CAHN, P., VIBHAGOO, A., SCHECHTER, M., SOTO-RAMIREZ, L., CAROSI, G., SMALL, F., JORDAN, J.C., PHARO, C.E., THOMAS, N.E. & STEEL, H.M. (2004). Predictors of adherence and virologic outcome in HIV-infected patients treated with abacavir- or indinavir-based triple combination HAART also containing lamivudine/zidovudine. *Current Medical Research Opinions*, *20* (7), 1115–1123.
- CHESNEY, M.A. (2000). Factors affecting adherence to antiretroviral therapy. *Clinical Infectious Diseases*, *30* (Supplement 2), S171–S176.
- COHEN, C., REVICKI, D.A., NABULSI, A., SAROCCO, P.W. & JIANG, P. (1998). A randomized trial of the effect of ritonavir in maintaining quality of life in advanced HIV disease. Advanced HIV Disease Ritonavir Study Group. *AIDS*, *12*, 1495–1502.
- CRAMER, J.A., MATTSO, R.H., PREVEY, M.L., SCHEYER, R.D. & OUELLETTE, V.L. (1989). How often is medication taken as prescribed? A novel assessment technique. *Journal of the American Medical Association*, *261*, 3273–3277.
- CRESPO-FIERRO, M. (1997). Compliance/adherence and care management in HIV disease. *Journal of the Association of Nurses in AIDS Care*, *8*, 43–54.
- CUNNINGHAM, W.E., SHAPIRO, M.F., HAYS, R.D., DIXON, W.J., VISSCHER, B.R., GEORGE, W.L., ETTL, M.K. & BECK, C.K. (1998). Constitutional symptoms and health-related quality of life in patients with symptomatic HIV disease. *American Journal of Medicine*, *104*, 129–136.
- FISCHL, M., RIBAUDO, H., COLLIER, A., ERICE, A., GIULIANO, M., DEHLINGER, M., ERON, J., SAAG, M., HAMMER, S., VELLA, S., MORSE, G.D. & FEINBERG, J.E., FOR THE ADULT AIDS CLINICAL TRIALS GROUP 388 STUDY TEAM (2003). A randomized trial of 2 different 4-drug antiretroviral regimens versus a 3-drug regimen, in advanced Human Immunodeficiency Virus disease. *Journal of Infectious Diseases*, *188*, 625–634.
- FLETCHER, C., TESTA, M., HAUBRICH, R., BRUNDAGE, R., JIANG, H., ICKOVICS, J., MARTINEZ, A., SNYDER, S. & GULICK, R. (2003). Relationships among four measures of medication adherence and virologic response in ACTG 359. Poster presented at the 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 10–14.
- FRANCHI, D. & WENZEL, R.P. (1998). Measuring health-related quality of life among patients infected with human immunodeficiency virus. *Clinical Infectious Diseases*, *26*, 20–26.
- FUMAZ, C.R., TULDRA, A., FERRER, M.J., PAREDES, R., BONJOCH, A., JOU, T., NEGREDO, E., ROMEU, J., SIRERA, G., TURAL, C. & CLOTET, B. (2002). Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens. *Journal of Acquired Immune Deficiency Syndrome*, *29*, 244–253.
- GARCIA DE OLALLA, P., KNOBEL, H., CARMONA, A., GUELAR, A., LOPEZ-COLOMES, J.L. & CAYLA, J.A. (2002). Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *Journal of Acquired Immune Deficiency Syndrome*, *30*, 105–110.
- GIFFORD, A.L., BORMANN, J.E., SHIVELY, M.J., WRIGHT, B.C., RICHMAN, D.D. & BOZZETTE, S.A. (2000). Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *Journal of Acquired Immune Deficiency Syndrome*, *23*, 386–395.
- HAN, C., PULLING, C.C., TELKE, S.E. & HUPPLER HULLSIEK, K. (2002). Assessing the utility of five domains in SF-12 Health Status Questionnaire in an AIDS clinical trial. *AIDS*, *16*, 431–439.
- HAUBRICH, R.H., LITTLE, S.J., CURRIER, J.S., FORTHAL, D.N., KEMPER, C.A., BEALL, G.N., JOHNSON, D., DUBE, M.P., HWANG, J.Y. & MCCUTCHAN, J.A. (1999). The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. *AIDS*, *13*, 1099–1107.
- HAYS, R.D., CUNNINGHAM, W.E., SHERBOURNE, C.D., WILSON, I.B., WU, A.W., CLEARY, P.D., MCCAFFREY, D.F., FLEISHMAN, J.A., CRYSTAL, S., COLLINS, R., EGGAN, F., SHAPIRO, M.F. & BOZZETTE, S.A. (2000). Health-related

- quality of life in patients with human immunodeficiency virus infection in the United States: results from the HIV Cost and Services Utilization Study. *American Journal of Medicine*, 108, 714–722.
- HECHT, F.M., COLFAX, G., SWANSON, M. & CHESNEY, M.A. (1998). Adherence and effectiveness of protease inhibitors in clinical practice. Poster presented at the Fifth Conference on Retroviruses and Opportunistic Infections, Chicago, IL.
- HOGG, R.S., YIP, B., CHAN, K.J., WOOD, E., CRAIB, K.J., O'SHAUGHNESSY, M.V. & MONTANER, J.S. (2001). Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *Journal of the American Medical Association*, 286, 2568–2577.
- HOLZEMER, W.L., CORLESS, I.B., NOKES, K.M., TURNER, J.G., BROWN, M.A., POWELL-COPE, G.M., INOUE, J., HENRY, S.B., NICHOLAS, P.K. & PORTILLO, C.J. (1999). Predictors of self-reported adherence in persons living with HIV disease. *AIDS Patient Care and STDS*, 13, 185–197.
- HURST, N.P., RUTA, D.A. & KIND, P. (1998). Comparison of the MOS short form-12 (SF12) health status questionnaire with the SF36 in patients with rheumatoid arthritis. *British Journal of Rheumatology*, 37, 862–869.
- JENKINSON, C., WRIGHT, L. & COULTER, A. (1994). Criterion validity and reliability of the SF-36 in a population sample. *Quality of Life Research*, 3, 7–12.
- KNOBEL, H., GUELAR, A., CARMONA, A., ESPONA, M., GONZALEZ, A., LOPEZ-COLOMES, J.L., SABALLS, P., GIMENO, J.L. & DIEZ, A. (2001). Virologic outcome and predictors of virologic failure of highly active antiretroviral therapy containing protease inhibitors. *AIDS Patient Care STDS*, 15, 193–199.
- KODRALIU, G., MOSCONI, P., GROTH, N., CARMOSINO, G., PERILLI, A., GIANICOLO, E.A., ROSSI, C. & APOLONE, G. (2001). Subjective health status assessment: evaluation of the Italian version of the SF-12 health survey. Results from the MiOS project. *Journal of Epidemiology and Biostatistics*, 6, 305–316.
- LIU, H., GOLIN, C.E., MILLER, L.G., HAYS, R.D., BECK, C.K., SANANAJI, S., CHRISTIAN, J., MALDONADO, T., DURAN, D., KAPLAN, A.H. & WENGER, N.S. (2001). A comparison study of multiple measures of adherence to HIV protease inhibitors. *Annals of Internal Medicine*, 134, 968–977.
- LORENZ, K.A., SHAPIRO, M.F., ASCH, S.M., BOZZETTE, S.A. & HAYS, R.D. (2001). Associations of symptoms and health-related quality of life: findings from a national study of persons with HIV infection. *Annals of Internal Medicine*, 134, 854–860.
- MACARTHUR, R.D., CHEN, L., MAYERS, D.L., BESCH, C.L., NOVAK, R., BERG-WOLF, M., VAN DEN, YURIK, T., PENG, G., SCHMETTER, B., BRIZZ, B. & ABRAMS, D. (2001). The rationale and design of the CPCRA (Terry Bein Community Programs for Clinical Research on AIDS) 058 FIRST (Flexible Initial Retrovirus Suppressive Therapies) trial. *Controlled Clinical Trials*, 22, 176–190.
- MANNHEIMER, S., FRIEDLAND, G., MATTS, J., CHILD, C. & CHESNEY, M. (2002). The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clinical Infectious Diseases*, 34, 1115–1121.
- McHORNEY, C.A., WARE, J.E., JR & RACZEK, A.E. (1993). The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical Care*, 31, 247–263.
- McHORNEY, C.A., WARE, J.E., JR, LU, J.F. & SHERBOURNE, C.D. (1994). The MOS 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care*, 32, 40–66.
- MELLORS, J., VAIDA, F., BENNETT, K., HELLMANN, N.S., DEGRUTTOLA, V. & HAMMER, S., FOR THE ACTG 398 STUDY TEAM (2002). Efavirenz hypersusceptibility improves virologic response to multidrug salvage regimens in ACTG 398. Presented at Ninth Conference on Retroviruses and Opportunistic Infections, Seattle, WA, February 24–28, p. 69.
- MONTANER, J.S., REISS, P., COOPER, D., VELLA, S., HARRIS, M., CONWAY, B., WAINBERG, M.A., SMITH, D., ROBINSON, P., HALL, D., MYERS, M. & LANGE, J.M. (1998). A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS trial. Italy, the Netherlands, Canada and Australia study. *Journal of the American Medical Association*, 279, 930–937.
- MONTESORI, V., WOOD, E., BEER, S.L., YIP, B., O'SHAUGHNESSY, M., HOGG, R. & MONTANER, J. (2000). Virologic success rates drop off sharply with decreasing levels of adherence to antiretroviral therapy. Poster presented at the 13th International AIDS Conference, Durban, South Africa.
- NICHOLAS, P.K., CORLESS, I.B., DAVIS, S.M., DOLAN, S.E. & MCGIBBON, C.A. (2002). Symptom status and quality of life in HIV disease. Poster presented at the 14th International AIDS Conference, Barcelona, Spain, July 7–12.
- NIEUWKERK, P.T., REIJERS, M.H., WEIGEL, H.M., LANGE, J.M. & SPRANGERS, M.A. (2000a). Quality of life in maintenance vs. prolonged induction therapy for HIV. *Journal of the American Medical Association*, 284, 178–179.
- NIEUWKERK, P.T., GISOLF, E.H., COLEBUNDERS, R., WU, A.W., DANNER, S.A. & SPRANGERS, M.A. (2000b). Quality of life in asymptomatic and symptomatic HIV infected patients in a trial of ritonavir/saquinavir therapy. The Prometheus Study Group. *AIDS*, 14, 181–187.

- NIEUWKERK, P.T., GISOLF, E.H., REIJERS, M.H., LANGE, J.M., DANNER, S.A. & SPRANGERS, M.A. (2001). Long-term quality of life outcomes in three antiretroviral treatment strategies for HIV-1 infection. *AIDS*, *15*, 1985–1991.
- NIEUWKERK, P.T., HILLEBRAND, M.E., VRIESENDORP, R., FRISSEN, P.H.J., DE WOLF, F., LANGE, J.M.A. & SPRANGERS, M.A.G. (2002). Effect on patients' quality of life (QoL) of starting HAART at different CD4 cell counts. Poster presented at the 14th International AIDS Conference, Barcelona, Spain, July 7–12.
- ORLANDO, G., GUARALDI, G., MURRI, R., WU, A., NARDINI, G., BEGHETTO, B., STERRANTINO, G.K., SBARAGLI, S., BORDERI, M., TALO, S., GROSSO, C., ERBA, C., CATTELAN, A.M., ANTINORI, A. & ESPOSITO, R. (2002). Does lipodystrophy affect quality of life? Poster presented at the 14th International AIDS Conference, Barcelona, Spain, July 7–12.
- PATERSON, D.L., SWINDELLS, S., MOHR, J., BRESTER, M., VERGIS, E.N., SQUIER, C., WAGENER, M.M. & SINGH, N. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine*, *133*, 21–30.
- RABOUD, J.M., HARRIS, M., RAE, S. & MONTANER, J.S. (2002). Impact of adherence on duration of virological suppression among patients receiving combination antiretroviral therapy. *HIV Medicine*, *3*, 118–124.
- REVICKI, D.A., MOYLE, G., STELLBRINK, H.J. & BARKER, C. (1999a). Quality of life outcomes of combination zalcitabine–zidovudine, saquinavir–zidovudine, and saquinavir–zalcitabine–zidovudine therapy for HIV-infected adults with CD4 cell counts between 50 and 350 per cubic millimeter. PISCES (SV14604) Study Group. *AIDS*, *13*, 851–858.
- REVICKI, D.A., SWARTZ, C., WU, A.W., HAUBRICH, R. & COLLIER, A.C. (1999b). Quality of life outcomes of saquinavir, zalcitabine and combination saquinavir plus zalcitabine therapy for adults with advanced HIV infection with CD4 counts between 50 and 300 cells/mm³. *Antiviral Therapy*, *4*, 35–44.
- SAMET, J.H., LIBMAN, H., STEGER, K.A., DHAWAN, R.K., CHEN, J., SHEVITZ, A.H., DEWEES-DUNK, R., LEVENSON, S., KUFE, D. & CRAVEN, D.E. (1992). Compliance with zidovudine therapy in patients infected with human immunodeficiency virus, type 1: a cross-sectional study in a municipal hospital clinic. *American Journal of Medicine*, *92*, 495–502.
- SINGH, N., SQUIER, C., SIVEK, C., WAGENER, M., NGUYEN, M.H. & YU, V.L. (1996). Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. *AIDS Care*, *8*, 261–269.
- SIPES, C.S., JONES, S.G., KAUSCHINGER, E., BROWN, B., JOHNSON, B., JOY, C., BUSCEMI, C., ROSSI, D., BERGER, B. & RELF, M. (2002). Tolerability of medication assessment (TOMA) instrument demonstrates correlation between severity of drug side effects, impact on activities of daily living (ADLs), and perceived quality of life (QOL). Poster presented at the 14th International AIDS Conference, Barcelona, Spain, July 7–12.
- SWINDELLS, S., MOHR, J., JUSTIS, J.C., BERMAN, S., SQUIER, C., WAGENER, M.M. & SINGH, N. (1999). Quality of life in patients with human immunodeficiency virus infection: impact of social support, coping style and hopelessness. *International Journal of STD and AIDS*, *10*, 383–391.
- VOGL, D., ROSENFELD, B., BREITBART, W., THALER, H., PASSIK, S., McDONALD, M. & PORTENOY, R.K. (1999). Symptom prevalence, characteristics, and distress in AIDS outpatients. *Journal of Pain Symptom Management*, *18*, 253–262.
- WARE, J., JR, KOSINSKI, M. & KELLER, S.D. (1996). A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Medical Care*, *34*, 220–233.
- WARE, J., KOSINSKI, M. & KELLER, S. (1998). *SF-12: how to score the SF-12 physical and mental health summary scales*. Rhode Island: QualityMetric Incorporated.
- WATERHOUSE, D.M., CALZONE, K.A., MELE, C. & BRENNER, D.E. (1993). Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. *Journal of Clinical Oncology*, *11*, 1189–1197.
- WU, A.W. (2000). Quality of life assessment comes of age in the era of highly active antiretroviral therapy. *AIDS*, *14*, 1449–1451.
- WU, A.W., RUBIN, H.R., MATHEWS, W.C., WARE, J.E., JR, BRYSK, L.T., HARDY, W.D., BOZZETTE, S.A., SPECTOR, S.A. & RICHMAN, D.D. (1991). A health status questionnaire using 30 items from the Medical Outcomes Study. Preliminary validation in persons with early HIV infection. *Medical Care*, *29*, 786–798.
- WU, A.W., HAYS, R.D., KELLY, S., MALITZ, F. & BOZZETTE, S.A. (1997). Applications of the Medical Outcomes Study health-related quality of life measures in HIV/AIDS. *Quality of Life Research*, *6*, 531–554.
- ZINKERNAGEL, C., LEDERGERBER, B., BATTEGAY, M., CONE, R.W., VERNAZZA, P., HIRSCHL, B. & OPRAVIL, M. (1999). Quality of life in asymptomatic patients with early HIV infection initiating antiretroviral therapy. Swiss HIV cohort study. *AIDS*, *13*, 1587–1589.