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ISSQoL: A new questionnaire for evaluating the quality of life of people living with HIV in the HAART era*

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Abstract

Objective: To design a Health-related Quality of Life (HRQoL) instrument for HIV-infected people in the era of highly active antiretroviral therapy (HAART). *Methods*: The self-administered questionnaire was developed by an Italian network including researchers, physicians, people living with HIV, national institutions and community-based organizations (CBO) through several steps: (1) review of existing HRQoL literature and questionnaires for HIV-infected people; (2) selection of relevant domains measuring HRQoL in HIV-infected people, and identification of new domains related to new aspects of HRQoL concerning HAART-treated individuals; (3) conduction of two pre-test analyses in independent groups of Italian HIV-positive people ($n \cong 100$) distributed throughout the country. The objectives of the first pre-test were to verify the usefulness of the questionnaire, to construct a form easily understandable by everyone, to define the domains and their significance; the second pre-test aimed at evaluating and reshaping the questionnaire based on a statistical analysis of the outcomes of first pre-test; (4) validation analysis. A large cohort of people with HIV infection was recruited for the last step. *Results*: The internal consistence reliability (Cronbach's α) was ≥ 0.70 for all domains. Most domains had Cronbach's coefficient > 0.80. All domains demonstrated convergent and discriminant validity. The final version of ISSQoL includes two sections: HRQoL Core Evaluation Form (9 domains) and Additional Important Areas for HRQoL (6 domains). The ISSQoL was administered together with two additional forms: a Daily Impact of Symptoms Form and a Demographic Information Form. The Additional Important Areas for HRQoL include social support, interaction with medical staff, treatment impact, body changes, life planning, and motherhood/fatherhood. *Conclusion*: The data reported in the present paper provide preliminary evidence of the reliability and validity of the ISSQoL questionnaire for the measurement of HRQoL in HIV-infected people. The direct involvement of HIV-positive people in all the phases of the project was a key aspect of our work.

Key words: HAART, HIV, MOS-HIV Health Survey, Quality of life, Questionnaire

*All the authors of this paper belong to ISSQoL Group.

Introduction

The introduction of highly active antiretroviral therapy (HAART) dramatically reduced both morbidity and mortality related to HIV infection [1]. As a consequence, life and needs of HIV-infected people taking HAART have profoundly changed. HAART transformed HIV infection from a terminal disease to a chronic one. In general, compared to the pre-HAART era, health status of HIV-infected people has significantly improved. Severe impairments of daily activities occur less commonly. Increasing attention is given to sexual life and sexual dysfunctions. More often than in the pre-HAART era, HIV-infected patients can study or work or have normal daily life activities. Social life is more intense. Life planning has become crucial. Motherhood/fatherhood desire has become stronger and, due to the significantly reduced risk of mother-to-child transmission of HIV by HAART-treated women, the number of pregnancies in HIV-infected people has increased. On the other hand, HIV-infected people often experience drug-related adverse events, changes in body image, and long-term toxicities. Taking antiretroviral drugs is a complex task, requiring a near-perfect level of adherence to prescriptions, and is likely to be lifelong [2]. Relationships with providers have become more frequent, as well as awareness on drugs and natural history of the disease. People require more detailed information. The impact that these aspects have on clinical variables such adherence to drugs drew the attention on the interaction between patient and medical staff.

Several questionnaires for HIV-infected people were designed and validated in the pre-HAART era [3–7]. People were then often seriously ill or disabled. Due to the changes occurred, previous validated instruments appear currently inadequate: increased life expectancy requires consideration of a wider range of aspects of health status. In the pre-HAART HRQoL instruments, questions on some important aspects are missing (for example sexual life, symptoms and body changes were not included in the MOS-HIV Health Survey) or outdated in evaluating other HRQoL domains (i.e. the Physical Functioning, Role Functioning and Pain domains of the MOS-HIV Health Survey focused on people seriously limited by the disease) or redundant in other aspects (i.e. physical environment or transportation domains in WHO-QOL-HIV). Since all the existing questionnaires were built before the advent of HAART, it seemed important to update items and areas of instruments according to the patients' new needs and lifestyle. Since survival has significantly improved, taking into account the HRQoL of HIV-infected persons has become a priority. International Guidelines on the use of HAART specify improvement of the quality of life of patients under treatment as one of the four main objectives [8].

The aim of our study was to build a new instrument for measuring HRQoL in HIV-infected persons consistent with the new needs and changes introduced by the use of HAART. In the present paper, we present and discuss the psychometric properties of the Istituto Superiore di Sanità-Quality of Life (ISSQoL) Survey.

Methods

Questionnaire development

A working team including researchers, physicians, persons living with HIV, national institutions and community-based organizations (CBOs), designed a study aiming to develop a self-reporting questionnaire for assessing the quality of life of HIV patients, the ISSQoL. The development process of ISSQoL went through the following steps.

Review of existing literature and content validity
The first step in the development of our instrument was to attain the so-called content validity, that is the extent to which a measurement reflects the specific intended domain of content [9]. The working team identified which of the HRQoL content domains had to be included in the new questionnaire. To this purpose, the HRQoL domains and items published in well established questionnaires (i.e., MOS-HIV, WHOQOL-HIV, MOL, FAHI, HOPES) [3, 5–7, 10, 11] were reviewed, and group discussions with HIV-infected opinion leaders were conducted.

As a result of regular meetings over a 1-year period, the working team agreed that some domains (*satisfaction with quality of life*, *physical*

well-being, *role well-being*, *social functioning*, *depression and anxiety*, *energy/vitality*, *health distress*, *cognitive functioning*, *sexual life*, and *symptoms*) should be kept in the new instrument because of their centrality in the measurement of the HRQoL of HIV-infected people in the era of HAART. Hereafter, we refer to these areas as the instrument's 'core domains'. Three domains (*medical staff interaction*, *treatment impact*, and *life planning*) were also considered as important health-related factors potentially affecting HRQoL in the HAART era. Hereafter, we refer to these new areas as 'Additional Important Areas for QoL'. As results of this step a list of 69 items and a list of 33 symptoms were obtained.

Pre-test analysis and face validity

The study protocol, for the pre-test and validation studies, was submitted to the Ethical Committees of the Clinical Centers as appropriate. Two pre-tests were conducted on independent groups of approximately 100 HIV-infected people from different parts of Italy. Participants were recruited in clinical centers or CBOs and were selected according to predefined entry criteria (age, gender, HIV transmission mode, time from diagnosis, education, and clinical status). Participants gave an informed consent. To be eligible for pre-test and validation studies, people had to be 18 years or older, taking HAART and able to complete a self-reporting questionnaire.

First pre-test. A group of 118 HIV+ people was recruited for the first pre-test. The preliminary list of items and an additional questionnaire asking for participants' feedback upon completion of the items were administered. The feedback questionnaire was added to evaluate the participants' perception of (a) item comprehension and linguistic appropriateness, (b) item consistency with the assessment of HRQoL of HIV-infected people (i.e., face validity), (c) item usefulness in evaluating quality of life.

A qualitative analysis of feedback questionnaires was done: the comprehension of the items was quite good (87% of the patients reported no problems in reading the items; 68% of the patients found all the items well understandable); the aff-ective reaction to the questionnaire was fair (62% of patients did not detect any particularly disturbing item); a quarter of respondents find the questionnaire too long, 18% found unnecessary items and 44% found that items did not investigate some important aspects of quality of life in the HAART era. Based on these results as well as on the qualitative analyses of missing values we modified the preliminary item list. We dropped out useless items (e.g., sport-related items such as 'Did you play sport?'), emotionally disturbing items (e.g., sexual-related items, such as 'Have you been successful in having sexual intercourses as you desired?'), readapted unclear items, and generated new items according to the comments from HIV-infected people. Since most of the newly suggested items referred the motherhood/fatherhood desire, we decided to modify the domains structure defined in Section 1.1 by adding up a new domain called *motherhood/fatherhood*. Thus, a first draft of the questionnaire with 14 domains and 71 items was obtained.

Second pre-test. The first draft of the questionnaire was tested on a second pre-test after 6 month. A new group of 116 HIV+ people was then recruited. Exploratory item-total correlation and internal consistency analyses were carried out to evaluate the item performance and to readapt the items on the basis of psychometric results (reliability and validity). Based on these analyses new items were generated and added to the already existing ones and other items were dropped. The main contribution of the second pre-test consisted in the expansion of the first draft domains. In particular, the psychometric analyses revealed that the social functioning domain included two items which were uncorrelated to the domain total score, thus bringing the domain internal consistency coefficient below the psychometric standard. A careful reading of these items revealed that both of them were elements of social support seeking. To keep this area in the questionnaire, since these items had been suggested as important by the HIV-infected people in the first pre-test, we decided to set up a new additional domain called *social support*.

The second pre-test resulted in a second draft of the questionnaire grouped in 15 domains. This was the final version of the instrument used for the validation analysis.

Questionnaire validation

For the questionnaire validation additional 332 HIV-infected persons from clinics and CBOs, equally distributed over 15 out of 21 regions of Italy were enrolled.

The sample size was defined on the basis of a common practice in psychometric studies, that is to enroll approximately five cases for each variable in the analysis. In the present validation study the case-to-variable ratio was approximately 4.7.

ISS-QoL final structure

The ISSQoL is a self-administered questionnaire and includes two sections: HRQoL Core Evaluation Form and Additional Important Areas for HRQoL. The ISSQoL was administered together with two additional forms: a Daily Impact of Symptoms Form and a Demographic Information Form. The HRQoL Core Evaluation Form (Table 2) includes 37 items grouped in 9 Core domains: *satisfaction with quality of life* (SQL), *physical well-being* (PW), *role well-being* (RW), *depression and anxiety* (DA), *energy and vitality* (EV), *health distress* (HD), *cognitive functioning* (CF), *social functioning* (SF), *sexual life* (SL). The Additional Important Areas for HRQoL includes 25 items grouped in 6 domains: *social support* (SS), *interaction with medical staff* (MS), *treatment impact* (TR), *body changes* (BC), *life planning* (LP), *motherhood/fatherhood* (MF). Social support refers to the degree of support that a person receives from family or friends. *Interaction* with *medical staff* refers to satisfaction with relationship with providers and with obtained information. *Treatment impact* refers to concerns about the effectiveness of therapy, its length and the related adverse events. *Body changes* refers to concerns about the current body image and eventual psychosocial consequences of the change. *Life planning* refers to attitude to plan the future. *Motherhood/fatherhood* refers to the desire of having a child and the influence that the HIV infection and its treatments have on this decision. A question dealing with the desire to have a child and the possible reasons for not desiring precedes the Motherhood/fatherhood section. Participants for which the question is not applicable were excluded from the analysis of this section.

The Daily Impact of Symptoms Evaluation Form includes a list of 32 most common HIV-related symptoms (Table 3). The Personal Information Form investigates demographic and personal data.

The items recall a period focused on the past four weeks before the administration. The ISSQoL uses five-point Likert scales. In particular, there are frequency scales (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always) and intensity scales (1 = not at all, 2 = little, 3 = somewhat, 4 = much, 5 = very much). The frequency scales are used for the PW, RW, SF, DA, EV, HD, and CF domains while the intensity scales are used for the SQL, SS, SL, MS, TR, BC, LP, MF domains and for the Daily Impact of Symptoms. The ISSQoL domains are scored as summated rating domains and transformed on a 0–100 scale, with 0 indicating the poorest health and 100 indicating the better health.

Statistical analysis

Validation analyses

Psychometric assumptions of reliability and validity were examined according to standard procedures [12] as well as by the analysis of multitrait/multi-item matrices [13].

Reliability

Reliability is defined as the degree to which repeated administrations of a questionnaire produce equivalent results under controlled conditions. An estimate of reliability can be indirectly obtained by looking at the consistency of the observed scores through these repeated administrations. In the present study, the ISSQoL questionnaire was given to research participants on a single occasion and for this reason the Cronbach's α coefficient was used as an estimate of the test reliability, instead of the Test–Retest correlation coefficient. No absolute standard for reliability coefficients exists. However the range 0.70–0.90 is considered as the minimum acceptable values of reliability for group comparison and for making individual decisions, respectively.

Validity

A measurement instrument is said to be valid if it actually measures what it is supposed to measure. There are several different types of validity that are

of interest to the researcher: face validity, content validity, criterion/concurrent validity, and construct validity [14–15].

In earlier stages of questionnaire development as well as in pre-test analyses, we mainly focused on content and face validity (see Sections 1.1 and 1.2). In the present validation study, we focused instead on the evaluation of questionnaire criterion and construct validity.

As to *criterion validity*, we assessed to what extent ISSQoL scores are correlated with external and independent measures of HRQoL. In particular, we examined whether different HIV status groups differ statistically in HRQoL scores. In our study, the CDC classification was self-reported.

An analysis of variance with each of the ISSQoL domains as dependent variables, and with HIV status (Asymptomatic or CDC group A according to the CDC Classification [16], Symptomatic or CDC group B, or AIDS or CDC group C) as an independent factor was carried out to provide evidence for the criterion validity of ISSQoL domains. It was expected that asymptomatic patients would report a better HRQoL (i.e., would have higher ISSQoL domain scores) than patients at a more advanced stage of the disease.

A special case of criterion validity is that of *concurrent validity*, that is, the extent to which ISSQoL scores are related to other self-reported assessments. Thus, we also examined the correlation between ISSQoL scores and the number of self-reported symptoms as collected by the Daily Impact of Symptoms Evaluation Form.

Construct validity – perhaps the most important form of validity – refers to the extent to which the relations between questionnaire scores reflect the expected relations between the concepts that these scores are supposed to measure. Construct validity can be broken down into two sub-types: convergent validity (i.e., the agreement among measures which theoretically should be related) and discriminant validity (i.e., the lack of a relationship among measures which theoretically should not be related).

Thus, we expected the ISSQoL items converging at the appropriate domain score (convergent validity) and diverging from other domain scores (discriminant validity). In our analysis, composite domain scores were computed and a Multi-trait scaling analysis [13] was performed to evaluate the convergence of items within a domain and item discrimination across domains. Item convergence is supported if an item correlates at a coefficient of 0.40 or more with the score of the domain it is supposed to belong to. The proportion of times that the convergence criterion is attained by all items within a domain provided us with an overall index of that domain's convergent validity. Conversely, the item discrimination is supported if the correlation between each item and its domain (i.e. the domain each item belongs to) is higher (i.e. $\Delta \geq 2$ standard error) then the correlation between each item and other domains of the questionnaire. Proportion of times that items of each domain achieved the discrimination criterion is used as an overall index of that scale's discriminant validity.

Interscale correlation

Different domains measure different aspects, but they all aim to evaluate the HRQoL. Therefore, they should correlate with one another, even though they represent individually distinct areas. As a standard rule, the interscale correlations should be within the range of correlation (0.40–0.80).

Missing data

Patients with missing data were not excluded from the sample to prevent from biasing statistical analyses. However, all analyses were carried out based on all the available patient information. In particular, individual domain scores were determined for each person if all items in given domain had been answered; in the case of missing items, no imputation was done, as the present study had only the purpose of validating the ISSQoL.

Results – validation analysis

Description of the sample

Table 1 shows the sample's demographic and clinical characteristics.

Three percent of the sample did not report any information. Only 19% of respondents reported living alone, while 25% were living with other HIV-infected persons. About half of the sample (44%) regularly attended meetings of associations engaged in the fight against AIDS.

Table 1. Sample characteristics

Sex: n (%)	
Female	118 (35.5)
Male	202 (60.8)
Missing information	12 (3.6)
Age (years)	
Mean ± SD (n, range)	40.0 ± 7.3 (312, 18–68)
Transmission route: n (%)	
Men having sex with men	68 (20.5)
Intravenous drug users	138 (41.6)
Heterosexual	117 (35.2)
Blood transfusion	4 (1.2)
Other/unknown	3 (0.9)
Missing information	2 (0.6)
Clinical status*: n (%)	
Asymptomatic (CDC A)	102 (30.7)
Symptomatic (CDC B)	143 (43.1)
AIDS (CDC C)	79 (23.8)
Missing information	8 (2.4)
Time from HIV diagnosis (years)	
Mean ± SD (n, range)	10.4 ± 5.4 (328, 0.5–24)
Education: n (%)	
No education	2 (0.6)
Primary school	22 (6.6)
Secondary School	158 (47.6)
High school	110 (33.1)
University	29 (8.7)
Missing information	11 (3.3)
Living: n (%)	
Alone	64 (19.3)
In family	103 (31.0)
With partner	108 (32.5)
With friends	12 (3.6)
Other	30 (9.0)
Missing information	15 (4.5)
Living with other HIV-infected people: n (%)	
Yes	84 (25.3)
No	217 (65.4)
Missing information	31 (9.3)
Attending associations fighting AIDS: n (%)	
Yes	147 (44.3)
No	180 (54.2)
Missing information	5 (1.5)

*CDC group A: not advanced stage of HIV disease; CDC group B: moderate advanced stage of HIV disease; CDC group C: advanced stage of HIV disease.

About 50% of subjects filled in all data while 51% reported missing values. Among these 93% omitted less then 10 items of the questionnaire.

Floor and ceiling effect are shown in Table 2. For people classified in CDC Group A, 3 domains had a consistent ceiling effect: PW (28%), RW (38%) and MF (21%). For people classified in CDC Group B, only the RW domain had a high ceiling effect (20% of patients). The AIDS group showed both floor and ceiling effects at RW (13% and 14%, respectively) and MF (17% and 12%, respectively), a ceiling effect at the SF domain (14%) and a floor effect at the TR (14%) and the LP domain (10%).

Daily impact of symptoms

The median value of intensity scale for each symptom stratified by clinical status is reported in Table 3. Missing data were relatively few. Median value for all symptoms was higher for people in the CDC group C compared to people in the CDC group A.

Reliability

Table 4 shows the internal consistency reliability coefficients for all the ISSQoL domains. Cronbach's α scores were all above the minimum accepted standard of 0.70. Ten out of 15 reliability coefficients were in the range between 0.80 and 0.88. Three out of 15 coefficients were 0.90 or greater.

Validity

Construct validity

Convergent and discriminant validity results are shown in Table 5.

As to the degree of convergent correlation, all domains but SS attained the standard convergent validity criteria ($r \geq 0.40$) for all items. Only one item out of four SS items had a item-total correlation of 0.31.

All items in the SF, HD, MS, TR, BC, LP and MF domains fully met the discriminant validity criteria. Very few items in the PW, RW, SS, DA, EV, CF, SL and SQL domains did not meet the discriminant validity criteria.

Overall, our multi-trait scaling analysis provided evidence that almost all of the ISSQoL items were more correlated (>2 standard error) with the

Table 2. Floor and ceiling effect of the ISSQoL domains

ISSQoL domains (item #)	Asymptomatic (CDC group A)*		Symptomatic (CDC group B)*		AIDS (CDC group C)*	
	% Floor	% Ceiling	% Floor	% Ceiling	% Floor	% Ceiling
QoL core evaluation form						
Satisfaction with quality of life (3)	–	1.0	4.3	0.7	5.1	2.5
Physical well-being (6)	–	28.3	0.7	5.0	4.0	4.0
Role well-being (2)	–	37.8	3.7	20.1	12.9	14.3
Social functioning (2)	1.0	–	1.5	8.1	3.9	14.3
Depression/anxiety (7)	–	2.0	0.7	–	–	–
Energy/vitality (4)	1.0	1.0	–	2.2	–	2.6
Health distress (4)	–	5.0	0.7	4.3	2.5	2.5
Cognitive functioning (4)	–	11.8	0.7	0.7	–	5.1
Sexual life (5)	–	2.1	3.0	–	8.1	–
Additional important areas						
Social support (4)	2.1	1.0	1.5	3.0	1.5	1.5
Interaction with medical staff (9)	–	1.1	–	0.8	–	1.4
Treatment impact (3)	10.1	4.0	10.8	0.7	14.3	2.6
Body changes (4)	1.0	2.9	2.8	0.7	5.2	5.2
Life planning (2)	1.0	3.9	7.1	1.4	10.5	5.3
Motherhood/fatherhood (3)	1.5	21.2	6.1	8.2	17.5	12.3

*CDC group A: not advanced stage of HIV disease; CDC group B: moderate advanced stage of HIV disease; CDC group C: advanced stage of HIV disease.

domain that they were hypothesized to belong to than with the scores of other domains.

Criterion/concurrent validity

Table 6 shows results of analysis of variance of the ISSQoL domains (dependent variables) by the HIV status (CDC groups A, B, and C; independent factors). Table 7 shows the correlation between ISSQoL scores and the number of self-reported symptoms. As hypothesized, all ISSQoL domain scores, except for the SS score, were negatively correlated ($p < 0.0001$) with the number of self reported symptoms.

Interscale correlation

Most correlations among the scales were significantly higher than zero ($p < 0.01$; $p < 0.05$), except for SS and MS (Table 8).

The SS domain only correlates with DA, EV, CF and SQL domains. The MS domain does not correlate with PW, BC, SS, or MF.

Discussion

Data of the present paper provide preliminary evidence of the reliability and validity of the ISSQoL questionnaire for the measurement of HRQoL in HIV-infected people in the HAART era.

The development process of the questionnaire was long and complex. However, it allowed us to incorporate some of the new aspects brought in by HAART. The final questionnaire resulted in a Core whose the content is close to old questionnaires. However, some domains or items were excluded (i.e. domains on pain, item on fatigue in the *energy/vitality* domain), some domains were added (*sexual life*, that can be considered part of the HRQoL core construct), some items were added to a domain (i.e. "does the therapy you are taking limit your social life?" was added to the *social functioning* domain of the MOS-HIV Health Survey) and some items were re-worded (i.e. "are you able to walk about 100 metres?" from the MOS-HIV Health Survey was changed in "Are you able to walk at least half an hour?" and the question "have you been unable to do certain kinds or amounts of work, housework, or schoolwork because of your health?" was changed in "have you been limited by your health to seek for or to maintain a job?"). Moreover, new Additional Areas, that were considered most important in influencing the HRQoL by focus groups during the questionnaire development

Table 3. Description of symptoms

Symptoms	Asymptomatic (CDC group A)[a]		Symptomatic (CDC group B)[a]		AIDS (CDC group C)[a]	
	N. respondents	Median value of intensity[b]	N. respondents	Median value of intensity[b]	N. respondents	Median value of intensity[b]
Pain	102	1	137	2	72	3
Fever	99	1	135	2	76	2
Fatigue	100	2	139	3	76	3
Loss of appetite	102	2	141	2	75	2
Loss of weight	101	1	142	2	75	2
Abnormal fat accumulation	102	1	135	1	77	1
Abnormal loss of fat	100	1	138	1	76	2
Difficulty to swallow	102	1	143	1	75	1
Alteration of the taste	101	1	142	1	75	1
Nausea	102	1	143	2	74	2
Vomit	102	1	141	1	75	1
Diarrhoea	101	2	142	2	77	2
Constipation	101	1	141	1	71	1
Burning/swelling to stomach	99	2	138	2	75	2
Mental confusion	102	1	141	1	75	2
Sleeping difficulty	101	2	141	2	76	2
Vision troubles	102	1	140	1	76	2
'Pins and needles' around the mouth	101	1	141	1	74	1
Dizziness, balance troubles	102	1	140	1	77	2
Breath difficulty	102	1	142	1	75	2
Cough	102	1	141	2	75	2
Pruritus	101	1	140	1	76	2
Sweating	100	2	139	2	76	2
Cutaneous intolerance	101	1	138	1	74	1
Nails becoming ingrown	100	1	136	1	69	1
Loss of hairs	102	1	142	1	75	1
Hand or feet swelling	101	1	139	1	76	1
Decreased sexual interest	100	1	140	2	73	3
Difficulty in reaching orgasm	92	1	125	2	63	2
Only for men: erection dysfunctions	64	1	83	1	48	2
Only for women: vaginal lubrication dysfunctions	36	1	59	1	20	2
Only for women: menstrual cycle anormalities	38	1	57	2	26	2

[a]CDC group A: not advanced stage of HIV disease; CDC group B: moderate advanced stage of HIV disease; CDC group C: advanced stage of HIV disease.
[b]Intensity scale: 1 = not at all, 2 = little, 3 = somewhat; 4 = much, 5 = very much.

Table 4. Results of item scaling test: reliablity

ISSQoL domains	Test domain – reliability	Mean (SD), range
QoL core evaluation form		
Satisfaction with quality of life	0.86	44.2 (18.1), 0–100
Physical well-being	0.90	69.5 (25.1), 0–100
Role well-being	0.83	65.8 (30.1), 0–100
Social functioning	0.82	60.0 (25.4), 0–100
Depression/anxiety	0.88	54.0 (20.3), 0–100
Energy/vitality	0.83	58.7 (19.1), 0–100
Health distress	0.90	55.3 (23.2), 0–100
Cognitive functioning	0.88	60.6 (21.9), 0–100
Sexual life	0.82	47.6 (23.8), 0–100
Additional important areas		
Social support	0.70	45.3 (22.1), 0–100
Interaction with medical staff	0.93	53.9 (19.3), 6–100
Treatment impact	0.82	34.6 (24.6), 0–100
Body changes	0.87	52.1 (25.0), 0–100
Life planning	0.77	51.0 (23.2), 0–100
Motherhood/fatherhood	0.83	54.8 (29.1), 0–100

Table 5. Results of item scaling test: validity

ISSQoL domains	Range of item correlation		Test item domain	
	Convergent validity	Discriminant validity	Convergent % success[a]	Discriminant % success[b]
QoL core evaluation form				
Satisfaction with quality of life	0.63–0.81	0.12–0.64	100	98
Physical well-being	0.61–0.83	0.02–0.70	100	98
Role well-being	0.71–0.71	0.09–0.76	100	87
Social functioning	0.70–0.70	0.04–0.63	100	100
Depression/anxiety	0.54–0.73	0.03–0.65	100	97
Energy/vitality	0.61–0.74	0.01–0.58	100	98
Health distress	0.77–0.82	0.04–0.65	100	100
Cognitive functioning	0.63–0.83	0.03–0.68	100	98
Sexual life	0.44–0.75	0.00–0.46	100	93
Additional important areas				
Social support	0.31–0.62	0.00–0.26	75	97
Interaction with medical staff	0.67–0.84	0.00–0.39	100	100
Treatment impact	0.61–0.74	0.01–0.48	100	100
Body changes	0.64–0.80	0.00–0.48	100	100
Life planning	0.63–0.63	0.00–0.52	100	100
Motherhood/fatherhood	0.56–0.80	0.02–0.39	100	100

[a]Convergent success is defined for any correlation between an item and the appropriate domain score of 0.40 or greater.
[b]Divergent success is defined for any correlation between an item and the appropriate domain score significantly higher (≥2 standard error) than with other domains.

process were added (*social support*, *interaction with medical staff*, *treatment impact*, *body changes*, *life planning*, *motherhood/fatherhood*. The Additional Areas may help in identifying causes related to an impairment of quality of life and may allow clinicians and researchers designing appropriate interventions. Researchers and/or practitioners may choose what of the Additional Areas investigate behind the Core part of the instrument according to the purposes of their study or clinical activity.

Table 6. Mean (SD) of each ISSQoL domain by HIV status (one-way analyses of variance)

ISSQoL domains	Asymptomatic (CDC group A)$_a$*	Symptomatic* (CDC group B)$_b$*	AIDS (CDC group C)$_c$*	*F*	Multiple comparison
QoL core evaluation form					
Satisfaction with quality of life	51.1 (12.9)	43.6 (16.7)	36.2 (22.3)	16.7, $p=0.000$	$p_{a\_b}=0.000$; $p_{a\_c}=0.000$; $p_{b\_c}=0.032$
Physical well-being	86.8 (14.5)	65.7 (22.8)	54.1 (27.4)	51.9, $p=0.000$	$p_{a\_b}=0.000$; $p_{a\_c}=0.000$; $p_{b\_c}=0.000$
Role well-being	82.7 (19.5)	64.7 (28.3)	44.3 (31.8)	42.5, $p=0.000$	$p_{a\_b}=0.000$; $p_{a\_c}=0.000$; $p_{b\_c}=0.000$
Social functioning	72.8 (19.3)	56.9 (23.2)	49.0 (29.0)	23.9, $p=0.000$	$p_{a\_b}=0.000$; $p_{a\_c}=0.000$; $p_{b\_c}=0.125$
Depression/anxiety	61.7 (17.3)	52.0 (19.3)	47.9 (22.9)	11.9, $p=0.000$	$p_{a\_b}=0.000$; $p_{a\_c}=0.000$; $p_{b\_c}=0.468$
Energy/vitality	65.0 (15.7)	57.9 (18.3)	51.5 (22.0)	11.8, $p=0.000$	$p_{a\_b}=0.004$; $p_{a\_c}=0.000$; $p_{b\_c}=0.091$
Health distress	61.5 (21.8)	54.4 (23.4)	48.9 (23.2)	6.9, $p=0.001$	$p_{a\_b}=0.051$; $p_{a\_c}=0.001$; $p_{b\_c}=0.251$
Cognitive functioning	70.3 (17.7)	58.4 (20.2)	52.1 (25.1)	18.4, $p=0.000$	$p_{a\_b}=0.000$; $p_{a\_c}=0.000$; $p_{b\_c}=0.165$
Sexual life	51.3 (21.0)	48.7 (22.5)	40.7 (28.1)	4.5, $p=0.012$	$p_{a\_b}=0.750$; $p_{a\_c}=0.023$; $p_{b\_c}=0.111$
Additional important areas					
Social support	48.3 (21.5)	45.4 (22.7)	41.0 (21.5)	2.1, $p=0.119$	$p_{a\_b}=0.681$; $p_{a\_c}=0.103$; $p_{b\_c}=0.472$
Interaction with medical staff	54.6 (17.9)	53.2 (19.3)	54.3 (21.1)	0.2, $p=0.848$	$p_{a\_b}=0.923$; $p_{a\_c}=1.000$; $p_{b\_c}=0.976$
Treatment impact	36.5 (25.7)	33.3 (23.3)	34.4 (25.5)	0.5, $p=0.617$	$p_{a\_b}=0.699$; $p_{a\_c}=0.937$; $p_{b\_c}=0.983$
Body changes	57.4 (23.4)	49.4 (24.4)	49.9 (27.5)	3.5, $p=0.032$	$p_{a\_b}=0.030$; $p_{a\_c}=0.159$; $p_{b\_c}=0.999$
Life planning	57.2 (18.5)	49.5 (23.2)	44.7 (26.7)	7.0, $p=0.001$	$p_{a\_b}=0.012$; $p_{a\_c}=0.002$; $p_{b\_c}=0.478$
Motherhood/fatherhood	64.8 (25.4)	50.9 (26.7)	50.0 (34.3)	5.7, $p=0.004$	$p_{a\_b}=0.003$; $p_{a\_c}=0.026$; $p_{b\_c}=0.997$

*CDC group A: not advanced stage of HIV disease; CDC group B: moderate advanced stage of HIV disease; CDC group C: advanced stage of HIV disease.

Table 7. Pearson's correlation coefficients between ISSQoL domains and symptoms

ISSQoL domains	Correlation between ISSQoL domains score and number of self-reported symptoms
QoL core evaluation form	
Satisfaction with quality of life	−0.594**
Physical well-being	−0.556**
Role well-being	−0.538**
Social functioning	−0.593**
Depression/anxiety	−0.606**
Energy/vitality	−0.575**
Health distress	−0.502**
Cognitive functioning	−0.578**
Sexual life	−0.495**
Additional important areas	
Social support	−0.103*
Interaction with medical staff	−0.300**
Treatment impact	−0.331**
Body changes	−0.250**
Life planning	−0.427**
Motherhood/fatherhood	−0.306**

*$p = 0.074$; **$p < 0.001$.

Demographic characteristics of the present cohort were similar to those of other cohorts of HIV-infected persons in Italy [17]. Missing data were relatively few. As expected, the ceiling effect was high for *role functioning* at any stage of HIV disease and for *cognitive functioning* in CDC Group A people. These results were similar to those of published studies, even though both floor and ceiling effects had lower percentages compared to those of the same domains in the previously published HIV-HRQoL questionnaires [3, 18]. Concerning the new included areas, the ceiling effect was high for the *motherhood/fatherhood* domain. However, this latter domain as well as the *life planning* area, also had a high floor effect in CDC Group C people. This means that stage of the disease probably has a significant impact on planning the future even in the era of HAART. The *treatment impact* domain had a high floor effect. However, despite taking HAART was an inclusion criterion in this study, we cannot be sure that people with the lowest values on the scale were really taking HAART at the moment of the interview.

The internal consistency of the questionnaire was good. The Cronbach's α was > 0.70 for all the domains. Only the *medical staff interaction* item had a Cronbach's α above 0.90. These results support the view that ISSQoL domain scores are able to reliably assess HRQoL without being redundant. Concerning the criterion validity, it is always difficult to find a 'gold standard' of health status to which to compare the new instrument. To date, the HIV disease stage is often used an indicator of the impact of HIV disease on the well-being of infected people even though, for this purpose, this classification system is outdated. Even taking into account the limitations of such an indicator, the ISSQoL scores well discriminated among different HIV statuses. Interestingly, only the items of *medical staff interaction* and *treatment impact* were not significantly different among CDC groups, which evidentiates the independence of these domains from the stage of HIV disease.

We demonstrated a good correlation between each domain of ISSQoL and the symptom score, except for the *social support* items. Since symptoms are one of the most important components of HRQoL, the high correlation between symptoms and each area of the questionnaire confirmed the convergent validity of the instrument. A high correlation between symptoms and HRQoL areas was previously reported for other questionnaires [19–21]. However, several authors reject the introduction of the symptoms assessment in a questionnaire on HRQoL since the two concepts, symptoms and HRQoL are too close [22].

We planned not to use the surrogate markers for the assessment of criterion validity. We think that such markers of disease (CD4 or HIV RNA) are predictive of the natural history of the disease, the efficacy of antiretroviral drugs, and eventually of survival, but they are not a good measure of how ill a person may feel. A low correlation with CD4 cell count and/or HIV RNA plasma levels was confirmed in previous published studies [23–25].

Data on convergent and discriminant validity provide further evidence of the goodness of the ISSQoL questionnaire. Only the *social support* item had a suboptimal convergent and discriminant validity. We concluded that the *social support* items do not belong to the HRQoL Core Evaluation form. However, the *social support* assessment has been demonstrated to be of great importance [26–28], and due to its potential influence on HRQoL, we decided to include this domain in the Additional Important Areas for HRQoL.

Table 8. Correlation among scales

ISSQoL domains	SQL	PW	RW	SF	DA	EV	HD	CF	SL	SS	MS	TR	BC	LP	MF
QoL core evaluation form															
SQL	1.000														
PW	579 **	1.000													
RW	**0.580** **	**0.780** **	1,000												
SF	**0.531** **	**0.598** **	**0.622** **	1.000											
DA	**0.649** **	**0.558** **	**0.568** **	**0.604** **	1.000										
EV	**0.666** **	**0.600** **	**0.637** **	**0.618** **	**0.637** **	1.000									
HD	**0.558** **	**0.474** **	**0.477** **	**0.558** **	**0.709** **	**0.527** **	1.000								
CF	**0.597** **	**0.575** **	**0.569** **	**0.514** **	**0.682** **	**0.590** **	**0.510** **	1.000							
SL	**0.487** **	324 **	**0.408** **	**0.516** **	**0.526** **	**0.455** **	**0.511** **	**0.435** **	1,000						
Additional important areas															
SS	0.184 **	0.169 **	0.139 (*)	0.074	0.162 **	0.207 **	0.077	0.117 (*)	0.059	1.000					
MS	0.374 **	0.082	0.127 (*)	0.148 (*)	0.261 **	0.249 **	0.200 **	0.276 **	0.206 **	0.006	1.000				
TR	0.207 **	0.136 (*)	0.170 **	0.307 **	0.299 **	0.116 (*)	0.357 **	0.284 **	0.356 **	−0.055	0.163 **	1.000			
BC	0.167 **	0.176 **	0.151 **	0.201 **	0.272 **	0.041	0.324 **	0.229 **	0.262 **	−0.021	0.059	0.465 **	1.000		
LP	0.471 **	0.350 **	0.348 **	0.457 **	0.544 **	0.411 **	0.481 **	0.457 **	0.492 **	0.036	0.233 **	0.366 **	0.288 **	1.000	
MF	0.349 **	0.346 **	0.278 **	0.317 **	0.237 **	0.191 **	0.357 **	0.252 **	0.254 **	−0.040	0.050	0.299 **	0.283 **	0.253 **	1.000

*$p < 0.05$; **$p < 0.01$.

Our approach to item selection was empirical. However, selection of the subscales to be included in the questionnaire was done through focus groups and structured interviews with HIV-infected persons. Since we are aware that observers are poor judges of how people feel about their HRQoL [29], we worked together with clinicians involved in the care of people with HIV infection, as well as with statisticians, sociologists, psychiatrists, psychologists, and HIV-infected persons themselves.

The participation of people living with HIV in the study group was essential for several reasons: to analyze new needs, to enhance the identification of 'priority' areas previously not included on most questionnaires, such as, sexual life, impact of body changes on physical and mental health, impact of antiretroviral therapy on well-being, short- and long-term life planning, motherhood/fatherhood, to incorporate a more appropriate patient's point of view; and to determine areas significantly less important in this era compared to the pre-HAART era.

The ISSQoL is primarily inspired by the MOS-HIV, the most widely used questionnaire for measurement of HRQoL in HIV-infected people. However, Wu and colleagues built the Medical Outcomes Study battery in 1991 [4]. Some important areas for people taking HAART, such as drug related adverse effects, changes in body image, long-term toxicities, motherhood/fatherhood, were absent. Other scales such the MQOL, the FACT, the HOPES [7, 8, 10] were used in a small number of studies and did not obtain the validation of instruments translated for countries outside the US.

The present study has several limitations. First, data on some demographic characteristics (employment, income), surrogate markers of the disease, antiretroviral therapy history, previous hospitalizations, and concurrent diseases are absent. In particular, we could not assess the ability of the ISSQoL to discriminate between persons taking or not taking HAART. Moreover, generalization of our findings is limited by the specific Italian health care system that guarantees all HIV-infected people free-of-charge access to care. A responsiveness assessment of the instrument is also needed.

In conclusion, the ISSQoL has preliminary evidence for reliability and validity in measuring HRQoL in HIV-infected people in the HAART era. We do agree that the assessment of HRQoL of people with HIV can only be done by asking the patient [22]. The measurement of HRQoL is useful, feasible, and should be performed more frequently in the clinical practice.

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