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The Measurement of Health-Related Quality of Life in Prospective Drug Therapy Studies in HIV-Infected Patients

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Abstract

The measurement of health-related quality of life (HRQOL) in patients infected with the HIV virus is becoming increasingly important in clinical trials of antiretroviral drugs, principally for two reasons: (1) the disease is becoming a chronic illness, in which the measurement of 'quality of survival' is gaining relevance as an outcome measure; and (2) the antiretroviral drugs used to treat the disease may have severe side effects which, in turn, affect the HRQOL of patients and threaten compliance with treatment.

A bibliographic review was conducted to locate currently existing HRQOL instruments developed specifically for HIV patients, with demonstrated sensitivity to change, and which may be used as a measure of clinical outcomes. The review also aimed to determine the frequency and adequacy of incorporation of HRQOL as an outcome variable in clinical trials and other prospective drug trials completed between 1990 and 1998 in this group of patients. Although 7 HIV-specific HRQOL instruments with demonstrated sensitivity to change were located (MOS-HIV, MQOL-HIV, HIV-PARSE, HOPES, EORTC-QLQ-HIV, FAHI and AIDS-HAQ), only 2.35% of publications were found to incorporate HRQOL as an outcomes variable. In addition, fewer than 40% of the instruments used to measure HRQOL in the publications reviewed were specific to HIV patients and had demonstrated sensitivity to change. This may be due to: (1) the lack, until relatively recently, of adequate instruments for measuring of HRQOL and changes in HRQOL in HIV patients; (2) the difficulty of measuring HRQOL in HIV patients and; (3) the low importance given to this aspect of the disease to date.

Key words

Quality of life. Questionnaire. Clinical trials.

Why is the measurement of HRQOL and its change in HIV patients important?

Health-related quality of life (HRQOL) is a concept which encompasses overall perception of health, physical functioning and aspects of emotional and social well-being. Its measurement requires the use of instruments that have been properly developed, validated and applied in order to take into account the concept's subjectivity, and the fact that it is subject to changes in patients' expectations, worries and needs throughout their lives.

The measurement of HRQOL in HIV patients is becoming increasingly important as patients want to know how the evolution of their illness, and its

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treatment, will affect their health state, and as health care institutions and health-care professionals become interested in the final results and consequences of medical treatment[1]. Thus, in clinical research in HIV/AIDS it is particularly important to guarantee the quality of the HRQOL instruments used. This implies determining that they are valid, i.e. that they measure what they are supposed to measure; that they are reliable, i.e. that scores remain stable when the conditions of measurement remain unchanged; and that they are sensitive to change, i.e. that they are capable of detecting change in HRQOL over time, whether it be due to the evolution of the illness or to treatment. The sensitivity to change of HIV/AIDS-specific instruments may help in detecting small differences in HRQOL associated with similar treatments[2]. Some of the benefits of including HRQOL instruments in longitudinal clinical studies (clinical trials, follow-up studies or cohort studies) of HIV/AIDS patients undergoing drug therapy are: (1) the evaluation of 'the quality of survival'; (2) comparisons between treatments which may be equally efficacious, but which may differ in the frequency and/or intensity of their side effects, with a concomitant impact on adherence to treatment; and (3) the study of the effectiveness of new antiretroviral treatments.

The objective of this paper was: (1) to review those instruments specifically designed to measure HRQOL in patients with HIV/AIDS and which have demonstrated sensitivity to change; and (2) to determine the frequency and adequacy of incorporation of HRQOL measurements in longitudinal drug studies with HIV patients carried out in the last 9 years.

Methods

Medline databases from 1990 to 1998 were reviewed using the descriptors 'quality of life', 'HIV' or 'AIDS', 'validation', 'sensitivity to change' or 'responsiveness' and 'longitudinal study' or 'clinical trial'. A hand search of articles found, and a manual search of abstracts from the 1996 and 1998 XI and XII International Conferences on AIDS, which included 'quality of life' or 'health measurement' in the title, were also performed. Publications which evaluated the sensitivity to change of HIV specific instruments, and papers on clinical trials or prospective drug studies in patients with HIV/AIDS, whether or not they included HRQOL as an outcome measure, were then selected. Instruments were classified into 5 categories: (1) HIV/AIDS-specific with demonstrated sensitivity to change; (2) HIV/AIDS-specific without demonstrated sensitivity to change; (3) generic HRQOL or instruments specific to other pathologies; (4) unnamed or '*ad hoc*' HRQOL instruments; and (5) measures of symptoms, functioning or psychological well-being.

Which disease-specific validated instruments currently exist to measure change in HRQOL in HIV/AIDS patients?

A number of HIV/AIDS-specific instruments have demonstrated sensitivity to change[3]. Seven instruments found in the bibliographical review are described below, as well as some of the studies in which they demonstrated sensitivity to change.

The Multidimensional Quality of Life Questionnaire for Persons with HIV/AIDS (MQOL-HIV)

The MQOL[4-7] questionnaire is a valid and reliable questionnaire consisting of 40 items with ordinal response categories and 10 HRQOL dimensions –mental and physical health, cognitive, physical, sexual, and social functioning, social support, economic status, partner intimacy, and medical care[4,5]. It provides a profile of HRQOL and a summary score by dimension. The questionnaire's sensitivity to change was evaluated in a 6-month observational study in a cohort of 92 HIV-infected patients[6]. The questionnaire was administered at baseline and again after 24 weeks. In both visits, CD4 count, haemoglobin level and symptom severity, using Whalen's HIV Symptom Scale, were recorded. Self-reported change in health status correlated significantly with changes on the MQOL-HIV index score (0.52) and with changes in MQOL-HIV dimensions (ranging from --0,20 for the cognitive functioning dimension to +0,44 with economic status), and with symptom severity (-0,44). No relationship was found between change in patients perceived HRQOL and CD4 count, though a slight but statistically insignificant correlation was found with changes in haemoglobin level (0.10). In a later 3-month study[7] of a cohort of 296 HIV positive patients beginning or switching highly active antiretroviral treatment (HAART), including indinavir, none of the dimensions showed a significant correlation with CD4 count or viral load, while all of them, except financial status, social support, partner intimacy and medical care correlated significantly with number of symptoms, with values between 0.31 and 0.42[7]. The effect size statistic, which measures the size of the effect or change, fluctuated between 0.16 to 0.27 for dimensions with statistically significant changes in pre-post treatment scores (social functioning, physical functioning, mental health, physical health, cognitive functioning and medical care). Scores on the dimensions of social support, financial status, partner intimacy and sexual functioning remained unchanged. The authors suggested that this may be due to the short duration of the study, as changes in these more social aspects may require more than 3 months to become apparent. Nevertheless, the study does show that dimensions which are more closely related to health status require a relatively short time to show changes[7].

The MOS-HIV Health Survey

The MOS-HIV[7-13] questionnaire was developed in 1987 from the Medical Outcomes Study Health Survey. The most recent version consists of 35 items covering 10 health dimensions -pain, physical function, mental health, general health perception, role functioning, social and cognitive functioning, energy/fatigue, worries about health, and quality of life- in addition to an item on changes in health. It produces a score for each dimension as well as summary scores for mental and physical health[11]. Numerous studies have demonstrated the reliability and validity of its indices[10,12,13].

One of the first studies to evaluate the sensitivity to change of the MOS-HIV was conducted in a cohort of 123 asymptomatic, symptomatic and AIDS patients observed over a period of 4 months[9]. Increases in the number of HIV-related symptoms was associated with statistically significant changes in the following dimensions: health perceptions, pain, physical, social and cognitive functioning, mental health and energy. In a study cited above[7], in a cohort of 296 HIV-infected patients beginning or switching to treatment with HAART, none of the dimensions showed a statistically significant correlation with CD4 count or viral load, although they all showed a statistically significant correlation with the number of symptoms (except for the dimension of health changes), with correlations ranging from weak (0.28) to moderate (0.49)[7]. Statistically significant effect sizes were obtained between visits, ranging from 0.18 to 0.36, for the dimensions of physical functioning, general perception of health, mental health, energy, worry over health and quality of life and the mental health summary score[7]. The pain and health transition dimensions and those more closely related with social aspects of HRQOL -role functioning and social function- were less sensitive and did not show statistically significant changes in score. Various clinical trials, such as that with ritonavir versus placebo in patients with CD4<100 cel/mL[13], have provided additional evidence of the instruments sensitivity to change.

The HIV Patient Reported Status and Experience Survey

The HIV-PARSE questionnaire[14-17], which was developed by adapting and modifying various MOS scales, is organised into 4 parts, the last of which consists of 35 items measuring health status and HRQOL, and which incorporates measurements of the perception of current health status, cognitive functioning/worry, physical, social and role functioning, pain, energy/fatigue, emotional well-being and quality of life[15]. A weighted index score is obtained and the instrument's reproducibility and construct validity have been evaluated[16]. The sensitivity to change of the HIV-PARSE was analysed in a clinical trial of zidovudine (200 mg/4 h) compared with zalzitabine (0.75 mg/8 h) as initial treatment, and which incorporated measurements of health status and other clinical variables every 3 months, over a period of 27 months in a group of 338 patients with HIV/AIDS[14,15]. In this study, differences over time on the individual scales and the global index correlated in a statistically significant manner with differences on other health measures included in the study, with mean correlations of 0.89 and 0.95, respectively.

HIV Overview of Problems-Evaluation System (HOPES)

The HOPES[18-20] is a multidimensional HRQOL instrument adapted from a cancer-specific HRQOL instrument, the Cancer Rehabilitation Evaluation System (CARES). The most recent version of the HOPES contains 142 items with ordinal response scales which are summarised in a global score and several partial scale scores -physical, psychological, sexual, partner, medical interaction and miscellaneous[20]. Statistically significant differences were found between scores on all of the HOPES dimensions, except that for partner, by CD4 count (above or below 200 cel/mL) and disease status[20]. In a 12 month observational study involving a cohort of 106 symptomatic HIV or AIDS patients[18], statistically significant lower scores were found on the physical scale at the end of the study, while scores on the psychological scale improved in the sixth month and remained stable until the end of the study. After 12 months of follow-up, differences appeared in the physical and sexual dimensions and in the HOPES global index between 19 patients with a stable or improving CD4 count and 46 patients whose CD4 count had decreased. While scores for the former patients remained stable or improved, patients with lower CD4 counts reported a statistically significant deterioration in the aforementioned dimensions[18]. Throughout the study, patients reported improvements in psychosocial functioning and an increase in physical problems, particularly those patients with a reduced CD4 count.

The European Organisation for Research and Treatment Cancer Core Quality of Life Questionnaire for HIV/AIDS patients (EORTC QLQ C-30-HIV)

The EORTC QLQ C-30-HIV[21] is a self-administered questionnaire which was originally developed to measure HRQOL in cancer patients. However, it was found to be applicable in symptomatic HIV patients and patients with AIDS and led to the development of a specific 20-item module for HIV to be administered together with the central module of the questionnaire[21]. The questionnaire is organised in 5 scales measuring functioning (physical, role, emotional, cognitive and social), 3 symptoms questions, and 6 additional items on breathlessness, problems sleeping, loss of appetite, diarrhoea, constipation, and economic status. It was shown to be valid and reliable in a 7-month follow-up study of 156 HIV patients recruited from two clinical trials of dideoxynosine or zidovudine in AIDS patients, and a follow-up study in which the patients took zidovudine as part of their habitual treatment[21]. The analysis showed a statistically significant deterioration in physical functioning and general quality of life and an increase in pain, breathlessness and constipation over the course of the study[21]. Emotional functioning was the only dimension to show a statistically significant improvement over the course of the study.

Functional Assessment of Human Immunodeficiency virus-FAHI

The FAHI[22-25] includes a cancer-specific HRQOL questionnaire, the Functional Assessment of Cancer Therapy: General (FACT-G) (27 items), and an HIV-specific subscale (17 items)[22]. The good psychometric properties of the FACT-G, its brevity and ease of administration, its focus on areas considered relevant to chronic illnesses, and good preliminary results as a measure of HRQOL in HIV patients[24,25], led to the development of an additional HIV-specific module. The questionnaire includes dimensions on physical, functional, social and cognitive well-being, emotional well-being living with HIV, and overall well-being. The sensitivity to change of the FAHI was evaluated in a 4-month observational study of 145 HIV/AIDS patients[22]. The FAHI global score discriminated between groups of patients with CD4 counts above and below 200 cel/mL[22]. Change in functional status, measured with the Karnofsky index, served as the criterion for evaluating the instrument's sensitivity to change. The dimensions of physical, functional and general well-being, as well as the global FAHI score were shown to be sensitive to improvement, deterioration or lack of change in functional status between measurements[23]. The emotional and functional well-being dimensions and the total FAHI score showed statistically significant changes in pre-post scores with anti-stress treatment conducted in a sample of 28 patients[22].

The AIDS Health Assessment Questionnaire (AIDS-HAQ)

The Health Assessment Questionnaire (HAQ)[26-29] was initially designed as a generic health instrument to measure HRQOL in patients with chronic illness and in the general population. Five scales were added to it (functional capacity related to the disease, treatment, drug toxicity, use of health services and quality of life items) in the context of the AIDS Time-Oriented Health Outcome Study (ATHOS)[26]. This study was intended to measure the health status of a sample of 482 HIV-infected patients who were asymptomatic, symptomatic or who had developed AIDS. The HRQOL items emphasised those aspects which had a greater impact on the HRQOL of these patients, and which were not reflected in the original questionnaire, including

Table 1. *Principal characteristics of the sensitivity to change studies.*

Instrument revised & references	Sample size and clinical status of patients	Follow-up (months)	Change criterion
MQOL – HIV[4-7]	92 asym patients	6	HIV-symptoms severity inventory and subjective perception of change
MOS – HIV[7-13]	123 asym, sym or AIDS patients	4	Clinical variables: CD4 count, symptoms and CDC disease stage
MQOL – HIV & MOS – HIV[7]	296 asym, sym or AIDS patients	3	Subjective health measures
HIV – PARSE[14-17]	338 AIDS patients	Not available	Health measures
HOPES[18-20]	106 sym or AIDS patients	12	CD4 count and changes in to the natural course of the disease
EORTC QLQ – C30 HIV[21]	94 clinical trial and 62 non-clinical trial sym and AIDS patients	12	Changes in the natural course of the disease
FAHI[22-25]	28 asym, sym and AIDS patients 145 AIDS patients	6 3/5	Total Mood Disturbance Score of the Brief Profile of Mood States Karnofsky Performance Status Classification
AIDS – HAQ[26-29]	482 asym, sym and AIDS patients	9	Changes in to the natural course of the disease

asym: asymptomatic patients; sym: symptomatic patients anxiety/depression, energy, social functioning, cognitive functioning, worry over health and specific HIV/AIDS symptoms. Data was obtained from these patients over the course of 9 months without treatment, and at the end of this period the scores for the AIDS patients had worsened for incapacity, general health, social function, cognitive functioning, energy/vitality and symptoms[28]. Symptomatic patients showed an overall deterioration in general health, disease symptoms, and incapacity. The score for the asymptomatic patients showed only changes related to disease symptoms[27-29]. The first dimensions to show statistically significant changes in score, in the various clinical states of the illness, were those related to physical health status (incapacity and symptoms dimensions). However, mental health did not show changes in score in any of the patient groups at the end of the 9-month period and social functioning showed changes only in the group of patients with AIDS.

Table 1 gives a brief description of the principal characteristics of some of the studies reviewed above. Although all of the instruments reviewed showed evidence of sensitivity to change, the inclusion of HRQOL measurements in prospective studies and clinical trials with HIV patients has been infrequent[30], as detailed below.

Quantity and quality of HRQOL measurement in longitudinal drug treatment studies with HIV patients

Table 2 shows the number of publications referring to prospective drug studies which have incorporated HRQOL as an outcome measure in patients with HIV/AIDS in the last 9 years. Of the 2715 publications found for the period 1990 to 1998, only 64[13,15,21,31-92] (2.35%) used at least one HRQOL instrument as an outcome measure after an intervention with drug therapy. The percentage of publications of this type fluctuated between 0.30% and 6.33% in 1995 and 1996, respectively, coinciding with the XI International Conference on AIDS in Vancouver, though there was an overall tendency towards increasing use of HRQOL instruments. 70% of all papers found were published between 1996 and 1998. Table 3 shows the number of times each type of instrument was used. HRQOL was measured using more than one instrument in 30 publications. Slightly over 35% of papers used HIV/AIDS-specific measures with proven sensitivity to change, whilst symptoms measures or health status measures focusing on functioning (i.e. Karnofsky Performance Status) or emotional well-being (i.e. Psychological Well-Being Index) accounted for almost 30% of publications. Over 20% either did not specify the HRQOL instrument used or used an instrument developed '*ad hoc*'.

Table 2. *Number (%) of publications referring to prospective drug studies which did and did not incorporate HRQOL measures in patients with HIV/AIDS, 1990-1998.*

Year	No. of publications without HRQOL *	No. (%) of publications with HRQOL #	Total
1990	167	3 (1.76)	170
1991	211	1 (0.47)	212
1992	248	3 (1.19)	251
1993	240	4 (1.63)	244
1994	313	6 (1.88)	319
1995	327	1 (0.30)	328
1996	340	23 (6.33)	363
1997	350	11 (3.04)	361
1998	455	12 (2.56)	467
Total	2651	64 (2.35)	2715

* according to Medline search; # according to Medline and hand search

Table 3. *Number (%) of times each type of instrument was used.*

Type of instrument	No. (%) of times
HIV/AIDS specific with demonstrated sensitivity to change	35 (37.23)
HIV/AIDS specific without demonstrated sensitivity to change	2 (2.13)
Generic and other disease-specific HRQOL	12 (12.76)
Unspecified or '*ad hoc*' HRQOL measures	19 (20.21)
Miscellaneous: Symptoms, functioning or psychological well-being	26 (27.66)
Total	94 (100)

What is the current position?

To date, over half a dozen HIV/AIDS-specific instruments have been shown to be sensitive to changes stemming from either the natural evolution of the illness or to antiretroviral treatment. In the questionnaires reviewed, the dimensions covering aspects of physical health (incapacity, functional well-being and physical health or symptoms) are the first to show deterioration or improvement in HRQOL. Dimensions of overall health and those for mental health, such as cognitive functioning, have also proven to be sensitive to change. There is evidence that emotional well-being tends to improve after the initial stages of the disease, perhaps due to an 'adaptation effect'[93]. On the other hand, the more social aspects of HRQOL, for example, social functioning, social support, or role functioning, are, in general, less sensitive to clinical change than the dimensions of physical and mental health, and the direction of change is less conclusive when it does occur. In general, it can be concluded that the impact of HIV infection and its treatment is adequately reflected by the longitudinal behaviour of dimensions in these questionnaires.

Given the side effects of antiretroviral treatment, which not only lead to poorer HRQOL in these patients, but also threaten treatment compliance[2], the number of studies incorporating HRQOL as an outcome measure in addition to the more traditional clinical and physiological measures is still very low. Furthermore, the HRQOL measures used in the few studies found do not always meet the necessary requirements for the measurement of a concept as complex as HRQOL. Some studies used measures which were insufficient, inadequate, or focused on limited aspects of HRQOL, whilst failing to reflect the global and multidimensional nature of the concept. These results are in line with the results of a recent study on the use of HRQOL measurement in clinical trials, in which the authors emphasised the infrequent inclusion of HRQOL as an outcome measure (between 0.63% and 4.2%, depending on the discipline, between 1980 and 1997) and the low quality of the measures included[30].

The apparently general reluctance to incorporate HRQOL as a clinical outcome measure in drug treatment studies, was compounded by several other issues. For example, until recently there were few specific HRQOL instruments for HIV/AIDS patients, and even fewer with adequate psychometric properties for the valid measurement of change in HRQOL due to psychosocial or drug interventions. Clinical research was oriented exclusively towards guaranteeing the survival of patients with HRQOL being considered of considerably lesser importance, if it was considered at all. The appearance of combination HAART therapy has meant greatly increased survival for AIDS patients, and a growing interest in their HRQOL.

This will presumably lead to an increased and better use of HRQOL measures developed in this context, in contrast to the variety of procedures and instruments used to date, such as the use of '*ad hoc*' HRQOL items. The use of such items demonstrates, firstly, that HRQOL measurement is often not considered to be a complex process requiring the use of adequately developed and validated measures which can ensure scientific rigor, and, secondly, that some of the measures used do not cover the full range of problems associated with HIV/AIDS infection, and have required '*ad hoc*' measures. Finally, to all this needs to be added the intrinsic difficulty of interpreting values which are meaningless on their own, and which correlate only weakly at best with clinical measures[94].

In conclusion, rigorous measurement of HRQOL in studies of drug treatment outcomes in HIV/AIDS has been infrequent to date, and in the majority of studies HRQOL measurement has been poor or non-existent. This might be partially explained by the earlier lack of available measures with adequately tested measurement properties, and the necessary focus on survival as the primary outcome parameter. However, the 'chronification' of the disease, the potency of new antiretroviral treatments, the availability of well-validated and responsive disease-specific instruments, and the increasing weight placed on HRQOL measurement by regulatory authorities[95] means that there are increasingly strong reasons for including HRQOL as a primary outcome indicator in the evaluation of drug therapies for HIV/AIDS patients, and for considerably improving the use of these instruments.

References

1. Wu A, Rubin H. Approaches to health status assessment in HIV disease overview of the conference. Psychol Health 1994; 9: 1-18.
2. Berzon R, Lenderking W. Evaluating the outcomes of HIV disease: Focus on health status measurement. In: Medical Outcomes Trust; Monitor 1998; 3: 1-20.
3. Badia X, Guerra L, García M, Podzamczer D. La evaluación de la calidad de vida en los pacientes con infección por el VIH y SIDA. Med Clin (Barc) 1999; 12: 739-44.
4. Avis N, Smith K. Development of the MQOL-HIV: The multidimensional quality of life questionnaire for persons with HIV-AIDS. Qual Life Newsl 1997; 17: 3-4.
5. Smith K, Avis N, Mayer K, Swislow L. Use of the MQOL-HIV with asymptomatic HIV-positive patients. Qual Life Res 1997; 6: 555-60.
6. Smith K, Avis N, Mayer K. Responsiveness of the MQOL-HIV to quality of life changes in a cohort of HIV+ men. XI International Conference on AIDS; Vancouver, 7-12 July 1996; 11 (1): 238. Abstract Tu.B.540.
7. Badia X, Podzamczer D, García M, López-Lavid C, Consiglio E and the Spanish MOS-HIV and MQOL-HIV Validation Group. A randomised study comparing instruments for measuring Health-Related Quality of Life in HIV-infected patients. AIDS 1999; 13: 1727-35.
8. Badia X, Podzamczer D, López-Lavid C, García M y Grupo Español de Validación de los cuestionarios MOS-HIV y MQoL-HIV. Medicina basada en la evidencia y la validación de cuestionarios de calidad de vida: La versión española del cuestionario MOS-HIV para la evaluación de la calidad de vida en pacientes infectados por el VIH. Enferm Infecc Microbiol Clín 1999; 17 (supl 2): 103-13.
9. Revicki D, Wu A, Murray M. Change in clinical status, health status, and health utility outcomes in HIV-Infected Patients. Med Care 1995; 33 (Suppl. 4): 173-82.
10. Wu A, Revicki D, Jacobson D, Malitz F. Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). Qual Life Res 1997; 6: 481-93.
11. Wu A, Rubin H, Mathews W, *et al.* A health status questionnaire using 30 items from the Medical Outcomes Study. Med Care 1991; 29: 786-98.
12. Revicki D, Sorensen S, Wu A. Reliability and validity of physical and mental health summary scores from the Medical Outcomes Study HIV Health Survey. Med Care 1998; 23: 126-37.
13. Nabulsi A, Revicki D, Conway D, *et al.* Quality of life consequences of adding ritonavir to current antiviral therapy for advanced HIV patients. XI International Conference on AIDS; Vancouver, 7-12 July 1996.
14. Berry S, Bozzette S, Hays R, Stewart A, Kanouse D. Measuring Patient Report Health Status and Experience in Advanced HIV Disease: The HIV-PARSE Survey Instrument. Santa Monica, California: RAND MR-342-NIAIS/SDAC, 1994.
15. Bozzette S, Kanouse D, Berry S, Duan N. Health status and function with zidovudine or zalcitabine as initial therapy for AIDS. JAMA 1995; 273: 295-301.
16. Bozzette S, Hays R, Berry S, Kanouse D. A Perceived Health Index for use in persons with advanced HIV disease: Derivation, reliability and validity. Med Care 1994; 32: 716-31.
17. Wu A, Hays R, Kelly S, Malitz F, Bozzette S. Applications of the Medical Outcomes Study health-related quality of life measures in HIV/AIDS. Qual Life Res 1997; 6: 531-54.
18. De Boer J, Sprangers M, Aaronson N, Lange J, Van Dam F. A study of the reliability, validity and responsiveness of the HIV overview of problems evaluation system (HOPES) in assessing the quality of life of patients with AIDS and symptomatic HIV Infection. Qual Life Res 1996; 5: 339-47.

19. Schag C, Ganz P, Kahn B, Petersen L. Assessing the needs and quality of life of patients infection: Development of the HIV overview of problems-evaluation system (HOPES). Qual Life Res 1992; 1: 397-413.
20. Ganz P, Coscarelli C, Kahn B, Petersen L, Hirji K. Describing the health-related quality of life impact of HIV infection: Findings from a study using the HIV Overview of Problems-Evaluation System (HOPES). Qual Life Res 1993; 2: 109-19.
21. De Boer J, Sprangers M, Aaronson N, Lange J, Van Dam F. The feasibility, reliability and validity of the EORTC QLQ-C30 in assessing the quality of life of patients with a symptomatic HIV infection or AIDS (CDC IV). Psychol Health 1994; 9: 65-77.
22. Cella D, McCain N, Peterman A, Mo F, Wolen D. Development and validation of the Functional Assessment of Human Immunodeficiency Virus Infection (FAHI) quality of life instrument. Qual Life Res 1996; 5: 450-61.
23. Peterman A, Cella D, Mo F, McCain N. Psychometric validation of the revised functional assessment of human immunodeficiency virus infection (FAHI) quality of life instrument. Qual Life Res 1997; 6: 572-84.

24 Cella D, McCain N. Validation of a quality of life instrument for people with human immunodeficiency virus infection. Proceedings of the 16th annual meeting of the society of behavioral medicine. Washington: 1995.

25. McCain N, Cella D. Correlates of stress in HIV disease. Western J Nur Res 1995; 17: 141-55.
26. Lubeck D, Fries J. Health status among persons infected with human immunodeficiency virus. A community-based study. Med Care 1993; 31: 269-76.
27. Lubeck D, Fries J. Assessment of quality of life in early stage HIV-infected persons: Data from the AIDS Time-Oriented Health Outcome Study (ATHOS). Qual Life Res 1997; 6: 494-506.
28. Lubeck D, Fries J. Changes in health status after one year for persons at-risk for and with HIV infection. Psychol Health 1994; 9: 79-92.
29. O'Dell M, Hubert H, Lubeck D, O'Driscoll P. Physical disability in a cohort of persons with AIDS: Data from the AIDS Time-Oriented Health Outcome Study. AIDS 1996; 10: 667-73.
30. Sanders C, Egger M, Donovan J, Tallon D, Frankel S. Reporting on quality of life in randomised controlled trials: Bibliographic study. BMJ 1998; 317: 1191-4.
31. Cohen C, Revicki D, Nabulsi A, Sarocco P, Jiang P and the Advanced HIV Disease Ritonavir Study Group. A randomized trial of the effect of ritonavir in maintaining quality of life in advanced HIV disease. AIDS 1998; 12: 1495-502.
32. De Boer J, Van Dam F, Sprangers M, Frissen P, Lange J. Longitudinal study on the quality of life of symptomatic HIV-infected patients in a trial of zidovudine versus sidovudine and interferon-α. AIDS 1993; 7: 947-53.
33. Revicki D, Brown R, Henry D, McNeill M, Rios A, Watson T. Recombinant human erythropoietin and health-related quality of life of AIDS patients with anemia. J Acqu Immune Defic Syndr 1994; 7: 474-84.
34. Wu A, Jacobson D, Clark B, Brookmeyer R, Feinberg J. Quality of life associated with valacyclovir vs. high and low-dose acyclovir for prophylaxis against cytomegaolvirus in AIDS. Abstracts of the 4th Conference on Retroviruses and Opportunistic Infections; 1997.
35. McGrath M, Damiano A, Wu A, Lynch J. Effects of nelfinavir mesylate on health-related quality of life: Results from two randomized, placebo-controlled trials. Abstracts of the 5th Conference of the International Society for Quality of Life Research. Qual Life Res 1998; 7: 637.
36. The Studies of Ocular Complications of AIDS Research Group. MSL-109 adjuvant therapy for cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome: The Monoclonal Antibody Cytomegalovirus Retinitis Trial. Arch Ophtalmol 1997; 115: 1528-36.
37. Waters D, Danska J, Hardy K, *et al.* Recombinant human growth hormone, insulin-like growth factor 1, and combination therapy in AIDS-associated wasting. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996; 125: 865-72.
38. Schambelan M, Mulligan K, Grunfeld C, *et al.* Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial. Serostim study group. Ann Intern Med 1996; 125: 873-82.
39. Scott-Lennox J, Mills R, Burt M. Impact of zidovudine plus lamivudine or zalcitabine on health-related quality of life. Ann Pharmacother 1998; 32: 525-30.
40. Weinfurt K, Willke R, Glick H, Freimuth W, Schulman K. The relationship between CD4 count, viral burden and quality of life over time in HIV-1 infected patients. 37th ICAAC; Toronto, 1997.
41. Chatterton M, Scott-Lennox J, Burt M, Collis P. Impact of the addition of lamivudine plus loviride on the quality of life of treatment-experienced HIV infected patients. 37th ICAAC; Toronto, 1997.
42. Nieuwkerk P, Gisolf E, Van Leeuwen R, Danner S, Sprangers M. Impact of ritonavir/saquinavir versus ritonavir/saquinavir/stavudine on patients' health-related quality of life: Preliminary results. XII World AIDS Conference; Geneve. 1998,
43. Coplan P, Pegion J, Cook J, *et al.* Impact of indinavir with zidovudine and lamivudine on the quality of life of HIV-positive patients with <= 50 CD4 count. XII World AIDS Conference; Geneve. 1998,
44. Wu A, Lichter S, Richardson W, *et al.* Quality of life in patients receiving clarithromycin for myobacterium avium complex infection and AIDS. VIII International Conference on AIDS; Amsterdam, 1992.
45. Wu A, Gray S, Brookmeyer R, Safrin S. Quality of life in a double-blind randomized trial of 3 oral regimens for mild-to-moderate *Pneumicystis carinii pneumonia* in AIDS (ACTG108). XI International Conference on AIDS; Vancouver, 1996.
46. Wu A, Rubin H, Bozzette S, *et al.* A longitudinal study of quality of life in asymptomatic HIV Infection. In: VII Internatinal Conference on AIDS; Florence, 1991.
47. Fischl M, Richman D, Hansen N, *et al.* The safety and efficacy of AZT in the treatment of subjects with mildly symptomatic human immunodeficiency virus type 1 (HIV) infection. A double-blind, placebo-controlled trial. Ann Intern Med 1990; 112: 727-37.
48. Chaisson R, Benson C, Dube M, *et al.* Clarithromycin for disseminated Mycobacterium avium-complex in AIDS patients. Ann Intern Med 1994; 121: 905-11.

49 Hooker M, Newberry A, Nunn A, *et al.* Changes in quality of life (QOL) indices by treatment group for Delta trial participants beginning HIV therapy. XI International Conference on AIDS; Vancouver, 1996.

50. Singer J, Thorne A, Raboud J, *et al.* The Canadian randomized open label trial of combination therapy for MAC bacteremia: Quality of life outcomes. XI International Conference on AIDS; Vancouver, 1996.
51. Cohen C, Duzube B, Day J, Andradas V, Gagnon S, Rieker P. The impact of pentoxifylline on quality of life. X International Conference on AIDS; Yohohama, 1994.
52. Silva M, Skolnik PR, Gorbach S, *et al.* The effect of protease inhibitors on weight and body composition in HIV-infected patients. AIDS 1998; 12: 1645-51.
53. Schulz R, Mullenix T, Googe H, Cooper L, Grant D. Quality of life and compliance with antiretrovirals. 5th Annual Conference of the International Society for Quality of Life Research. Qual Life Res 1998; 7: 659.
54. Wu A, Rubin H, Mathews W, *et al.* Functional status and well-being in a placebo-controlled trial of zidovudine in early symptomatic HIV infection. J Acqu Immune Defic Syndr 1993; 6: 652-458.
55. Wu A, Mathews W, Brysk L, *et al.* Quality of life in a placebo-controlled trial of zidovudine in patients with AIDS and AIDS-related complex. J Acqu Immune Defic Syndr 1990; 3: 683-90.
56. Remick S, McSharry J, Wolf B, *et al.* Novel oral combination chemotherapy in the treatment of intermediate-grade and high-grade AIDS-related non-hodgkin's lymphoma. J Clin Oncol 1993; 11: 1691-702.
57. Bhasin S, Storer T, Asbel-Sethi N, *et al.* Effects of testosterone replacement with a nongenital, transdermal system, androderm, in human immunodeficiency virus-infected men with low testosterone levels. J Clin Endocrinol Metab 1998; 83: 3155-62.
58. Miller K, Corcoran C, Armstrong C, *et al.* Transdermal testosterone administration in women with acquired immunodeficiency syndrome wasting: A pilot study. J Clin Endocrinol Metab 1998; 83: 2717-25.

59. Coodley G, Coodley M. A trial of testosterone therapy for HIV-associated weight loss. AIDS 1997; 11: 1347-52.
60. Gold J, High H, Li Y, *et al*. Safety and efficacy of nandrolone decanoate for treatment of wasting in patients with HIV infection. AIDS 1996; 10: 745-52.
61. Gange S, Jacobson LP, Kass N, *et al*. Quality of life among HIV seropositive men on monotherapy and combination antiretroviral therapy. XI International Conference on AIDS; Vancouver, 1996.
62. Ferri R, Witt R. Immune-Boostin Drug Improves quality of life. Clinic Rev 1996; 6: 127.
63. Grinspoon S, Corcoran C, Askari H, *et al*. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998; 129: 18-26.
64. Mayanja-Kizza H, Oishi K, Mitarai S, *et al*. Combination therapy with fluconazole and flucytosine for cryptococcal meningitis in Ugandan patients with AIDS. Clin Infect Dis 1998; 26: 1362-6.
65. Leiberick P, Engeter M, Olbrich E, *et al*. Longitudinal development of distress, coping and quality of life in HIV-positive patients. Psychother Psychosom 1997; 66: 237-47.
66. Colon J, Encarnación G, Ortiz M, Rodríguez M, Santiago E, Marchand A. Survival and quality of life in HIV-positive patients treated with a polyantigenic immunomodulator. P R Health Sci 1997; 16: 9-14.
67. Timpone J, Wright D, Li N, *et al*. The safety and pharmakinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 Study Group. AIDS Res Hum Retroviruses 1997; 13: 305-15.
68. Kaplan R, Conant M, Cundiff D, *et al*. Sustained-release morphine sulfate in the management of pain associated with acquired immune deficiency syndrome. J Pain Symptom Manage 1996; 12: 150-60.
69. Burack J, Cohen M, Hahn J, Abrams D. Pilot randomized controlled trial of Chinese herbal treatment for HIV-associated symptoms. J Acquir Immune Defic Syndr Hum Retrovirol 1996; 12: 386-93.
70. Hengge U, Bauman M, Maleba R, Brockmeyer N, Goos M. Oxymetholone promotes weight gain in patients with advanced human immunodeficiency virus (HIV-1) infection. Br J Nutr 1996; 75: 129-38.
71. Jabs D. Design of clinical trials for drug combinations: Cytomegalovirus retinitis-foscarnet and ganciclovir. The CMV retinitis retreatment trial. Antiviral Res 1996; 29: 69-71.
72. Presant C, Scolaro M, Kennedy P, *et al*. Liposomal daunorubicin treatment of HIV-associated Kaposi's sarcoma. Lancet 1993; 341: 1242-3.
73. Henry D, Beall G, Benson C, *et al*. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. Ann Intern Med 1992; 117: 739-48.
74. [Authors not listed] Double blind dose-response study of zidovudine in AIDS and advanced HIV infection. Nordic Medical Research Councils'HIV therapy group. BMJ 1992; 304: 13-7.
75. Rabeneck L, Palmer A, Knowles J, *et al*. A randomized controlled trial evaluating nutrition counseling with or without oral supplementation in malnourished HIV-infected patients. J Am Diet Assoc 1998; 98: 434-8.
76. Jacobson J, Greenspan J, Spritzler J, *et al*. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. N Engl J Med 1997; 336: 1487-93.
77. Singh N, Squier C, Sivek C, Wagener M, Hong M, Yu V. Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: Prospective assessment with implications for enhancing compliance. AIDS Care 1996; 8: 261-9.
78. Wilson I, Cleary P. Clinical predictors of declines in physical functioning in persons with AIDS: Results of a longitudinal study. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 16: 343-9.
79. Singh N, Squier C, Sivek C, Nguyen M, Wagener M, Yu V. Determinants of nontraditional therapy use in patients with HIV infection. A prospective study. Arch Intern Med 1996; 156: 197-201.
80. Olliaro P, Dautzenberg B. Control of the body burden of M. Avium complex is associated with improved quality of life and prolonged survival of patients with AIDS: A prospective trial with rifabutin combined with isoniazid, clofazimine, ethambutol. J Chemother 1994; 6: 189-96.
81. Rabkin J, Wagner G, Rabkin R. Effects of sertraline on mood and immune status in patients with major depression and HIV illness: An open trial. J Clin Psychiatry 1994; 55: 433-9.
82. The SOCA Research Group. Combination foscarnet and ganciclovir therapy vs. monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. Arch Ophthalmol 1996; 114: 23-33.
83. Feinberg J, Cooper D, Hurwitz S. For the ACTG 204/Glaxo. Phase III international study of valciclovir (vacv) for cytomegalovirus (cmv) prophylaxis in patients with advanced HIV disease. XI International Conference on AIDS. Vancouver, 1996.
84. Scott-Lennox J, McLaughlin Miley C, Mauskopf J. Impact of lamivudine and zidovudine therapy on quality of life (QOL). XI International Conference on AIDS. Vancouver, 1996.
85. Revicki D, Swartz C. Quality of life outcome of saquinavir, zalcitabine, and combination saquinavir-zalcitabine therapy for advanced HIV-infection. Abstracts 4th Conf Retroviruses Opportun Infect Washington 1997.
86. Safrin S, Finkelstein D, Feinberg J, *et al*. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii pneumonia* in patients with AIDS. Ann Intern Med 1996; 124: 792-802.
87. Nabulsi A, Revicki D, Conway D, Maurath C, Mills R, Leonard J. Quality of life consequences of adding ritonavir to current antiviral therapy for advanced HIV patients. XI International Conference on AIDS. Vancouver, 1996.
88. Volderbing P, Lagakos S, Koch M, *et al*. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med 1990; 322: 941-9.
89. Hooker M, Newberry A, Nunn A, *et al*. Changes in quality of life (QOL) indices by treatment group for delta trial participants beginning HIV therapy. XI International Conference on AIDS. Vancouver, 1996.
90. Benson C, Cohn D, Williams P and the ACTG196/CPCRA 009 Study Team. A phase III prospective, randomized, double-blind study of the safety and efficacy of clarithromycin (CLA) vs. rifabutin (RBT) vs. CLA + RBY for the prevention of *Mycobacterium avium* complex (MAC) disease in HIV + patients with CD4 counts ≤ 100 cells/μL. Proceedings of the Third Conference on retroviruses and Opportunistic Infections. Washington, 1996.
91. Virgin G, Wolf E, Zander K, *et al*. Efficacy of peptide T in the palliative treatment of neurological HIV-related symptoms. XI International Conference on AIDS. Vancouver, 1996.
92. Cohen C, Duzube B, Day J, Andradas V, Gagnon S, Rieker P. The impact of pentoxifylline on quality of life. 10th International Conference on AIDS. Yokohama, 1994.
93. Wu A, Witt W. The impact of HIV infection on health-related quality of life. In: Badia X, Podzamczer D. Calidad de vida asociada a la salud e infección por el VIH. Barcelona, 1999 (In press).
94. García M, López-Lavid C. Utilidad clínica e interpretación de las puntuaciones obtenidas con instrumentos de medida de la CVRS. In: Badia X, Podzamczer D. Calidad de vida asociada a la salud e infección por el VIH. Barcelona, 1999 (In press).
95. Beitz J, Gnecco C, Justice R. Quality-of-life end points in cancer clinical trials: the U.S. Food and Drug Administration perspective. J Natl Cancer Inst Monogr 1996; 20: 7-9.