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Health-related quality of life and patient–provider relationships in HIV-infected patients during the first three years after starting PI-containing antiretroviral treatment

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Abstract The aim of this study was to investigate factors associated with better health-related quality of life (HRQL) during the first three years after starting PI-containing antiretroviral treatment. Clinical, social and behavioural data from the APROCO cohort enabled us to analyze simultaneously the association between HRQL and patients' relationships with their health care providers. A self-administered questionnaire collected information about HRQL (MOS-SF36) and relationships with medical staff (trust and satisfaction with information). Two aggregate scores, the physical (PCS) and mental (MCS) component summaries (adjusted for baseline HRQL), were used as dependent variables in the linear regressions to identify factors associated with HRQL. We had complete longitudinal data for 360 of the 611 patients followed through M36. Factors independently associated with a high MCS were (male) gender, no more than one change in treatment, (few) self-reported symptoms and trust in the physician. Factors independently associated with high PCS levels were employment, no children, (few) self-reported symptoms and satisfaction with the information and explanations provided by the medical staff. These results underline the need to improve patient–provider relationships to optimize long-term HRQL. Socio-behavioural interventions should focus on this goal.

Introduction

The prognosis of patients with HIV infection has improved dramatically since highly active antiretroviral treatment (HAART) was introduced late in 1995, as demonstrated by the

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reductions reported in mortality, opportunistic infections (Aalen *et al.*, 1999; Allardice *et al.*, 1998; Mocroft *et al.*, 1998) and length of hospitalization (Mouton *et al.*, 1997; Torres & Barr, 1997).

HAART has indirectly led to a renewed emphasis on co-morbidities (Tedaldi *et al.*, 2003) and treatment-related toxicities (Bonnet *et al.*, 2002; Vigouroux *et al.*, 1999), which cause an increasing portion of the morbidity and mortality in HIV-infected individuals.

The variety of treatment options improves the chances of virological success for patients with prior treatment failure, but it also lengthens patients' experience with treatment and their short- and long-term side effects. Now that some therapeutic options may provide equivalent levels of sustained virological success, the assessment of health-related quality of life (HRQL) in these patients has become a priority, for their wellbeing may be influenced not only by their response to treatment but also by other dimensions, including treatment-related toxicity. At the same time, psychosocial factors may mediate patients' self-perception of their health.

Because HAART has the potential to transform a progressively fatal disease into a chronic condition, we considered that the physical and mental components of HRQL were the dimensions best able to reflect the obstacles faced by patients with chronic disease. To date, most studies dealing with HRQL in HAART-treated patients have been cross-sectional: they reveal the impact of various sociodemographic characteristics or clinical features on HRQL (Arpinelli *et al.*, 2000; Miners *et al.*, 2001).

Several have been performed as part of the clinical trial of new antiretroviral regimens (Bucciardini *et al.*, 2000; Nieuwkerk *et al.*, 2000; Wu *et al.*, 2002). Little is currently known about how and to what extent psychosocial factors, in particular those related to patient–provider relationships, affect mental and physical HRQL in the HAART era.

Using three years of longitudinal HRQL data from the French APROCO cohort of HIV-infected individuals enrolled at the initiation of a regimen including protease inhibitors (PI), we aimed to disentangle the effects of psychosocial factors from those of sociodemographic and HIV-related characteristics on the mental and physical dimensions of HRQL.

Methods

Biomedical data collection

The French APROCO-ANRS/EP11 study was established in 1997 to study socio-behavioural, clinical and biological characteristics of HIV-1-positive patients beginning a combination antiretroviral therapy. Patients in 47 French hospital departments specialized in HIV care were enrolled when they began HAART (M0) and were seen every four months thereafter.

At each visit, the treating physician completed a questionnaire including clinical and biological data (HIV plasma RNA, CD4 cell counts, clinical stage) and the current antiretroviral regimen. All AIDS-defining events and major (grade 3 and 4) adverse events were diagnosed by medical evaluation, from the laboratory data of each participating centre, and later confirmed by a committee that independently reviewed medical records.

The medical questionnaire at enrolment (M0) included retrospective data about the patient's HIV history: HIV transmission group, time from HIV diagnosis to initiation of medical treatment and history of antiretroviral treatment before beginning HAART.

Patients' questionnaires

Patients were asked to complete a questionnaire at enrolment (M0) and every eight months thereafter. The questionnaire collected personal data (age, gender, education level, employment, etc.) at each visit.

At M0, M12, M28 and M36 it contained the Medical Outcome Study Short Form Health Survey (MOS-SF; McHorney *et al.*, 1993, 1994; Ware & Sherbourne, 1992), which has been validated in French (Leplege *et al.*, 1995, 2001; Ware *et al.*, 1995). This survey contains one multi-item scale that assesses eight health concepts. For each dimension of quality of life, responses to the relevant question were summed and converted to a 0–100 score, with 100 the best possible quality of life. The SF-36 scores were combined to obtain two aggregate scores—the physical component summary (PCS) and the mental component summary (MCS; Taft *et al.*, Karlsson & Sullivan, 2001; Ware *et al.*, 1995; 1998; Ware *et al.*, 1998).

At each study visit, the self-administered questionnaire contained questions about the patient's relationship with the medical environment and about the social support received. Specifically, the questionnaire asked about the patient's trust in the HIV specialist, the way medical staff spoke about problems, the patient's satisfaction or dissatisfaction with the information and explanations from the medical staff, and social support from partner, family and friends.

The Center for Epidemiological Studies Depression (CES-D) Scale was used to measure depressive symptoms. This 20-item self-administered questionnaire assesses the frequency of depressive symptoms during the previous week. A CES-D score of 16 or above is the standard cut-off point for identifying a 'high' risk of depression or general psychological distress (Fuhrer, 1989; Katz *et al.*, 1996).

Statistical methods

The present analysis includes all patients from the APROCO cohort for whom we had complete clinical data at M0, M12, M28 and M36 and who completed the self-administered questionnaire at enrolment and thereafter missed no more than one questionnaire during follow-up (M12, M28, M36). Respondents were compared with non-respondents for age, gender, HIV transmission group and main clinical characteristics.

To identify the pattern of factors characterizing high levels of mental and physical HRQL at any visit, we used linear regression models based on Generalized Estimating Equations (GEE). These models allow us to consider the correlation of within-subject repeated measures (Liang & Zeger, 1986; Twisk, 1997; Zeger & Liang, 1986). Paired t-tests were used to assess changes in psychosocial characteristics. The univariate analysis used simple linear regression to identify factors associated with PCS and MCS scores; variables with p-values lower than 0.25 were entered in the corresponding multiple regression model. A forward procedure based on the quasi-likelihood ratio test produced the final model.

Statistical analyses were performed with the SPSS PC for Windows (version 11.0; SPSS, Inc., Cary, NC) and STATA 5.0 (Stata Corp., College Station, Texas) software.

Results

The APROCO cohort enrolled 611 patients from May 1997 through June 1999 for whom we had complete biomedical data from enrolment through 36 months of treatment. Complete HRQL data were available for 360 of these patients, who were included in the present

analysis. We compared the 360 eligible patients with the 251 excluded patients and found no significant differences at baseline for age, gender, antiretroviral naivete at enrolment, clinical stage or CD4+ cell count. Table 1 also shows that roughly half the respondents were contaminated through homosexual contact (46.7%), had completed high school (42.8%) and were employed at enrolment (62.5%).

Changes in clinical and psychosocial characteristics over three years of treatment

After three years of HAART, 62.5% of the patients had undetectable plasma viral loads. Of those with CD4+ cell counts below 200 mm^3 at baseline, 88.4% had 200 cell counts over 200 mm^3 after three years of treatment. The median (IQR) variation of CD4+ cell counts over three years of HAART was 225 (84; 362).

The median number of changes in treatment (IQR) at M36 was 1.8 (1.6). Nonetheless, at that point, 62.6% of the patients were still treated with regimens including a PI, while 27.2% had switched to regimens without PI. The median number of adverse events at M36 was six (5). The median (IQR) time elapsed since the first positive HIV test was 48 months (10–93).

Patients who had had antiretroviral treatments before starting PI had received a non-PI antiretroviral treatment for a median (IQR) duration of 19 months (9–37).

The median (IQR) number of self-reported symptoms decreased slightly, from M12 (9.9; 9–11) to M36 (7; 4–11).

Individuals who reported strong social support did not change significantly from enrolment (79.4%) through M36 (71.9%), nor did individuals classified as depressed (34.7% at baseline, 28.1% at M36).

Table 1. *Sociodemographic and medical characteristics of respondent and non-respondent patients (APROCO cohort; n = 611 patients)*

	Non-respondent (1) n (%) 251	Respondent (2) n (%) 360	p (1) versus (2)
Unemployment			
No	89 (46.8)	132 (37.5)	0.035 [b]
Yes	101 (53.2)	220 (62.5)	
HIV viral load (log copies/ml), median (IQR)	4.42 (3.74–5.06)	4.25 (3.54–4.95)	0.030 [a]
Education			
< high school	54 (73.3)	206 (57.2)	<0.001 [b]
≥ high school	56 (26.7)	154 (42.8)	
CD4+ cell count/mm^3			
<200	102 (41)	95 (26.4)	
≥200	147 (59)	265 (73.6)	<0.001 [a]
HIV infection transmission category			
Injecting drug users	62 (24.7)	41 (11.4)	<0.001 [b]
Homosexuals	80 (31.9)	168 (46.7)	
Heterosexuals	82 (32.7)	111 (30.8)	
Others	27 (10.8)	40 (11.1)	
Antiretroviral naive			
No	151 (60.2)	243 (67.5)	0.062 [b]
Yes	100 (39.8)	117 (32.5)	

[a]Mann–Whitney test; [b]chi-square test.

At M0, approximately half the patients (47.2%) reported they were very satisfied with the information supplied by the medical staff they dealt with; this proportion was slightly lower at M36 (40%). At enrolment, most (88.3%) reported trust in their physician, and this proportion remained relatively constant at each follow-up visit (91.9% at M12, 84.7% at M28 and 83.6% at M36).

Figure 1 shows that over the three-year study period, a quarter of the patients always had MCS scores above the median, a quarter always had MCS scores below the median and half experienced fluctuations over time in their mental HRQL. These proportions were similar for PCS changes over time (Fig. 2).

Factors associated with better quality of life

Table 2 shows the relations between the sociodemographic, clinical and psychosocial factors and high MCS scores. These scores were associated with employment, female gender, comfortable housing and childlessness, and were inversely associated with HIV infection through injection drug use and with injecting drug use. MCS was lowest among those known to be HIV-positive for more than eight years. Clinical characteristics, including CD4+ cell-count ≥ 200 mm^3, few adverse events, few self-reported symptoms and more than two changes in treatment, were also significantly associated with high MCS scores at each visit.

Positive relationship factors, including trusting their physician, satisfaction with the explanations given by the medical staff and satisfaction with social support from partner, family and friends, were significantly associated with higher MCS scores at each visit.

Table 2 shows the factors independently associated with high MCS: male gender, no more than one change in treatment, few self-reported symptoms and trusting one's physician.

Table 3 summarizes the relationship between sociodemographic, clinical and psychosocial factors and high PCS scores. These levels were significantly associated with employment, HIV-infection through sexual contact, education (higher than a high school certificate) and childlessness and were inversely associated with age and active or past injecting drug use. PCS was poorest among those known to be HIV-positive for more than eight years. Clinical characteristics, CD4+ cell count ≥ 200 mm^3, few severe adverse events, few self-reported symptoms and clinical stage A or B were also significantly associated with higher PCS values at any given visit. Psychosocial characteristics such as satisfaction with the explanations given by the medical staff, lack of depression, not discussing problems with members of the medical
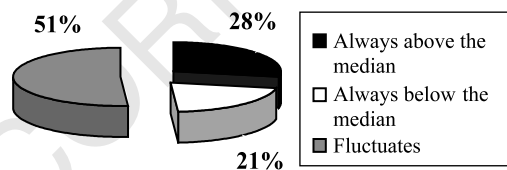

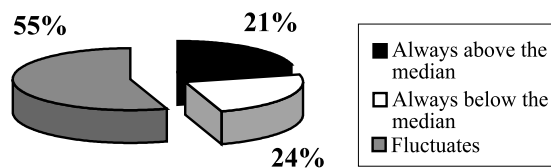FIG. 1. *Change in mental health-related quality of life over three years.*

FIG. 2. *Change in physical health-related quality of life over three years.*

Table 2. *Factors associated with good mental health-related quality of life at study visits during the first three years following initiation of a PI-containing ARV treatment (APROCO cohort; N = 360); simple and multiple linear regression based on generalized estimating equations*

Variables	B coefficient	95% CI	p	Adjusted B coefficient	95% CI	p
Baseline mental HRQL	0.50	(0.43; 0.58)	<0.001	0.40	(0.33; 0.47)	<0.001
Females	−6.05	(−8.72; −3.38)	<0.001	−3.06	(−5.24; −0.88)	0.006
Had children at M0	−3.05	(−5.18; −0.92)	0.005			
Employment at M0	6.44	(3.55; 9.33)	<0.001			
Comfortable home at M0	4.10	(2.02; 6.18)	<0.001			
HIV transmission category						
Injecting drug users						
Homosexuals	6.10	(2.86; 9.34)				
Heterosexuals	4.04	(0.54; 7.54)				
Others	7.16	(3.12; 11.19)	<0.001			
Time since first HIV-positive test ≥8 years	−3.33	(−5.36; 1.31)	<0.001			
2 or more changes in treatment since M0	−2.83	(−4.40; −1.26)	<0.001	−1.92	(−3.37; −0.47)	0.005
At relevant visit						
Active injecting drug users	−5.18	(−8.40; −1.95)	0.002			
Clinical stage of AIDS	1.76	(−0.98; 4.51)	0.208			
Number of severe adverse events	−0.61	(−1.08; −0.15)	0.009			
Number of self-reported symptoms	−0.01	(−0.013; −0.008)	<0.001	−0.007	(−0.009 −0.005)	<0.001
Trusts HIV physician	2.56	(1.12; 4.00)	<0.001	1.83	(0.54; 3.12)	0.009
Satisfied with information provided by the HIV medical staff	3.30	(0.75; 5.85)	0.011			
Depression	−13.56	(−15.15; −11.94)	<0.001			
Strong social support by partner, family and friends	9.06	(4.04; 14.07)	<0.001			

All variables with $p < 0.25$ in the baseline HRQL adjusted model were eligible for the multivariate model.

Table 3. *Factors associated with good physical health-related quality of life at study visits during the first three years following initiation of a PI-containing ARV treatment (APROCO cohort; N = 360); simple and multiple linear regression based on generalised estimating equations*

Variables	B coefficient	95% CI	p	Adjusted B coefficient	95% CI	p
Baseline physical HRQL	0.47	(0.39; 0.54)	<0.001	0.30	(0.23; 0.37)	<0.001
Age	−0.17	(−0.25; −0.08)	<0.001			
Had children at M0	−4.08	(−5.58; −2.58)	<0.001	−1.93	(−2.98; −0.88)	<0.001
Employment at M0	4.99	(3.41; 6.56)	<0.001	1.90	(0.71; 3.09)	<0.001
≥ high-school graduates	2.26	(0.83; 3.69)	0.002			
Comfortable home at M0	1.38	(0.05; 2.82)	0.060			
HIV transmission category						
Injecting drug users						
Homosexuals						
Heterosexuals	4.63	(2.11; 7.15)	<0.001			
Others	0.08	(−3.36; 3.52)	0.964			
Time since first HIV-positive test ≥8 years	−1.92	(−3.76; −0.07)	0.042			
At relevant visit						
Active injecting drug users	−3.78	(−6.36; −1.21)	0.004			
CD4+ cell count ≥200 mm3	1.23	(0.17; 2.29)	0.023			
Clinical stage of AIDS	−2.69	(−4.52; −0.87)	0.004			
Number of severe adverse events	−2.08	(−4.16; −0.01)	0.049			
Number of self-reported symptoms	−0.009	(−0.010; −0.008)	<0.001	−0.006	(−0.008; −0.005)	<0.001
Trusts HIV physician	0.39	(−0.001; 0.800)	0.056			
Satisfied with information provided by the HIV medical staff	2.40	(0.48; 4.31)	0.014	2.13	(0.44; 3.83)	0.013
Depression	−1.71	(−2.85; −0.57)	0.003			
Speaking about problems with members of medical staff	−1.85	(−3.29; −0.40)	0.012			
Strong social support	3.68	(1.43; 5.94)	0.001			

All variables with $p <0.25$ in the baseline HRQL adjusted model were eligible for the multivariate model.

staff and strong social support were significantly associated with higher PCS values. Viral load was not associated with physical quality of life.

Table 3 shows that the factors independently associated with higher PCS levels were employment, childlessness, few self-reported symptoms and satisfaction with the explanations of the medical staff.

Discussion

In this study of a cohort of HIV-infected patients enrolled when they began HAART, we focused primarily on the impact of factors related to the patient–health care provider relationship and to other known co-factors for quality of life. The results show that patients' HRQL, defined as the SF-36 physical and mental composite scores, did not vary significantly during the first three years of HAART. Known co-factors, including baseline HRQL values, social status and number of perceived symptoms, were confirmed to be associated with HRQL. More specifically, high HRQL scores, physical or mental, were closely related to baseline 'pre-HAART' HRQL. Accordingly, the component of HRQL varying at any follow-up visit and unexplained by baseline HRQL is attributable to patients' sociodemographic characteristics (sex for mental HRQL and children and employment for physical HRQL) and treatment experience (treatment changes, adverse events for mental HRQL), as well as by the patient–provider relationship (trust in the physician for mental health, satisfaction with medical staff explanations for physical HRQL).

More generally, all the psychosocial factors defining the patient–provider relationship in this study, as well as those associated with social support, played a major role in determining HRQL, for all were significantly related to both HRQL dimensions in the univariate analysis.

These results also underline the importance of the dynamics that link social and psychological factors to illness behaviours and patients' demands during the long-term course of HIV management and suggest how improving these relationships may improve HRQL dimensions. The relation with physicians and medical staff has already been shown to play an essential role in HRQL (Spitzy, 2002). These results are also consistent with findings for cancer (Lutgendorf *et al.*, 2002), asthma (Harris & Shearer, 2001; Lagerlov *et al.*, 1998) and diabetes (Auerbach *et al.*, 2002; Rose *et al.*, 2002), although further study may be necessary to help us understand the relative impact of these factors for HIV care and management (Giron *et al.*, 2002; Tassinari *et al.*, 1998) and the extent to which an improvement in the patient–provider relationship may improve patient HRQL. This issue may be crucial now that HAART has suddenly decreased the number of hospitalizations related to HIV disease and thus has transferred much HIV management and care to outpatient services. This transfer has made not only access to HIV care, but also the relationship between patients and providers, much more routine and everyday.

Better patient–provider relationships should facilitate patient–provider communication, and a greater communication between patient and provider are associated with patients' medical decision making (Marelich & Murphy, 2003). Indeed, in a trustful context, patients can give information which can make it possible for the physician to better understand the patient and to optimize their living condition, for example by modifying their treatment. In addition, there is also an association between patient–provider relationship and adherence (Cederfjall *et al.*, 2002). The type of patient–provider relationship seems to have an important impact on the two current principal problems of HIV infection: HRQL and adherence.

Social support received from partner, family and friends has a major impact on mental HRQL, as shown even before the introduction of HAART (Friedland *et al.*, 1996; Remor, 2002; Safren *et al.*, 2002; Sowell et al., 1997; Swindells *et al.*, 1999).

The importance of gender in HRQL variations appears to be growing. Our results show that the HRQL of HIV-infected women is significantly worse than that of their male counterparts and this result is consistent with previous results (Cederfjall *et al.*, 2001; Cook *et al.*, 2002; Cowdery & Pesa, 2002; Rotheram-Borus, 2001; Rotheram-Borus & Miller, 1998). Nonetheless, in view of the close association between HRQL and the number of perceived HAART-related symptoms, the former may be unable to capture gender variation in the perception of HAART-related symptoms.

First, studies have shown a gender difference in virologic response to HAART (Moore *et al.*, 2001). Moreover, some studies suggest that there are gender differences in the frequency and severity of adverse reactions to antiretroviral drugs. The reasons for these differences in adverse drug events are unclear, but may include differences between men and women in body mass index, fat composition, hormonal effects on drug metabolism, etc. (Currier *et al.*, 2000; Ofotokun & Pomeroy, 2003; Rotheram-Borus, 2000; Wilson *et al.*, 2002).

In the analysis of factors associated with high physical HRQL, employment and childlessness remained significant predictors of high HRQL. The univariate coefficient estimate of each factor was higher than the adjusted figure, thereby indicating that the two factors partially overlap: the most severely impaired may thus be women with children, who are frequently unemployed and poor as well.

Employment, a proxy of social status, is also known to influence HRQL. Our analysis shows that employed patients report better physical HRQL. These results are similar to those from another cross-sectional study on the subject (Blalock *et al.*, 2002).

We found no clinical factors that were associated with good physical HRQL. These results point out the importance of considering self-reported symptoms as well as medical relationships in improving HRQL and in choosing therapeutic strategies. It is important to note that the patients in this study had better clinical characteristics than the average HIV-infected population. In all, 246 patients maintained a CD4 cell count superior to 200 mm^3 at all visits, and only three patients had a viral load greater than 10,000 copies throughout the study.

Some methodological limitations of our study must be acknowledged. The psychometric instrument that we used, MOS-SF-36, is a generic HRQL measurement tool that may not adequately reflect the impact of HIV disease and symptoms specific to HAART (Guyatt & Jaeschke, 1997). It also neglects or does not sufficiently assess some important dimensions of individuals' HRQL (especially its social, sexual affective, cognitive and sleep dimensions).

This study was conducted among patients who began a regimen containing a protease inhibitor (PI), and most maintained such a regimen during follow-up. We cannot exclude the possibility that a regimen without PIs would provide different results, since the reduced toxicity of these alternative easier-to-take combinations may affect HAART-related perceived toxicity differently and may influence the results for all dimensions.

On the other hand, the APROCO cohort enrolled a higher proportion of social minorities than most clinical trials or other longitudinal studies carried out in other countries. This may be due to the fact that the French health care system guarantees all HIV-infected patients free-of-charge access to care and antiretroviral treatment.

Despite—or because of—these limitations, it seems quite clear that new HRQL investigations can make decisive contributions to AIDS management and help social scientists suggest improvements in AIDS care that take into account the subjective assessment of the psychological, social and physical problems encountered by patients with their treatment.

Beyond the demonstration that high HRQL is a direct determinant of adherence (Dorz et al., 2003; Penedo et al., 2003) to ARV therapy, it is now necessary to determine which factors are important to establish and maintain a high level of HRQL in HIV-infected patients receiving long-term antiretroviral treatment.

Socio-behavioural interventions should also focus on improving the provider–patient relationship in order to improve HRQL. It seems also important to study the dynamic of patient–provider relationship and more specifically factors associated with change in the relationship between patient and physician.

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