JAIDS Journal of Acquired Immune Deficiency Syndromes
28:240–249 © 2001 Lippincott Williams & Wilkins, Inc., Philadelphia

Importance of Mental Health Assessment in HIV-Infected Outpatients

*Christine Zinkernagel, †Patrick Taffé, †Martin Rickenbach, ‡Regula Amiet, §Bruno Ledergerber, †Anne-Christine Volkart, ¶Udo Rauchfleisch, **Alexander Kiss, *Verena Werder, ‡Pietro Vernazza, and *Manuel Battegay, for the Swiss HIV Cohort Study

**Basel Center for HIV-Research, Outpatient Department of Internal Medicine, University Hospital Basel; †Coordination and Data Center of the Swiss HIV Cohort Study, University of Lausanne; ‡Department of Internal Medicine, Cantonal Hospital St. Gallen; §Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich; ¶Institute of Clinical Psychology and Outpatient Department of Psychiatry, University Basel; **Division of Psychosomatics, Department of Internal Medicine, University Hospital Basel, Basel, Switzerland*

Summary: HIV infection, even when well controlled, may be associated with important mental health problems. We sought to investigate anxiety, depression, and health-related quality of life using screening measurements in patients with HIV infection and to examine their dependency on biosocial parameters relating to HIV. Prospective clinical, virologic, and immunologic data were obtained in a cross-sectional study within the Swiss HIV Cohort Study. Four self-reported questionnaires were used in 397 HIV-infected individuals. The scores for anxiety and depression were high as measured by the Hospital Anxiety and Depression Scale (HADS) and the State Trait Anxiety Inventory (STAI). Half the population scored <75 on a visual analog scale (VAS) Patients were also affected in their quality of life as measured by the HIV Medical Outcome Study (HIV-MOS). Almost all scores were significantly worse for intravenous drug users compared with other transmission groups. People who were employed, with a higher education or with higher CD4 count tended to score better, whereas those who had been hospitalized within the last 6 months, infected for a longer time, with higher viral load, or loss of weight scored significantly worse. A multivariate analysis showed higher education, being employed, low viral load, female gender, and shorter HIV disease duration to be associated with better scores. This study highlights the importance of mental health assessment regardless of HIV-disease parameters. **Key Words:** HIV—Highly active antiretroviral therapy—Anxiety—Depression—MOS—Health-related quality of life.

Potent antiretroviral therapy has drastically lowered HIV-associated morbidity and mortality in recent years (1–3). Nevertheless, as with other chronic medical conditions, greater attention to the mental health of HIV-infected individuals is needed. Mental health afflictions with a high, stable prevalence (approximately 12–13%) in the general population, such as anxiety and depression are of particular interest (4). To date, studies on mental health in HIV-infected individuals have focused mainly on psychiatric disorders, in particular major depression disorder (5–9). This study was designed to screen for anxiety and depression and to assess health-related quality of life.

This cross-sectional study was carried out with an unselected cohort of HIV-infected outpatients followed within the Swiss HIV Cohort Study (1,3). Anxiety and depression were screened for, as was health-related quality of life. Possible relationships with biosocial parameters were investigated. Many previous studies have had

Address correspondence and reprint requests to Manuel Battegay, Basel Center for HIV-Research, Outpatient Department of Internal Medicine, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland; e-mail: mbattegay@uhbs.ch

Manuscript received March 16, 2001; accepted July 30, 2001.

This study was approved by the local ethical committee, and oral informed consent was obtained from participating patients.

certain population bias, either through selective recruitment or because the recruitment methods used were subjective or did not result in enrollment from all sectors of the HIV-infected community (6,10–12). The Swiss HIV Cohort Study has a high representation of women and intravenous drug users, making it a valuable population for performing a well-balanced study. In this study we demonstrate that HIV infection, despite dramatic improvement of prognosis, is associated with important mental health problems.

METHODS

Participants and Data Collection

The Swiss HIV Cohort Study has a continuing enrollment of HIV-infected individuals aged 16 years or older. Enrollment is independent of disease stage or degree of immunodeficiency, and data are collected prospectively according to standardized criteria at registration and at 6-month follow-up visits. A detailed history of HIV-associated diseases and of medications is obtained at every follow-up. CD4 counts are measured by flow cytometry, and viral load is quantified using the Roche Amplicor HIV-1 Monitor assay (Roche Diagnostics, Basel, Switzerland; lower limit of quantitation, 400 copies/ml). The study design has been described in more detail in previous and recent publications (1,3,13). For this study, the HIV RNA and CD4 counts were obtained at the closest date possible before the date of answering the questionnaire and not more than 7 months previously. For the investigation of possible relationships with somatic health parameters, the two previous measurements taken nearest to the time of inquiry were used. AIDS was defined according to category C clinical conditions of the Centers for Disease Control and Prevention classification system for HIV infection, as revised in 1993 (14). Three hundred ninety-seven consecutive HIV-infected outpatients aged 16 years or older were enrolled (Table 1) from Basel and St. Gallen, two clinical centers participating in the Swiss HIV Cohort study. Each patient population in these two centers was representative for the entire cohort (e.g., regarding percentage of women or age distribution). These patients had consulted their treating physicians for a general follow-up between October 1, 1998, and January 30, 1999. For both the Swiss HIV Cohort Study and this study, local ethical committee approval was obtained, and patients gave their informed consent. Of these 397 individuals, biosocial follow-up data were available for 374 patients (94.2%) after a median follow-up of 363 days (standard deviation, ±90.7).

Psychometric Tools

The questionnaires were distributed as a booklet in the order described in the following and explained to patients by their treating physician or the attending study nurse. Patients carried out the tests in the absence of any health care personnel, with a total completion time of approximately 20–30 minutes.

HIV Medical Outcome Study (HIV-MOS)

The HIV-MOS questionnaire measures health-related quality of life (15). It was derived from the Medical Outcomes Study that was designed to measure outcomes in primary care and general patient populations. We used the well-established version of the questionnaire as described by Wu et al. (15,16). A two-factor analysis-summary score, the Mental Health Summary, and the Physical Health Summary scores were generated. The Physical Health Summary was calculated from the subscores of physical function, pain, role function, social function,

TABLE 1. *Characteristics of the study population (*n = *397)*

Characteristic	*N* patients (%)	Mean	Median	Range [min–max]
Female/male	134/263 (34/66)			
Age (y)		40	38	20–76
Level of education[a]				
Low	115 (32)			
Medium	187 (51)			
High	60 (17)			
Employed during previous month	224 (61)			
Transmission route				
Heterosexual contact	147 (37)			
Sex between men	125 (31)			
Intravenous drug use	110 (28)			
Other, unclear	15 (4)			
HIV duration (*mo*)		85	80	1–198
≥1 hospitalization during last 6 *mo*	47 (12)			
CD4 count (cells/mm^3)		445	403	0–1529
CDC stage of disease				
A	149 (37)			
B	145 (37)			
C	103 (26)			
Viral load ($\log_{10}$ copies/ml)		2.2	2.15	Undetectable-10^6
Viral load <400 copies/ml	231 (59)			
Antiretroviral therapy				
Receiving therapy	311 (78)			
No therapy	86 (22)			

[a] Data available from 362 participants.

general health, and vitality (17). The Mental Health Summary was derived from the subscores of mental health, health distress, quality of life, cognitive function, and vitality (17). The development, conceptual and measurement model, reliability, validity, responsiveness, and availability of validated language adaptations are described elsewhere (15, 16,18). We used the validated German version (19).

EuroQoL Visual Analogue Scale

We used an adapted visual analog scale similar to a thermometer as developed by the EuroQoL Group (20,21). This self-rating scale indicates a patient's personal assessment of his or her health. The text instructs patients to indicate their perception of their present health status on a continuous scale from 0 (worst imaginable health state) to 100 (best imaginable health state), in 5-unit increments.

Hospital Anxiety Depression Scale (HADS)

The HADS (22) is a short self-assessment questionnaire used to screen for the level of general anxiety over the preceding 4 weeks: we used the validated German version (23). Situation- or environment-dependent anxiety is not assessed. This scale also evaluates mild symptoms of depression; it was developed specifically for an internal medicine context in which milder forms of anxiety and depression are more likely to be seen, because patients with more disabling degrees of these symptoms are generally treated by psychiatric specialists (22,23). The HADS specifically identifies anxiety and depression as symptoms and not as syndromes; accordingly, results give an indication of anxiety and depression and should not be interpreted as a diagnosis or as an absolute measure of prevalence. The data obtained on anxiety and depression are in the form of summary scores based on 7 questions and rated on a scale from 0–3. Scores were retained if $\leq$1 item was missing.

State-Trait Anxiety Inventory (STAI)

The STAI screens for environment-dependent anxiety, which is additionally influenced by various underlying mental processes. We used the validated German version, consisting of two scales to assess state and trait anxiety (24). State anxiety is an emotional state characterized by tension, worry, nervousness, restlessness, fear of impending events, and higher activity of the autonomic nervous system, which varies in time and depends on the situation. Trait anxiety is a relatively stable characteristic of an individual, associated with the tendency to perceive a situation as harmful. Individuals with a more anxious personality tend to interpret more situations as harmful and to react with higher levels of state anxiety. State and trait values are generated by summing up the 20 questions on the questionnaire with answers rated on a scale from 1 to 4.

For the trait scores of the STAI, both scores of the HADS, and both HIV-MOS summary scores, a T-value transformation of the raw scores was performed as described in the scoring guidelines. Therefore, the scores are centered to the value of 50 with a standard deviation of ±10.

Biosocial Parameters

Social, clinical, virologic, and immunologic patient characteristics used as parameters to be assessed for any relationship with psychometric test results were age, education, employment, HIV transmission route, presence and type of therapy, CD4 count, viral load, duration of HIV infection, change in body weight, and hospitalization. Age was divided into quartiles for bivariate analysis, and a continuous scale was used for multivariate regression. Education was divided into three levels for bivariate analysis (low, no completed school or only mandatory school; medium, finished apprenticeship or bachelor; high, higher professional education, higher technical or commercial school, or university), but two levels (low and medium/high) were used for regression analysis, because no statistical difference was found between the medium and high groups. A person's employment status was categorized as either working or not working. Transmission routes were classified for bivariate analysis as heterosexual sex, sex between men, intravenous drug use, or other. For multivariate analysis, transmission by intravenous drug use was compared with the other routes. Whether patients were on therapy was documented, as was the type of therapy (monotherapy, dual therapy, or highly active antiretroviral therapy [HAART], including protease inhibitors). CD4 counts were classed as $\leq$200 cells/mm^3, 201–500 cells/mm^3, or >500 cells/mm^3. A change in CD4 count was classified as a reduction if there was a decrease of >30% between two measurements, and as an increase if the value rose by >30%. Plasma viral load was recorded as being in 1 of 4 categories for bivariate analysis: HIV RNA $\leq$400 copies/ml, 401–5000 copies/ml, 5001–50,000 copies/ml, or >50,000 copies/ml. The same criteria for viral load reduction/increase were used for as for changes in CD4 count (>30% change). The weighted HIV RNA increase was defined as the absolute increase in viral load weighted by time (1/time) between the last two measurements to give more weight to more recent measurements.

The duration of HIV infection was calculated as the number of months between the date of answering the questionnaire and seroconversion when this was known, otherwise the date of the first HIV test documented as positive, if known, or the registration date into the Swiss HIV Cohort Study. Loss of weight during the last two measurements was determined and again weighted by time (1/time) between the two measurements to accentuate more recent data. When hospitalization had occurred at least once within the last 6 months, this was documented.

Statistical Methods

To study the association of different psychometric scores with the social and clinical variables the analysis was conducted as follows. Raw associations were assessed using the nonparametric Mann-Whitney *U* test and Kruskal-Wallis test (bivariate analysis). For this purpose continuous variables were categorized into quartiles of their distribution. After this, we considered, in a multivariate analysis, potentially confounding factors. We used T-scores wherever supplied by the scoring instructions and applied multivariate linear regression. T-scores are transformed scores so that the final distribution looks as "normal" as possible, with a mean of 50 and a standard deviation of ±10.

No T-scores exist for the visual analog scale and the State scores; therefore we used the raw data. For these two variables we calculated different transformations (logarithmic, inverse, square root) to improve the "normality of distribution" and stabilize variances. Because we found no suitable transformation, we used the raw scores.

We determined associations between social and clinical factors (independent variables) and different test scores (dependent variables). For this, we started with a model containing all covariables and then discarded factors one by one, on the basis of their *p* values, the coefficient of determination R^2, and the assessment of their potentially confounding effect. Strong leverages and outliers were discarded (not more than 1 or 2 observations) to adjust for most measurements and make the analysis more robust. This procedure is appropriate, because it excludes atypical scores having too much influence on estimations.

RESULTS

Of 397 HIV-infected individuals enrolled in this study, 34% were women, the mean age was 40 years (range, 20–80), 68% were educated beyond the level of mandatory schooling, and 61% were employed. The routes of HIV acquisition were heterosexual contact (37%), sex between men (31%), intravenous drug use (28%), or unknown (4%) as shown in Table 1. Median duration of HIV infection was 80 months (mean, 85 months), and 12% of all participants had been hospitalized within the last 6 months. As classified by the Centers for Disease Control and Prevention definition, 37% were in disease stage A, 37% in stage B, and 26% in stage C. Median CD4 count was 403 cells/mm^3 (range, 0–1529), and 59% of individuals had a viral load <400 copies/ml. HAART, including protease inhibitors, was prescribed in 64%, whereas 22% were not receiving antiretroviral therapy.

The questionnaire was completed by 318 of the 397 patients (80.1%) seen in this period. The remaining 79 patients (19.8%) did not respond to the questionnaires: 46 patients stated that this was due to difficulties in understanding the German language, 11 were not interested, 2 did not understand the questions, and the remaining 20 individuals did not specify a reason for not answering.

Patients who responded to at least one of the questionnaires ($n = 318$) were compared with those patients who did not respond at all on the basis of gender, age, education, work, route of transmission, study center, stage of disease progression, presence and type of therapy, last CD4 count, viral load, body weight measurements before answering the questionnaire, number of months since HIV infection, and any hospitalization during the last 6 months. The only significant differences (χ^2 and Mann-Whitney U tests) were found for the group not responding being slightly younger ($p = .035$), less educated ($p < .001$), and infected more recently ($p = .001$). In addition, drug addicts were overrepresented in the survey ($p < .001$).

The distribution of all psychometric scores used is shown in Figure 1. The visual analog scale revealed that 50% of the population assessed their state of health as being <75 out of a possible best 100.

In the bivariate analysis (Table 2), the distribution of scores in relation to different patient characteristics is shown. People who had reached higher levels of education and were employed seemed to be less depressed, less anxious, and had better health-related quality of life scores. Intravenous drug users demonstrated significantly worse scores than individuals in other transmission categories, with the exception of depression. Pa-

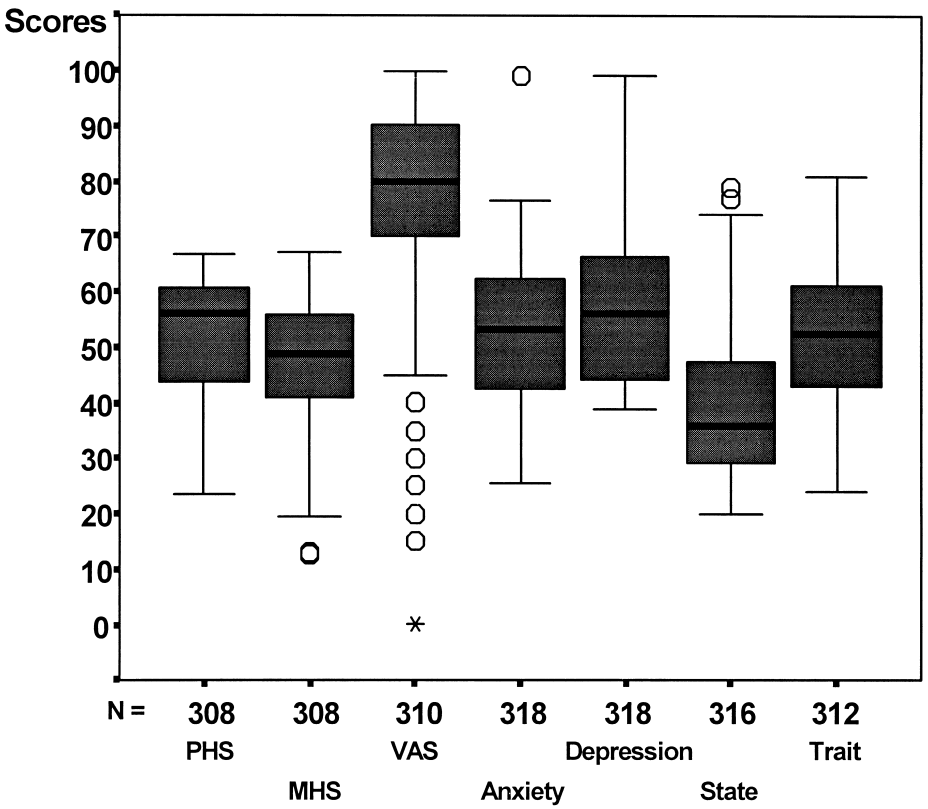

FIG 1. Distribution of psychometric questionnaire scores. *N* = number of respondents out of the total study population of 397 individuals; PHS and MHS, Physical and Mental Health Summary scores of the HIV-MOS; VAS, Visual Analogue Scale; anxiety and depression of the HADS; state and trait of STAI. The *y*-axis depicts the test scores. Higher values indicate a worse psychometric score, except for the PHS, MHS, and VAS. All T-scores are centered to 50 with a SD of ±10. This means that their distributions are concentrated on the positive axis around the value of 50. However, the "VAS" is defined over the entire interval of 0–100, whereas the scoring of the "State" is defined over the interval of 20–80. The box plots indicate the median, interquartile ranges (median ± 25%); *Open circles*, outliers; *asterisks*, extreme values.

TABLE 2. *Bivariate associations of psychometric scores for different patient characteristics (shown as* p *values)*

Questionnaire	Score	Gender men	Older age	Higher education	Employed	Risk group IVU	Longer HIV-duration	Disease stage B,C	HAART	Therapy type No. of drugs	Higher CD4 count	CD4 reduction >30%	CD4 increase >30%	Higher RNA count	RNA reduction >30%	RNA increase >30%	Weight loss	Hospital yes
PHS	Better			.040	<.001				.168	.423	.003		.591		.155			
	Worse	.859	.174			.004	.021	.001				.356		.004		.103	.004	.035
MHS	Better			.018	<.001				.074	.782	.034		.416		.149			
	Worse	.991	.586			.004	<.001	.223				.361		.006		.139	.007	.073
VAS	Better			.112	<.001				.130	.731	<.001		.499		.023			
	Worse	.166	.838			<.001	.001	.001				.1.03		<.001		.004	.031	.004
Anxiety-HADS	Better			.034	.002				.045	.881	.164		.341		.622			
	Worse	.672	.458			.067	.007	.287				.453		.012		.230	.384	.528
Depression-HADS	Better			.241	.002				.230	.439	.105		.854		.258			
	worse	.197	.457			.135	<.001	.307				.104		.050		.163	.012	.031
State-STAI	Better			.028	.006				.033	.934	.047		.595		.749			
	Worse	.513	.934			.035	.004	.245				.229		.030		.415	.118	.048
Trait-STAI	Better			.015	.007				.280	.918	.029		.113		.122			
	Worse	.099	.983			.004	.001	.301				.247		.037		.200	.027	.066

Bivariate associations (indicated as *p* values) measuring the association of scores versus the considered variable. For example, the groups of persons characterized by high education, working, high CD4 cell counts have significantly better PHS scores than persons with lower education, not working, or lower CD4 cell counts. PHS, Physical Health Summary Scores of the HIV-MOS; MHS, Mental Health Summary Scores of the HIV-MOS; VAS, Visual Analog Scale; HADS, Hospital Anxiety Depression Scale; HAART, highly active antiretroviral therapy; STAI, State Trait Anxiety Inventory; M, male sex; HIV duration in number of months. For definition of study parameters such as age, education, etc., see Methods section.

tients in more advanced stages of disease had lower Physical Health Summary scores on the HIV-MOS test and lower scores on the visual analog scale. Patients receiving treatment displayed less general anxiety (HADS) and less state anxiety (STAI). A longer duration of HIV infection (Fig. 2) and a change of body weight worsened scores in all assessed psychologic domains (Table 2). Hospitalization within the last 6 months was associated with higher scores for depression and diminished health-related quality of life. Individuals with higher CD4 counts had higher scores for health-related quality of life and on the visual analog scale and were less anxious as measured by the STAI. Those with higher viral loads scored lower in all assessed psychologic domains (Table 2). Neither gender nor age differences had a significant impact on a patient's psychometric score.

In the multivariate analysis (Table 3), possible associations between variables and scores were explored. An association was found for gender, with men displaying more state ($p = .035$) and trait ($p = .001$) anxiety than women and having lower scores on the visual analog scale ($p = .028$). A higher level of education was associated with lower levels of anxiety but not depression. Employment was associated with better scores for health-related quality of life (both Mental Health Summary and the Physical Health Summary scores) and on the visual analog scale ($p = .001$) and with less depression ($p = .020$). A longer duration of HIV infection was associated with diminished Mental Health Summary ($p = .002$) and visual analog scale ($p = .089$) scores, and with higher scores for anxiety (HADS, $p = .061$; STAI state, $p = .001$), and depression ($p = .027$) (Fig. 2). Lower viral load was associated with better functioning in all scores, except for the visual analog scale. Loss of weight at the last two measurements was associated with lower scores in all questionnaires, except for the HADS. Recent hospitalizations were negatively associated only with health-related quality of life (Physical Health Summary, $p = .015$; Mental Health Summary, $p = .009$), and visual analog scale scores ($p < .001$). The low coefficients of determination observed show that, despite extensive measurements with the nominated psychometric tools, important factors may not have been accounted for. An exception to this observation is the Physical Health Summary score, for which $R^2 = 0.424$. Disease stage, presence or type of therapy, and CD4 count showed no association with any score.

To examine whether anxiety, depression, or impairment of health-related quality of life had any influence on disease markers, we formed quartiles of psychometric scores and examined the course of CD4 cell counts, viral load, and weight (median follow-up time: 363 days; range, 20–689) for each of these quartiles. In the analyzed time period we could not identify any significant

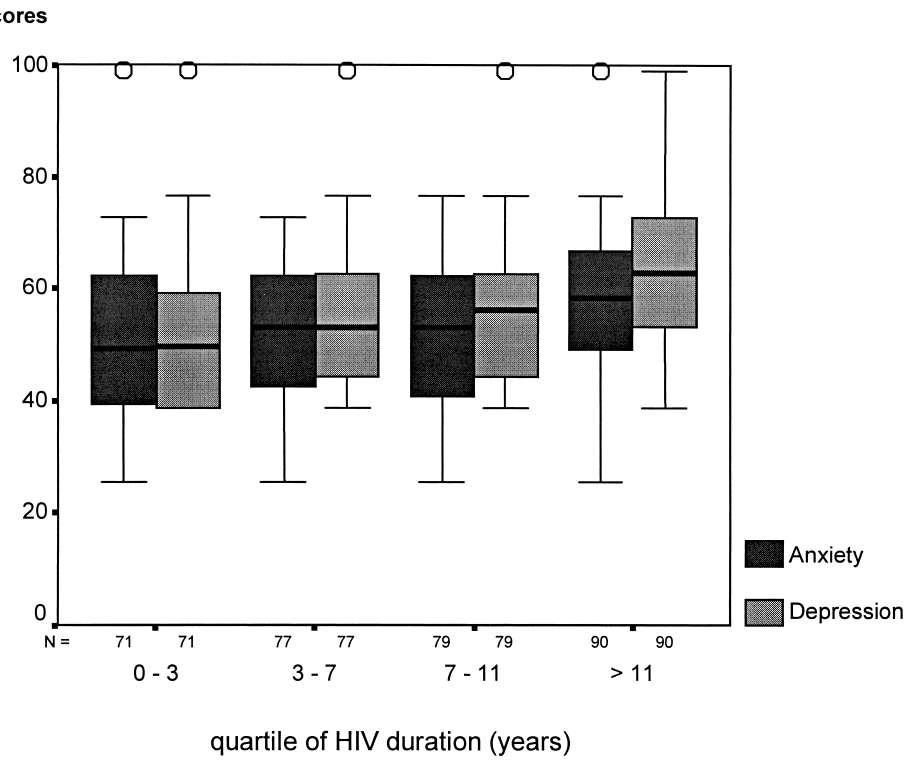

FIG 2. The relationship between Hospital Anxiety and Depression Scale (HADS) score and duration of HIV infection. *y*-axis: Scores of HADS. *x*-axis: number of patients and quartiles of length of HIV duration in years. The box plots indicate the median, interquartile ranges (median ± 25%); *Open circles*, outliers.

TABLE 3. *Association of social, clinical, virologic, and immunologic variables with psychometric scores multivariate variate regression analysis: coefficients and* p *values*

Questionnaire	BLV	Gender men	Higher education	Employed	Longer HIV-duration (*mo*)	RNA <400	RNA increase >30%	RNA weighted increase	Loss of weight	Hospital yes	R^2
PHS	45.527			9.927		3.501[a]		−0.00012	−2.933[b]	−3.886	.424
p value				<.001		.006		.007	.035	.015	
MHS	44.964		2.824	3.736	−.041	4.590[a]			−3.206[b]	−5.353	.214
p value			.056	.008	.002	.003			.066	.009	
VAS	78.454	−5.622	6.297	8.570	−.036		−6.001		−6.375[b]	−13.308	.255
p value		.028	.023	.001	.089		.032		.043	<.001	
Anxiety-HADS	55.934		−4.574		.028	−4.770					.070
p value			.009		.061	.003					
Depress-HADS	59.577			−4.508	.041	−4.535					.073
p value				.020	.027	.018					
State-STAI	38.602	3.453	−6.410		.050	−4.116[a]			4.486[b]		.134
p value		.035	<.001		.001	.001			.025		
Trait-STAI	50.806	6.364	−7.087		.057	−4.687[a]			4.605		.168
p value		<.001	<.001		<.001	.012			.026		

Multivariate regression analysis determining association of variables with psychometric scores. The results indicate that variables such as risk group or CD4 cell counts are not any longer associated with scores. The variable BLV is the average baseline value of the regarding score when a person does not belong to any of the categories defined by the nonzero values of the model. For example, a person who is working has about 10 points more for the PHS score than a person who is not working. For hospitalization the negative value of the coefficient shows that a hospitalized person has, on average, 4 points less for the PHS score than someone who has not been hospitalized. In the same way, undetectable viremia (RNA <400) results in a PHS score about 4 points higher than a viremic person, and short-term viremia increase or loss of weight implies a reduction of the PHS score. However, for these two variables only the sign and *p* value have to be interpreted; the amplitude of the coefficient should not be interpreted. PHS, Physical Health Summary Scores of the HIV-MOS; MHS, Mental Health Summary Scores of the HIV-MOS; VAS, Visual Analogue Scale; HADS, Hospital Anxiety Depression Scale; STAI, State Trait Anxiety Inventory; M, male sex. HIV duration in number of months. For definition of study parameters such as education, work, HIV-duration, see Methods section.

[a] Categories RNA < 400 and 401 ≤ RNA ≤ 5000 have been merged.

[b] Variable weighted by inverse time between two measures.

association between psychometric scores and assessed outcomes.

DISCUSSION

Potent antiretroviral therapy has significantly changed the clinical course of HIV infection by drastically lowering morbidity and mortality (1–3). HIV infection, even when well controlled, may be associated with important mental health problems. The most important findings of this analysis were that 1) validated screening tests showed anxiety and depression to be relevant, 2) there was a significant association between social parameters such as employment status and a patient's psychometric scores, 3) higher viral load was negatively associated with all scores, whereas lower CD4 counts were not and, importantly, 4) longer duration of disease, independent of other factors, was associated with anxiety and depression.

In the general population, estimates for point prevalences for mild anxiety and mild depression lie between 2% and 5% and 2% and 10%, respectively. In a survey investigating the population of Basel (25) (where many study participants live), 1-month and lifetime prevalences for a symptomatic depressive episode were about 1% and 4.5%, respectively. In comparison, hospitalized patients with cancer showed a prevalence of 13% for anxiety and of 9% for depression using the HADS (26). Most studies on HIV-infected persons, usually performed before HAART was introduced, assessed prevalences of psychiatric disorders such as major depression or anxiety disorders, finding remarkably high prevalences. Atkinson et al. (5) described lifetime rates of 39% for generalized anxiety disorder and 30% for major depression in ambulatory homosexual men. Lyketsos et al. (7) found that in HIV-infected patients attending a medical outpatient clinic, 46 of 50 of whom had never before received medical care for HIV infection, 54% suffered from a psychiatric disorder, a much higher percentage than in the general population. The setting of the latter trial was similar to this study. These and other studies discussed in the following indicate the importance of mental health assessment in HIV-infected persons.

Self-assessment screening questionnaires for depression or anxiety such as the HADS (22,23) and the STAI (24) have rarely been used for HIV-infected persons (10, 27,28). The tendency of high scores as shown in Figure 1 of anxiety, depression, and impaired health-related quality of life found in our study is striking, because the

population was comparatively healthy in terms of HIV disease markers, for example, with 59% having a viral load <400 copies/ml. The population in this study may more accurately represent HIV-infected outpatient populations, because many transmission groups are represented, with a high percentage of women. Also, more than 50% of individuals showed a good response to therapy. Many of the studies performed to date have investigated isolated groups of HIV-infected individuals, such as homosexual or bisexual men (5,10,12,27) with very few studying a wider patient population. Many of the studies on quality of life assessment, using for example the HIV-MOS (10,29–31), have focused on the impact of medical therapies of a defined population. An example is that depressive symptoms declined among persons on HIV protease inhibitors (32). Importantly, quality of life benefit was reported to be higher in symptomatic patients (33). In the bivariate analysis we found that almost all scores were worse for intravenous drug users compared with other transmission groups, although no clear association was found in the multivariate analysis. As shown in the multivariate analysis, our results also indicate that men were more anxious and perceived their health status as worse. This is in contrast to an earlier study that showed that HIV-infected women were more distressed than men (34). These findings stress the need to develop specific assessment and intervention that is gender-specific.

In this study of the Swiss HIV Cohort Study, there was a significant correlation between biosocial factors and psychologic parameters, with lower education and unemployment associated with higher scores for anxiety and depression, respectively. Accordingly, multivariate analysis in a study by Dickey et al. (35) showed that homosexual men who were not in full-time employment were likely to have higher levels of psychiatric symptoms. A longitudinal study by Swindells et al. (9) found that employment but not education was associated with health-related quality of life. Less social support and more cumulative depressive symptoms have also been described as linked to a faster progression to AIDS (36). Other authors, however, found no evidence that depressive symptoms are an independent prognostic factor for worse outcomes of HIV infection (37). Our results support these latter findings, because we found no association of psychometric results with disease markers in the follow-up. The lack of association between different psychometric scores and measured outcomes could primarily be due to the rather short follow-up in our study.

A longer duration of disease per se was associated with higher levels of both anxiety and depression. Many people who do well physically may nevertheless encounter problems when their circumstances change. However, these problems may not always be recognized by physicians (38). In our experience the optimistic atmosphere when talking with a patient about successful long-term treatment (in particular about CD4 and RNA values) may make it difficult to address in particular anxiety and depression as well as health-related quality of life issues. We found that short-term change in CD4 count had no association with anxiety, depression, or health-related quality of life. In accordance with this finding, an Australian group found that CD4 count did not predict state or trait anxiety or depression (39). Also, psychologic adjustment to illness was found to be associated with physical limitations rather than with laboratory markers (40). However, in this study, increases in viral load seemed to be particularly harmful to physical well-being. Our findings are supported by a recent randomized prospective trial that demonstrated that quality of life assessment may be discordant with conventional clinical end points (29). Also, improvement of health-related quality of life was associated with nonclinical end points (i.e., lower initial viral load and with increases in CD4 counts) (41). In multivariate analyses of 2864 HIV-infected individuals, HIV-related symptoms were strongly associated with physical and mental health, whereas race, gender, health insurance status, disease stage, and CD4 count were at most weakly associated with physical and mental health (42). Several symptoms were described to be associated with worse health-related quality of life and more disability days in persons with HIV infection (e.g., pain in the mouth, lips, or gums were associated with worse perceived health) (43). Taken together these findings indicate that care of HIV-infected patients should on the one hand target disease-related symptoms and on the other hand psychosocial well-being, in particular long-term care.

Interestingly, in this study of the Swiss HIV Cohort, the presence or type of medication was not linked with anxiety, depression, or health-related quality of life. Previous data from the Swiss HIV Cohort Study have suggested that initiation of antiretroviral therapy is influenced by social factors, in particular at early time points of HIV infection when therapy may not be absolutely indicated (44). When interpreting the findings of the current study, one might speculate that HIV-infected individuals not receiving therapy were most often not severely immunodeficient and hence did not encounter major medical or social problems; conversely, patients now receiving therapy may have gained health-related quality of life during recent years.

A potential limitation of this study is that possible short-term problems encountered by patients that may

have influenced their responses were not specifically addressed. There was no clinical psychiatric judgment included in this analysis; however, because the validated questionnaires used are for assessment of patients in a medical setting, we believe that the findings of this study accurately reflect the situation of HIV-infected outpatients. Nevertheless, complex mental states such as anxiety or depression cannot be completely evaluated, despite careful selection of a wide variety of biosocial parameters for analysis. The question of how the used tests relate to each other is beyond the scope of this article but will be investigated in a further analysis. It must also be noted that not all of this study group completed the questionnaires, mostly because of language difficulties. It is difficult to judge the direction of any possible bias, for instance the population analyzed may have better scores for anxiety and depression according to education but lower scores according to route of transmission and duration of HIV infection. This study was conducted in 2 of 7 clinical Centers of the Swiss HIV Cohort Study. The demographics of the investigated patients are very similar to the entire cohort (13). Despite the fact that individuals followed in the Swiss HIV Cohort Study represent a large percentage of clinically followed HIV-infected persons in Switzerland, it may be that individuals followed at Cohort Centers are more aware and possibly more sensible about the implications of HIV infection than HIV-infected individuals not seeking medical assistance in such a setting.

In summary, this study demonstrates that HIV infection remains a serious psychologic burden, despite the dramatic reduction of morbidity and mortality in recent years, which has been attributed to antiretroviral therapy. Patients are prone to anxiety and depression, and long-term care must address the social and mental health problems of HIV-infected individuals (45). Such measures may enhance adherence to antiretroviral medication (46), as well as enabling and supporting coping strategies. Since completion of this analysis, treatment practice at the involved centers has been changed to include more thorough discussion with patients on their mental well-being. This has been found to be beneficial to patient care and warrants further study in controlled trials to determine whether and to what extent this can positively influence clinical outcome.

APPENDIX

Members of the Swiss HIV Cohort Study include R. Amiet, M. Battegay (Chairman of the Scientific Board), E. Bernasconi, H. Bucher, Ph. Bürgisser, M. Egger, P. Erb, W. Fierz, M. Flepp (Chairman of the Clinical and Laboratory Committee), P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011- Lausanne), H.J. Furrer, M. Gorgievski, H. Günthard, P. Grob, B. Hirschel, Th. Klimkait, B. Ledergerber, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, W. Pichler, J.-C. Piffaretti, M. Rickenbach (Head of Data Center), C. Rudin, P. Sudre, V. Schiffer, J. Schupbach, A. Telenti, P. Vernazza, R. Weber.

Acknowledgments: This study has been financed by the Swiss Federal Office of Public Health (Grant no. 3600.010.1), the Swiss National Science Foundation (Grant no 3345–062041), and an unrestricted educational grant by Abbott Switzerland. We would like to thank all the patients who participated in this study and the many doctors who cared for these patients. The authors thank Niklaus Gyr for valuable discussion of the manuscript and Michèle Girard for her excellent secretarial assistance.

REFERENCES

1. Egger M, Hirschel B, Francioli P, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study. *BMJ* 1997;315:1194–9.
2. Palella FJJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338:853–60.
3. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. *Lancet* 1999;353:863–8.
4. Murphy JM, Sobol AM, Neff RK, et al. Stability of prevalence. Depression and anxiety disorders. *Arch Gen Psychiatry* 1984;41: 990–7.
5. Atkinson JH Jr, Grant I, Kennedy CJ, et al. Prevalence of psychiatric disorders among men infected with human immunodeficiency virus. A controlled study. *Arch Gen Psychiatry* 1988;45:859–64.
6. Maj M. Depressive syndromes and symptoms in subjects with human immunodeficiency virus (HIV) infection. *Br J Psychiatry* 1996;168 (Suppl 30):117–22.
7. Lyketsos CG, Hanson A, Fishman M, et al. Screening for psychiatric morbidity in a medical outpatient clinic for HIV infection: the need for a psychiatric presence. *Int J Psychiatry Med* 1994;24: 103–13.
8. Holland JC, Tross S. The psychosocial and neuropsychiatric sequelae of the acquired immunodeficiency syndrome and related disorders. *Ann Intern Med* 1985;103:760–4.
9. Swindells S, Mohr J, Justis JC, et al. Quality of life in patients with human immunodeficiency virus infection: impact of social support, coping style and hopelessness. *Int J STD AIDS* 1999;10:383–91.
10. Burgess A, Dayer M, Catalan J, et al. The reliability and validity of two HIV-specific health-related quality-of-life measures: a preliminary analysis. *AIDS* 1993;7:1001–8.
11. Krikorian R, Kay J, Liang WM. Emotional distress, coping, and adjustment in human immunodeficiency virus infection and acquired immune deficiency syndrome. *J Nerv Ment Dis* 1995;183: 293–8.
12. Rabkin JG, Ferrando SJ, Jacobsberg LB, et al. Prevalence of axis I disorders in an AIDS cohort: a cross-sectional, controlled study. *Compr Psychiatry* 1997;38:146–54.
13. Sudre P, Rickenbach M, Taffe P, et al. Clinical epidemiology and research on HIV infection in Switzerland: The Swiss HIV Cohort Study 1988–2000. *Schweiz Med Wochenschr* 2000;130:1493–500.

14. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep* 1992;41:1–19.
15. Wu AW, Hays RD, Kelly S, et al. Applications of the Medical Outcomes Study health-related quality of life measures in HIV/AIDS. *Qual Life Res* 1997;6:531–54.
16. Wu AW, Revicki DA, Jacobson D, et al. Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). *Qual Life Res* 1997;6:481–93.
17. Revicki DA, Sorensen S, Wu AW. Reliability and validity of physical and mental health summary scores from the Medical Outcomes Study HIV Health Survey. *Med Care* 1998;36:126–37.
18. Wu AW, Jacobson DL, Berzon RA, et al. The effect of mode of administration on medical outcomes study health ratings and EuroQol scores in AIDS. *Qual Life Res* 1997;6:3–10.
19. Zander KJ, Palitzsch M, Kirchberger I, et al. HIV infection and health related quality of life: psychometric testing of the German version of the "MOS-HIV" questionnaire. *AIDS-Forschung (AIFO)* 1994;9:241–9.
20. The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
21. Nord E. EuroQol©: health-related quality of life measurement. Valuations of health states by the general public in Norway. *Health Policy* 1991;18:25–36.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
23. Herrmann C, Buss U, Snaith R. HADS-D Hospital Anxiety and Depression Scale—Deutsche Version. *Testdokumentation und Handanweisung* Bern: Verlag Hans Huber, 1995.
24. Spielberger C, Gorsuch R, Lushene R. *Manual for the State-Trait Anxiety Inventory.* Palo Alto, CA: Consulting Psychologists Press, 1970.
25. Wacker H. Angst und Depression—*Eine epidemiologische Untersuchung.* Bern: Verlag Hans Huber, 1995.
26. Aass N, Fosså SD, Dahl AA, et al. Prevalence of anxiety and depression in cancer patients seen at the Norwegian Radium Hospital. *Eur J Cancer* 1997;33:1597–604.
27. Jadresic D, Riccio M, Hawkins DA, et al. Long-term impact of HIV diagnosis on mood and substance use—St. Stephen's cohort study. *Int J STD AIDS* 1994;5:248–52.
28. Savard J, Laberge B, Gauthier JG, et al. Evaluating anxiety and depression in HIV-infected patients. *J Pers Assess* 1998;71: 349–67.
29. Bucciardini R, Wu AW, Floridia M, et al. Quality of life outcomes of combination zidovudine-didanosine-nevirapine and zidovudine-didanosine for antiretroviral-naive advanced HIV-infected patients. Instituto Superiore di Sanita 047 Study. *AIDS* 2000;14: 2567–74.
30. Zinkernagel C, Ledergerber B, Battegay M, et al. Quality of life in asymptomatic patients with early HIV infection initiating antiretroviral therapy. Swiss HIV Cohort Study. *AIDS* 1999;13:1587–9.
31. Revicki DA, Moyle G, Stellbrink H-J, et al. Quality of life outcomes of combination zalcitabine-zidovudine, saquinavir-zidovudine, and saquinavir-zalcitabine-zidovudine therapy for HIV-infected adults with CD4 cell counts between 50 and 350 per cubic millimeter. PISCES (SV 14604) Study Group. *AIDS* 1999; 13:851–8.
32. Low-Beer S, Chan K, Wood E, et al. Qual Health related quality of life among persons with HIV after the use of protease inhibitors. *Life Res* 2000;9:941–9.
33. Nieuwkerk PT, Gisolf EH, Colebunders R, et al. Quality of life in asymptomatic- and symptomatic HIV infected patients in a trial of ritonavir/saquinavir therapy. The Prometheus Study Group. *AIDS* 2000;14:181–7.
34. Kennedy CA, Skurnick JH, Foley M, et al. Gender differences in HIV-related psychological distress in heterosexual couples. *AIDS Care* 1995;7(Suppl 1):33–8.
35. Dickey WC, Dew MA, Becker JT, et al. Combined effects of HIV-infection status and psychosocial vulnerability on mental health in homosexual men. *Soc Psychiatry Psychiatr Epidemiol* 1999;34:4–11.
36. Leserman J, Jackson ED, Petitto JM, et al. Progression to AIDS: the effects of stress, depressive symptoms, and social support. *Psychosom Med* 1999;61:397–406.
37. Lyketsos CG, Hoover DR, Guccione M, et al. Depressive symptoms as predictors of medical outcomes in HIV infection. Multicenter AIDS Cohort Study. *JAMA* 1993;270:2563–7.
38. Fontaine A, Larue F, Lassaunière J-M. Physicians' recognition of the symptoms experienced by HIV patients: how reliable? *J Pain Symptom Manage* 1999;18:263–70.
39. Perdices M, Dunbar N, Grunseit A, et al. Anxiety, depression and HIV related symptomatology across the spectrum of HIV disease. *Aust N Z J Psychiatry* 1992;26:560–6.
40. Griffin KW, Rabkin JG, Remien RH, et al. Disease severity, physical limitations and depression in HIV-infected men. *J Psychosom Res* 1998;44:219–27.
41. Weinfurt KP, Willke RJ, Glick HA, et al. Relationship between CD4 count, viral burden, and quality of life over time in HIV-1-infected patients. *Med Care* 2000;38:404–10.
42. Hays RD, Cunningham WE, Sherbourne CD, et al. Health-related quality of life in patients with human immunodeficiency virus infection in the United States: results from the HIV Cost and Services Utilization Study. *Am J Med* 2000;108:714–22.
43. Lorenz KA, Shapiro MF, Asch SM, et al. Associations of symptoms and health-related quality of life: findings from a national study of persons with HIV infection. *Ann Intern Med* 2001;134: 854–60.
44. Bassetti S, Battegay M, Furrer H, et al. Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued? Swiss HIV Cohort Study. *J Acquired Immune Defic Syndr* 1999; 21:114–9.
45. Sherbourne CD, Hays RD, Fleishman JA, et al. Impact of psychiatric conditions on health-related quality of life in persons with HIV infection. *Am J Psychiatry* 2000;157:248–54.
46. Singh N, Berman SM, Swindells S, et al. Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy. *Clin Infect Dis* 1999;29:824–30.