Progression to AIDS: The Effects of Stress, Depressive Symptoms, and Social Support

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infection. **Methods:** Eighty-two HIV-infected gay men without symptoms or AIDS at baseline were followed up every 6 months for up to 5.5 years. Men were recruited from rural and urban areas in North Carolina as part of the Coping in Health and Illness Project. Disease progression was defined using criteria for AIDS ($CD4^+$ lymphocyte count of $<200/\mu l$ and/or an AIDS-indicator condition). **Results:** We used Cox regression models with time-dependent covariates, adjusting for age, education, race, baseline $CD4^+$ count, tobacco use, and number of antiretroviral medications. Faster progression to AIDS was associated with more cumulative stressful life events ($p = .002$), more cumulative depressive symptoms ($p = .008$), and less cumulative social support ($p = .0002$). When all three variables were analyzed together, stress and social support remained significant in the model. At 5.5 years, the probability of getting AIDS was about two to three times as high among those above the median on stress or below the median on social support compared with those below the median on stress or above the median on support, respectively. **Conclusions:** These data are among the first to demonstrate that more stress and less social support may accelerate the course of HIV disease progression. Additional study will be necessary to elucidate the mechanisms that underlie these relationships and to determine whether interventions that address stress and social support can alter the course of HIV infection. **Key words:** HIV, AIDS, stress, social support, depression.

HIV = human immunodeficiency virus; HDRS = Hamilton Depression Rating Scale; CDC = Centers for Disease Control and Prevention.

INTRODUCTION

There is growing evidence that psychosocial factors, such as stress and depression, may have a harmful impact on the outcome of a variety of diseases (1–6). For example, among cancer patients, severe life stress has been associated with a greater probability of relapse (5), and psychosocial interventions to improve coping with stress have resulted in longer survival (3, 4). Although there is evidence that stress and depression may impair cellular immunity (7–12), the clinical relevance of these alterations has not been established in HIV.

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Given the multifactorial nature of HIV disease, and the wide variability in the progression of HIV infection, recent studies have examined the impact of psychological variables on the course of this disease (13–21). We found stress-associated reductions in killer lymphocytes in HIV-infected men at baseline (16) and recently reported that severe stress and depressive symptoms were related to declines in several lymphocyte subsets over a 2-year period (20). Furthermore, we found that severe stress was associated with a greater risk of early HIV disease change in men studied for up to 3.5 years (21). For the investigation described in this report, we followed the same cohort for up to 5.5 years to examine the effects of stress, depressive symptoms, and social support on progression to AIDS.

Findings on the importance of stress and depression in predicting decline in immune status and disease course have been inconsistent. In one meta-analysis, depressive symptoms, but not stressors, were shown to be longitudinally related to self-reported symptoms of HIV infection (17). Furthermore, neither stress nor depressive symptoms were related to changes in $CD4^+$ lymphocyte numbers in peripheral blood or other commonly accepted markers of HIV disease progression. Stress, however, was associated with declines in natural killer cell cytotoxicity and numbers of natural killer cells, a finding consistent with those of our recent studies (16, 20). The mixed findings in the meta-analysis may be explained by the cited studies having short follow-up periods and measuring depressive symptoms only at baseline rather than making repeated assessments more proximal to disease change.

More recent studies, conducted over longer time intervals, have found significant relationships be-

tween depressive symptoms and HIV disease progression. In the San Francisco Men's Health Study, a 9-year longitudinal study of seropositive men, researchers found that higher levels of depression at entry were associated with faster progression to AIDS (19). Median time to first AIDS diagnosis was 6.2 years for those who were depressed at baseline, compared with 7.6 years for those who were not depressed. These findings at 9 years are at odds with earlier data at 5 years from the same cohort. The earlier data showed no relationship between baseline depression and AIDS diagnosis, although an association between depression and decline in $CD4^+$ lymphocytes was found at this time point (14). In another recent analysis of the same cohort, researchers found that those who had elevated depression symptoms at every visit had a 1.7 times greater risk of mortality compared with those who never had an elevated depression score (18).

An initial analysis from the Multicenter AIDS Cohort Study found no relationship between depression at study entry and progression of HIV infection, defined as time to AIDS, death, or decline in $CD4^+$ lymphocytes (15). In later analyses of these data, researchers found that self-reported depressive symptoms seemed to rise 1.5 years before AIDS diagnosis (22). The researchers interpret these findings as an indication that depression may increase toward the later stages of HIV infection and thus be a manifestation of the disease process. A subsequent survival analysis of these data, however, using level of depressive symptoms during the 6 months before AIDS diagnosis, showed no relationship between depression and time to death (23).

Fewer studies have examined the impact of stress and social support on disease progression. In previous analyses of our cohort, we showed that the risk of early HIV disease progression was doubled with every severe stressor per 6-month study interval (21). Stress was measured by interview using ratings based on the context or specific circumstances surrounding the events or difficulties. In addition, we found that stress and depressive symptoms, especially in combination, were associated with decreases in natural killer and $CD8^+$ cytotoxic T lymphocyte numbers, but not declines in number of $CD4^+$ T-helper cells, from entry to 2-year follow-up (20). Using a similar interview-based stress rating to that used in the present study, the San Diego Neurobehavioral HIV Center found that those who reported no severe life stress and few depressive symptoms had less decline in the percentage of $CD4^+$ lymphocytes after 6 months compared with those with higher scores on these psychological risk factors (24). Similarly, Ironson et al. (25) found that men with greater distress at the time of HIV serostatus notification had a greater chance of developing HIV-related clinical symptoms at 2-year follow-up. Another study showed that the stress of bereavement before study entry was associated with more rapid decline in $CD4^+$ count over 3 to 4 years (26). It is noteworthy that studies using short follow-up periods and/or questionnaire methods to assess life stress have not shown an association of stress with reduction in $CD4^+$ lymphocyte counts over time (27–29).

Studies that have examined the effects of social support on HIV disease progression are lacking. In a small study of hemophiliac patients, those with less social support had faster deterioration in $CD4^+$ lymphocyte counts over a 5-year period (30). Another study showed that HIV-infected subjects were more likely to become symptomatic after 6 months if they had less social support, but only among those with low initial $CD4^+$ lymphocyte counts (31).

In this article, we report findings in a cohort of gay men studied every 6 months for up to 5.5 years. We hypothesized that higher scores on measures of depression, more stressful life events, and less social support would put men at greater risk for faster HIV disease progression to AIDS. The study design included several notable features: (1) stressful life events were based on contextual ratings from a semistructured interview, (2) time-dependent covariates in survival analysis were used to assess psychosocial effects on disease progression, (3) subjects were followed prospectively for up to 5.5 years, and (4) none of our subjects were taking protease inhibitors before disease change—(protease inhibitors are the most effective medical treatment for preventing HIV viral replication).

METHODS

Study Group

Data were collected in North Carolina as part of an ongoing longitudinal study, the Coping in Health and Illness Project. The study was approved by the University of North Carolina School of Medicine Committee for the Protection of the Rights of Human Subjects, and all subjects provided written informed consent. The study group included 82 HIV-infected gay men recruited from rural and urban areas of North Carolina from 1990 to 1992. All subjects were clinically asymptomatic with $CD4^+$ lymphocyte counts above $200/\mu l$ at study entry. Men were assessed at 6-month intervals for up to 5.5 years (12 visits). All subjects had at least two visits (mean number of visits = 8.52, SD = 2.99).

All volunteers were screened to exclude from initial participation those with (1) less than 10 years of education; (2) age of less than 18 or more than 50 years; (3) previous intravenous drug use; (4) significant medical illness (eg, heart, lung, or kidney disease); (5) preexisting neurological disorder or trauma (eg, head injury, stroke, or seizures); (6) past treatment for alcoholism or current heavy alcohol use (>60 drinks per month); (7) present or past heavy recreational drug use; (8) use of zidovudine or other antiretroviral

medications; and (9) HIV-related symptoms, that is, those meeting the 1987 CDC criteria for AIDS or AIDS-related complex (32) (eg, night sweats; herpes zoster; oral candidiasis; hairy leukoplakia; shingles; unexplained temperature, diarrhea, weight loss, or fatigue in the presence of other symptoms).

Procedure

Subjects were evaluated every 6 months at the General Clinical Research Center at the University of North Carolina, Chapel Hill. Subjects underwent systematic medical, neurological, neuropsychological, and psychiatric assessments performed by specialists in these areas. All subjects were asked to abstain from over-the-counter medications known to affect immune response, recreational drugs, and alcohol consumption for at least 2 weeks before each study visit; we did not perform a toxicology screen to confirm compliance.

At each visit, subjects took nothing by mouth starting at midnight before blood was drawn the next morning. Subjects were recumbent, and an intravenous line was started at 8:00 AM in an antecubital vein, which was kept patent with a slow normal saline drip. To control for circadian effects, and the possibility of acute stress reaction from insertion of the intravenous line, blood was drawn after 70 minutes of rest after line placement (33).

Measurement

All psychological, psychosocial, and medical variables were measured every 6 months, except social support, which was assessed yearly. To take advantage of the data gathered at each time point, we used survival analysis with time-dependent covariates, as explained in the statistical section of this article. For more details on the measures, see our previous articles (16, 20).

Depression

To determine whether subjects had a major depression during each 6-month interval, all men underwent a structured psychiatric interview (modified Structured Clinical Interview for DSM-III-R Disorders) (34); diagnoses were assigned at consensus diagnostic conferences (35). Severity of depressive symptoms was measured with the interviewer-based HDRS (36). We eliminated six of the 17 medical symptom items (eg, somatic symptoms, weight loss, and retardation) that overlapped with symptoms of HIV disease to help avoid confounding the measure with disease progression. In a previous article, we reported a high correlation between the original scale (HDRS-17) and the 11-item version (HDRS-11) (20). Higher scores on the HDRS-11 indicated more depressive symptoms during the previous week.

Stressful Life Events

To obtain information about stressful life events and difficulties, we modified the semistructured interview, the Psychiatric Epidemiology Research Interview (37). Subjects indicated which of the 111 stresses they had experienced during the preceding 6 months. Interviewers questioned subjects in detail about the context of endorsed events (discrete incidents, eg, losing a job, a death, or relationship breakup) and difficulties (chronic stresses occurring over a 1-month period or more, eg, financial difficulties, caretaking, or ongoing conflict at work). Stresses were objectively rated using a manual of norms and vignettes, a methodology similar to that developed by Brown and Harris (38) and modified by Patterson et al. (24) and Grant et al. (39). Norms for each stress were based on the degree of threat that most people would experience given the particular circumstances (eg, financial impact, degree of control, life threat, and personal involvement). The objective threat rating was made independent of the subject's rating and his way of coping with the stress, to reduce the possibility that worsening disease led to poorer coping and higher stress scores.

One of two trained raters (previously shown to have high interrater reliability) (16) used the manual to rate, from 0 (no threat) to 4 (severe threat), the long-term impact (1 week after the event) of each stressful event and the threat associated with each difficulty. All ratings for each stressful event and difficulty were summed at each visit, except that we removed those stresses that we knew were likely to be caused by disease progression (eg, drop in $CD4^+$ count or retirement due to HIV worsening).

Social Support

To assess the degree of satisfaction with social support, we administered the Sarason Brief Social Support Questionnaire (40) on a yearly basis (Cronbach's α at baseline = 0.89) (41). The scale can range from 1 (very dissatisfied with the support received) to 6 (very satisfied). Support scores from the previous yearly interval were used to estimate scores at each 6-month visit. The correlation between visits 1 year apart ranged from 0.40 to 0.68. The Sarason Brief Social Support Questionnaire also allows for quantification of number of support persons.

Disease Status

All of the men knew their HIV status at baseline, which was based on enzyme-linked immunosorbent assay screening with Western blot analysis for confirmation of the presence of anti-HIV antibodies. We defined disease progression as the first time point when a subject met the CDC AIDS surveillance case definition (42), that is, reduction in $CD4^+$ lymphocytes to below 200/μl and/or presence of an AIDS-indicator condition (clinical stage C). A comprehensive physical examination was performed every 6 months by a clinician trained to assess HIV disease stages. Peripheral blood $CD4^+$ lymphocyte counts were performed by flow cytometry using commercially prepared monoclonal antibodies (Becton Dickinson, Mountain View, CA). Absolute $CD4^+$ count was derived from $CD4^+$ cell percentages $\times$ total lymphocytes $\times$ 100.

Control Variables

We assessed the number of antiretroviral medications used (eg, zidovudine, dideoxyinosine, and dideoxycytidine) every 6 months. No subjects were on antiretroviral medication at study entry; however, the number of antiretroviral medications used ranged from zero to three during the study. Age, years of education, race (nonwhite or white), and use of tobacco (presence or absence) were obtained at baseline by questionnaire.

Statistical Methods

We computed descriptive statistics and performed t tests (χ^2 for race and tobacco use) for all baseline control variables, comparing those who progressed to AIDS with those who did not. Kaplan-Meier estimates and log rank tests were obtained to estimate the survival probability for psychological and psychosocial variables, which were grouped by dividing subjects at the median on their average scores for these variables. Averages were computed using all time points before the visit when AIDS was diagnosed or using all available time points for those without AIDS.

Cox regression models with time-dependent covariates (SAS procedure PROC PHREG with the EXACT method for handling ties) (43) were used to calculate the risk of AIDS associated with each psychosocial variable. We used time-dependent covariates at regular intervals for number of antiretroviral medications, stressful life events, depression, depressive symptoms, and social support. Because we hypothesized that these variables might have an additive effect on disease progression, we used cumulative averages of the measures. The time-dependent scores at each visit were based on the average of scores before that visit if progression to AIDS occurred at that visit; for subjects who had not progressed at that visit, we used the average of scores up to and including that visit. For example, a subject's stress score at visit 3 was the average of scores for visits 1 and 2 if AIDS was diagnosed at visit 3; for those who had not progressed at this visit, stress scores were the average of visits 1 through 3. All survival analyses were done adjusting for the following variables: number of antiretroviral medications, treated as a time-dependent covariate, and baseline age, years of education, race, $CD4^+$ count, and tobacco use. We first fit the model with only control variables. Next, we examined the effect of each psychosocial variable separately, adjusting for control variables. We first examined psychosocial variables separately because the correlations between psychosocial variables might obscure some of the findings. Finally, we fit the model with psychological and psychosocial variables entered simultaneously with control variables.

For the small number of men who missed visits but continued to participate in the study, these missing data points were estimated from the previous 6-months data. We checked the proportionality assumption of the time-independent variables by testing the statistical significance of the interactions between those variables and follow-up time; none were significant. We checked the linearity of the covariate effects by adding in the squared term of each covariate; the squared term was always nonsignificant. We also checked for outliers by examining the distributions of depressive symptoms and stressful life events as well as performing square root transformations on depressive symptoms; outliers did not account for our results. Because of our strict initial exclusion criteria, we had so few men with DSM-III-R alcohol dependence ($N = 6$) or drug dependence ($N = 1$) that we were unable to evaluate the effects of these variables.

RESULTS

At entry, the 82 men were an average of 30.3 years old (SD = 5.9 years) and had an average of 14.3 years of education (SD = 2.4 years). Seventy-nine percent were white; all but one of the nonwhites were African American. At the beginning of the study, all men were clinically asymptomatic (CDC stage A1 or A2) with a mean $CD4^+$ lymphocyte count of 397.4 (SD = 133.6).

During the study, 33% progressed to AIDS; the average time to AIDS progression was 2.6 years (SD = 1.4 years). The average length of time in the study was 3.6 years (SD = 1.7 years) for those without AIDS. The number of men studied at 1, 2, 3, 4, 5, and 5.5 years was 77, 69, 62, 55, 21, and 13, respectively. The last year had far fewer men because many had not been scheduled for their 5-year visit. Only eight of the 82 (9.8%) men died of HIV-related causes during this 5.5-year period. The mean stress scores at all visits ranged from 3.0 to 9.9 (range of individual scores = 0–23). The mean depressive symptoms scores at all visits ranged from 1.5 to 2.5 (range of individual scores = 0–21). The mean social support scores at all visits ranged from 4.9 to 5.2. No subjects were taking protease inhibitors before diagnosis of AIDS or before study participation ended for those without disease change.

Table 1 provides descriptive information about the baseline control variables, comparing men who progressed to AIDS to those without AIDS. There were no statistically significant differences between those with and without AIDS in race, age, education, and tobacco use. As expected, men who developed AIDS tended to have lower $CD4^+$ lymphocyte counts at baseline than men who did not progress.

Survival analysis techniques were used to show the simultaneous effects of control variables on HIV progression to AIDS (Table 2). Race and baseline $CD4^+$ lymphocyte count were significant predictors of AIDS diagnosis. White men had five times the risk of developing AIDS compared with nonwhite men. For every 1-cell/μl decrease in $CD4^+$ T-helper cell count at baseline, the risk of developing AIDS increased by about 1%. Likewise, for every 100-cell/μl decrease in $CD4^+$ T-helper cell count, a man had slightly more than a two-fold increased risk of AIDS. Note that age, years of education, tobacco use, and number of antiretroviral medications were not significant in predicting disease progression.

Figures 1, 2, and 3 show the Kaplan-Meier estimates of the distributions of time until AIDS diagnosis, dividing subjects by the medians of stressful life events (median = 5.4), depressive symptoms (median = 1.65), and social support (median = 5.15). There were significant differences between the survival distributions based on grouped data for stress ($p = .01$), depressive symptoms ($p = .007$), and social support ($p =$

TABLE 1. Descriptive Data on Control Variables at Entry by Disease Progression Status

Control Variables at Entry	AIDS Progression		
	With AIDS ($N = 27$)	Without AIDS ($N = 55$)	p[a]
Race (% white)	88.9	74.5	.13
Age (yr)[b]	30.1 ± 5.2	30.3 ± 6.3	.87
Education (yr)[b]	14.3 ± 2.3	14.1 ± 2.5	.70
$CD4^+$ lymphocyte count (cells/μl)[b]	337.9 ± 97.4	426.7 ± 139.9	.001
Tobacco use (% yes)	44.4	41.8	.82

[a] p values for age, education, and $CD4^+$ lymphocyte count were based on t tests comparing those with AIDS with those without AIDS; p for race and tobacco use were based on χ^2 tests.
[b] Mean ± SD.

TABLE 2. Cox Regression Model: Hazard of AIDS Diagnosis With Control Variables[a]

	β	p	Hazard Ratio	95% Confidence Interval
Age	−0.02	.51	0.98	0.91–1.05
Education	−0.05	.61	0.95	0.78–1.16
Race[b]	1.61	.01	5.01	1.37–18.33
Baseline $CD4^+$ count (cells/μl)	−0.01	.0003	0.99	0.99–1.00
Tobacco use[c]	0.23	.61	1.26	0.52–3.04
Number of antiretrovirals	−0.11	.83	0.90	0.33–2.43

[a] Results are from a Cox regression model with number of antiretroviral medications used (0 to 3) as a time-dependent covariate using cumulative proportions. Other variables are baseline measures. All variables were simultaneously entered into the models. β refers to the unstandardized regression coefficient estimate.
[b] 0 = nonwhite; 1 = white.
[c] 0 = no; 1 = yes.

.008) but not for major depression (p = .13). At 66 months, those below the median on stressful life events had a 28% higher probability of being free of AIDS compared with those above the median. Likewise, those below the median on depressive symptoms at 66 months had a 39% higher probability of being free of AIDS compared with those above the median at that time. Finally, at 66 months, those above the median on social support had a 40% higher probability of being free of AIDS compared with those below the median.

Table 3 shows the separate effects of each psychological and psychosocial variable (as time-dependent covariates) on the risk of progressing to AIDS, adjusting for control variables. For each 1-point increase in cumulative average stressful life events (range of cumulative averages from 0 to 23), the risk of AIDS progression increased by 21%. For every 4-point increase in average stressful life events, the equivalent of one severe stressor or two moderate stressors, the risk of AIDS was doubled.

For each 1-point increase in cumulative average depressive symptoms (HDRS-11) (range of cumulative average = 0–11.7), there was a 30% increased risk of AIDS. Likewise, for every 3-point increase in average depressive symptoms, the equivalent of one severe symptom, the risk of AIDS progression doubled. Identical results were found using the original HDRS-17. Although not significant, there was a trend for major depression to be associated with faster AIDS progression. Having at least one major depression (before disease progression or end of study participation) was more common among those with AIDS (33.3%) compared with those without AIDS (16.4%) (χ^2 = 3.04, p = .08).

Table 3 also shows that for each point increase in cumulative average social support satisfaction (range of cumulative average = 2.3–6.0), the risk of AIDS progression decreased by 63%. Stated another way, with each 1-point decrease in cumulative average social support satisfaction, the risk of AIDS increased 2.7 times. Number of social support persons was unrelated to AIDS progression.

In the last step, we tested stress, depressive symptoms, and social support in the model together with control variables (see Table 4). Note that race, baseline $CD4^+$ lymphocyte count, stressful life events, and social support remained significant in the model. Depressive symptoms was reduced to nonsignificance by the variables of stressful life events and social support. Depressive symptoms was somewhat correlated with both stressful life events (median r = 0.21) and social support (median r = −0.21). This shared variance may have diminished the association of depressive symptoms with disease progression. None of the interactions between psychosocial variables were significant in predicting progression to AIDS.

DISCUSSION

It is widely believed that stress can affect one's health. Studies have found that stressful events are related to decreases in immune status in a variety of populations (7, 9). Our study is among the first long-term prospective studies to provide preliminary evidence that the cumulative experience of stressful events and difficulties and social support may have a measurable impact on disease progression in HIV-infected men.

Specifically, we showed that for every 4-point increase in cumulative average stressful life events, equivalent to one severe stressor or two moderate stressors, the risk of AIDS was doubled. For each 1-point decrease in cumulative average social support, the risk of AIDS increased almost three-fold. At 5.5 years, the probability of getting AIDS was about two to three times higher among those above the median on stress or below the median on social support as compared with those below the median on stress or above the median on support, respectively.

Although depressive symptoms was also related to increased risk of AIDS, only stress and social support remained significant in the model when the three psychological variables were considered together. Depressive symptoms was moderately correlated with the stress and social support measures, perhaps explaining a similar part of the variance in AIDS progression. The effects of stress and social support were shown after controlling for possible confounding factors (eg,

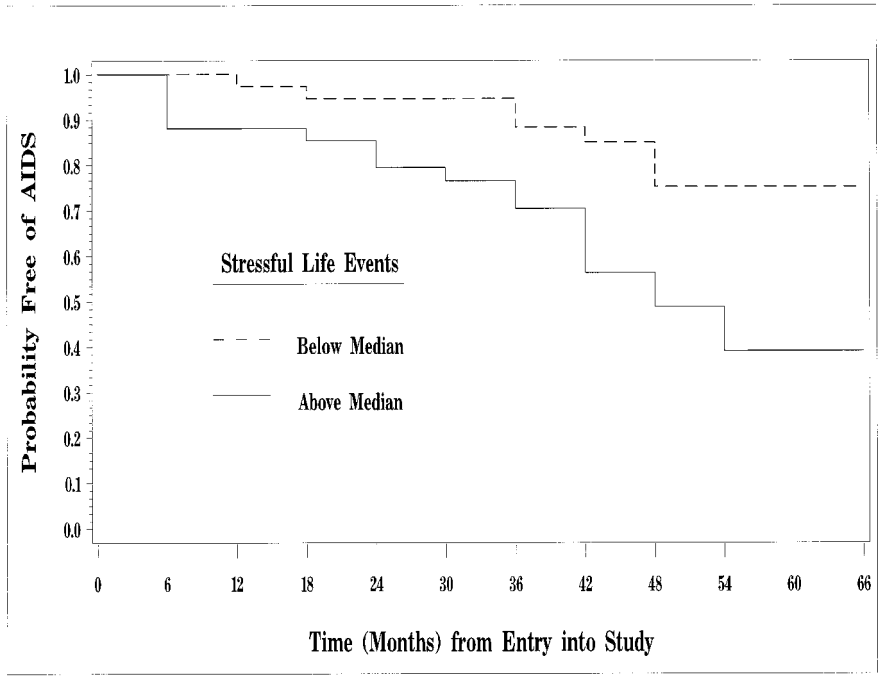

Fig. 1. Kaplan-Meier estimate of the distribution of time (in months) until AIDS diagnosis by stressful life events.

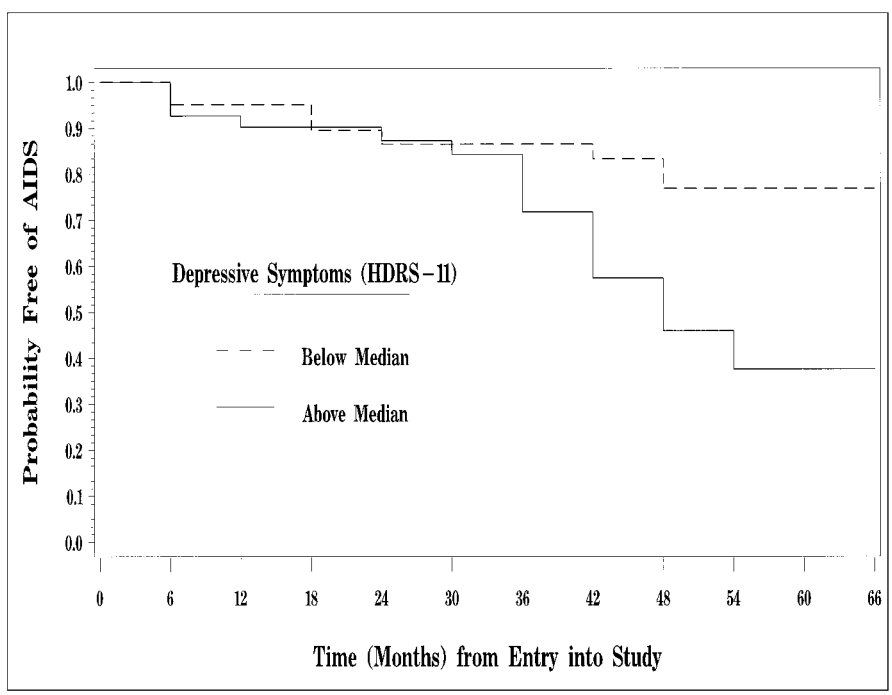

Fig. 2. Kaplan-Meier estimate of the distribution of time (in months) until AIDS diagnosis by depressive symptoms.

age, education, race, baseline helper cells, tobacco use, and number of antiretroviral medications); none of our men were taking protease inhibitors before the onset of AIDS.

Major depression episodes were not significantly related to AIDS progression; there was a nonsignificant trend for those with AIDS to be twice as likely to have had one or more major depressions before AIDS onset compared with those who did not progress. Few men were depressed at any time point, which may explain why the diagnosis of depression was unrelated to AIDS progression, whereas the depressive symptoms

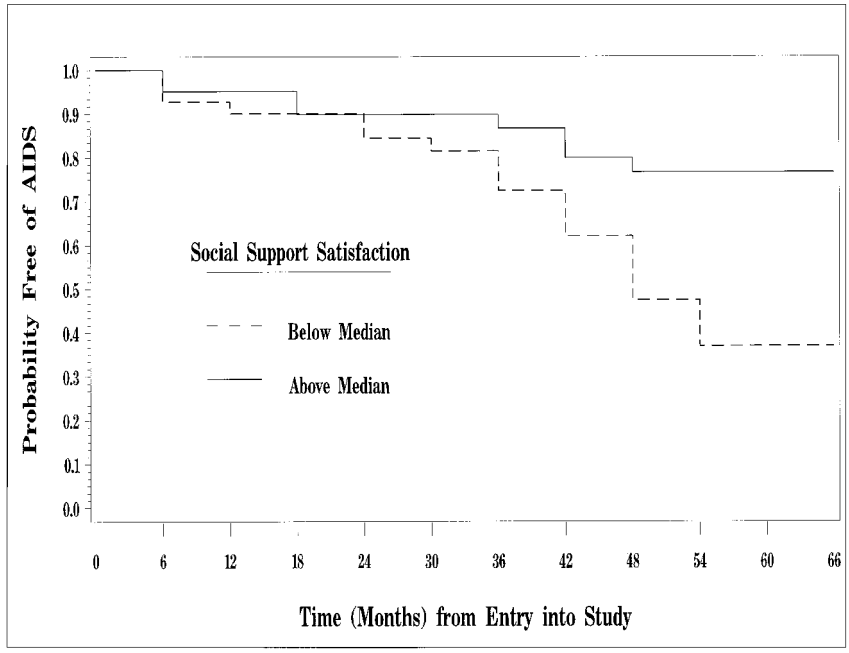

Fig. 3. Kaplan-Meier estimate of the distribution of time (in months) until AIDS diagnosis by social support satisfaction.

TABLE 3. Four Cox Regression Models: Hazard of AIDS Diagnosis With Time-Dependent Psychological and Psychosocial Variables[a]

	β	p	Hazard Ratio	95% Confidence Interval
Stressful life events	0.19	.002	1.21	1.07–1.36
Major depression diagnosis	1.38	.09	3.96	0.80–19.57
Depressive symptoms (HDRS-11)	0.26	.008	1.30	1.07–1.58
Social support satisfaction	−0.99	.0002	.37	0.22–0.63

[a] Results are from four Cox regression models with each time-dependent predictor variable (using cumulative proportions) run separately holding constant the number of antiretroviral medications used (time-dependent covariate) and baseline age, education, race, $CD4^+$ count, and tobacco use. β refers to the unstandardized regression coefficient estimate.

TABLE 4. Cox Regression Model: Hazard of AIDS Diagnosis With Control Variables and Time-Dependent Psychological and Psychosocial Variables[a]

	β	p	Hazard Ratio	95% Confidence Interval
Age	0.03	.45	1.03	0.95–1.11
Education	−0.09	.41	0.92	0.75–1.12
Race[b]	1.51	.03	4.52	1.12–18.30
Baseline $CD4^+$ count (cells/μl)	−0.01	.0005	0.99	0.98–1.00
Tobacco use[c]	0.89	.07	2.45	0.92–6.53
Number of antiretrovirals	0.25	.65	1.28	0.44–3.68
Stressful life events	0.15	.03	1.16	1.01–1.33
Depressive symptoms (HDRS-11)	0.06	.61	1.07	0.84–1.36
Social support satisfaction	−0.82	.006	0.44	0.24–.79

[a] Results are from one Cox regression model with all variables entered into the equation simultaneously. Number of antiretroviral medications used, stressful life events, depressive symptoms, and support satisfaction are time-dependent covariates using cumulative proportions; the other variables are baseline values. β refers to the unstandardized regression coefficient estimate.
[b] 0 = nonwhite; 1 = white.
[c] 0 = no; 1 = yes.

measure, which allowed for more variance, was related to AIDS progression in the absence of other psychosocial variables. The lack of variance on major depression may not allow us to evaluate its effects.

Our present data on men studied for up to 5.5 years are consistent with those of some recent studies that followed HIV-infected men over long time periods (18, 19, 26). Furthermore, the current data extend earlier findings from this cohort that severe stress was associated with first change in HIV disease stage (21) and that severe stress and depressive symptoms were related to declines in several lymphocyte subsets (20).

Previously, we examined the effects of severe stresses on early disease progression and immune change; however, this analysis focused on total stresses (mild, moderate, and severe). Although the time-dependent measure of severe stress at each visit was also predictive of AIDS progression ($\beta = 0.25$, $p = .01$, hazard ratio = 1.29, 95% confidence interval = 1.06–1.56), we used the total stress score because these findings tended to be more robust.

We must be cautious in interpreting the data from our study. First, we do not know whether our findings can be generalized beyond our sample, a group of gay men from both rural and urban areas of North Carolina. We may not be able to generalize our results to such groups as women, intravenous drug users, and those in other geographic areas. Second, we could not control for length of time with HIV infection because date of infection was unknown; however, our findings remained after controlling for baseline helper count, an approximation of disease stage. Consistent with other investigators (14, 15, 19, 44), we found that men with low helper counts at baseline had faster disease progression. It would also be useful to replicate our findings in studies using viral load as the indicator of disease progression.

A third caution for data interpretation is the problem of establishing the causal direction of relationships between psychological variables and disease progression. Do depressive symptoms contribute to disease progression, or are these psychological changes an early manifestation of the disease process? This latter hypothesis was suggested by Lyketsos et al. (22) to explain their finding that depressive symptoms seem to increase before clinical AIDS is diagnosed. Other researchers consider psychological factors like depression to be risk factors for the development of HIV-related symptoms, especially when the psychological variables are shown to occur before clinical progression (18, 19). We attempted to address this causal issue in several ways. First, we used time-dependent psychological variables during the time points before AIDS diagnosis. Second, we excluded somatic symptoms associated with HIV disease progression (eg, weight loss and gastrointestinal symptoms) from the measure of depressive symptoms. More importantly, we used measures of stressful life events and social support, which may be less likely to reflect early manifestations of HIV disease progression. The measure of stressful life events excluded stressors that might be caused by disease progression, such as losing one's job because of a change in HIV status. Stressful events were also scored independently from the subject's perception of the stress and way of coping. This objective stress rating helped reduce the possibility that worsening disease may have led to poorer coping and higher stress scores. Thus, this measure of stressful life events may be the best evidence of an effect of psychosocial variables because it is the least likely to be confounded with disease progression.

The fact that a variety of psychosocial measures are related to disease progression seems to support our findings and may indicate that some underlying factor related to these variables may be predictive of disease progression. Although we controlled for smoking and number of antiretroviral medications used, perhaps other health behaviors (eg, amount of sleep, diet, exercise, and compliance with medication use) and neuroendocrine and immune variables might mediate the relationship of stress and social support with disease progression. Our earlier studies showing reductions in $CD8^+$ and natural killer lymphocyte subsets among men with scores above the median on both stress and depressive symptoms (16, 20) might support a mediating role of these lymphocyte subsets.

Although we found that African American subjects had slower HIV disease progression than white subjects, other studies have not shown such an effect of race(19, 44–46). The race effect in the current study may be limited to our sample and needs further study.

In conclusion, the finding regarding the cumulative effects of stressful life events, a psychosocial measure less likely to be confounded with disease progression, is perhaps among the most compelling evidence to date linking psychosocial variables with HIV disease progression. Men averaging two moderate stressors had a two-fold increased risk of AIDS progression compared with men with no stressors. It will be important to determine whether other long-term longitudinal studies can replicate our findings in HIV-positive women and to determine whether stress, depressive symptoms, and social support are risk factors for mortality in HIV infection. Additional study will be necessary to elucidate the mechanisms that underlie these relationships. In addition, we will need to determine whether cognitive behavioral interventions that have been shown to reduce distress and improve social support (47–49) can alter the course of HIV infection. Shedding light on the nature of the relationships between HIV disease progression and psychological variables may help with the treatment of those infected with HIV.

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