RELATIONSHIP OF PSYCHOSOCIAL FACTORS TO HIV DISEASE PROGRESSION[1,2,3]

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ABSTRACT

Based on the existing empirical evidence that psychosocial variables may predict the course of human immunodeficiency virus (HIV) illness, disease progression (described by advance in symptoms, decline in CD4+ cell count, and mortality) in 414 HIV-positive (HIV+) males was studied using Cox Proportional Hazards Models (survival analysis). Depressive symptoms predicted shorter longevity after controlling for symptoms and CD4+ cell count. Large social network sizes predicted longevity among those with acquired immune deficiency syndrome (AIDS)-defining symptoms at baseline, but not among other subjects. Therefore, psychosocial variables and affective states may be related to disease outcome only during later stages of HIV disease. Although the results provide support for psychoneuroimmunologic effects in HIV, other confounding explanations may still apply.

(Ann Behav Med 1996, *18*(1):30–39)

INTRODUCTION

As the human immunodeficiency virus (HIV) pandemic enters its second decade of scientific study, vaccines or cures for HIV infection or HIV-related illnesses have yet to be identified. However, the advent of antiretroviral medications and improved treatment for HIV-related opportunistic infections have increased the average longevity by several years (1,2). Despite these gains in the average longevity, wide variability in the course of human immunodeficiency virus illness persists. Several explanations for the broad range in course of illness have been conjectured, including differential virulence, biological host factors, psychosocial factors, or various interactions between these three factors (3).

Research into the role of psychosocial factors and affective states in relation to HIV disease progression has yielded inconsistent and inconclusive findings. Discrepant findings have been linked to a variety of methodological issues including small sample sizes, correlational and cross-sectional data analyses, different methods of assessing psychological constructs, the absence of estimated dates of seroconversion, limited variability on stage of illness variables, neglect of clinical status outcome variables, and the questionable biological significance of some of the immune parameters considered (4). Despite limitations, these studies provide an important foundation for current research efforts in the field of psychoneuroimmunology and HIV/acquired immune deficiency syndrome (AIDS).

The primary objective of this study was to address several of the methodologic issues of previous studies and to test the basic psychoneuroimmunologic question in HIV disease using a large and well-characterized sample, theoretically important psychosocial variables, and a prospective research design. Specifically, this study examined the effects of depressed mood, negative life events, social support, and coping on rate of HIV disease progression using multiple outcomes.

In the 1980s, medical and social science researchers from the field of psychoneuroimmunology recognized HIV disease as an appropriate model for testing the effects of psychosocial variables on physical illness (5). Both the immune and neural systems appeared to be central to HIV progression, and the course

[1] Preparation of this manuscript was supported in part by NIMH Center Grant 5 P50 MH45294 (HIV Neurobehavioral Research Center). Additional support was provided by 5 R01 MH43298 (Neuropsychiatric Sequelae of HTLV-III Infections), 5 R29 MH45688 (Object-oriented Simulation of HIV- and CNS/HIV infection), 1 R01 MH46255 (Psychosocial Moderators of Disease Progression in AIDS), 1 R01 NS27810 (Role of Immune Responsiveness in HIV Encephalopathy), and the Henry M. Jackson Foundation for the Advancement of Military Medicine (Tri-service Biopsychosocial HIV Study, Lydia R. Temoshok, P.I.).

[2] The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

[3] The authors gratefully acknowledge the assistance of William F. Koch in data management, compilation, and analysis.

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of HIV illness varied substantially among infected individuals, suggesting that a variety of factors were related to disease progression. The psychoneuroimmunologic hypothesis in HIV has been tested empirically using a variety of markers of HIV disease progression. These outcomes include CD4+ lymphocyte count (6,7), percent CD4+ lymphocytes (8), CD4+/CD8+ ratio (9,10), natural killer (NK) cell cytotoxicity (9,11), absolute NK cell count (12), time from seroconversion to AIDS diagnosis (10), survival time (13), symptoms of HIV illness (14,15), degree of physical impairment (7), as well as a host of other biologic markers for HIV disease progression. Of these outcome measures, the most frequently used is CD4+ cell count, the immune marker most closely linked to the clinical consequences of HIV infection (16–18).

The 1993 revised classification system for HIV infection, which takes into account both CD4+ cell count and clinical symptoms, has not been used to test the influence of psychosocial variables on disease progression. The revised classification scheme reflects the clinical observation that HIV disease progression can be monitored in several ways. Although some HIV-positive (HIV+) individuals with low T-cell count remain largely symptom-free, others develop opportunistic infections and related complications even though their immune system appears to be relatively intact. Accordingly, the measurement of HIV disease progression should take into account both immune changes and development of symptoms over time.

A wide spectrum of psychosocial variables has been examined in relation to the course of HIV infection; however, depressed mood, life stress, social support, and coping have received the most research attention. Two recent articles published in the *Journal of the American Medical Association* highlighted the inconsistent nature of findings related to depressive symptoms and immune function in HIV infection (19,20). Burack and associates (19) found that rate of change of CD4+ count (expressed as a slope) was associated with baseline depressive symptoms in 277 HIV-positive men; however, depression did not predict AIDS-free survival or mortality. In the accompanying report by Lyketsos and associates (20), depressive symptoms were unrelated to a number of HIV health outcomes, including time until AIDS diagnosis, time until death, and CD4+ count decline. Similarly, Rabkin and associates (7,15) found no relationship between psychosocial distress and measures of immune status or physical symptoms among HIV+ gay men.

Researchers also have hypothesized that stressful life events may be associated with biological markers of HIV disease progression. Although negative life events have been shown to be related to psychological distress (21,22) and NK cell activity (23) among HIV-positive subjects, there is less support for the connection between life events and disease progression. Kessler (14) found no association between stressful life events and symptom development or decline in CD4+ lymphocyte count. However, Patterson and associates (8) reported that the interaction of life adversity x depressive symptoms was a significant predictor of decline in percent CD4+ lymphocytes over a six-month period. The implication is that life events may influence immunity in HIV only when paired with psychological distress.

Social support is another psychosocial variable that has been examined as a moderator of HIV disease progression. Although social support is consistently related in an inverse direction to psychological distress among asymptomatic HIV-positive gay males (21,24), associations with physical symptoms are less supported. Social support may act indirectly on physical health by easing the emotional or tangible burden of increased physical symptoms (24); however, this stress-buffering hypothesis has not been tested prospectively among HIV-positive individuals.

Coping is another psychosocial factor that has been examined in relation to the course of HIV disease progression. Antoni and associates (9) studied the relationship between coping, intrusive thoughts about AIDS, and immune response in men preparing for notification of HIV status. They found that denial coping was related to both fewer intrusive thoughts about AIDS and stronger lymphocyte proliferative responses to phytohemagglutinin (PHA). This finding suggests that avoidant coping may help to alleviate the ruminations and intrusive thoughts about HIV that, in turn, may be associated with compromised immunity. In other research with HIV+ gay men, passive coping was negatively correlated with total CD4+ count (10), whereas active coping was associated with higher NK cell cytotoxicity (11). Keet and associates (25) found no association between coping skills and progression to symptomatic HIV infection. Although these studies offer mixed findings, the discrepancies may be attributable to disparate conceptualizations of coping (e.g. state versus trait, disease-specific versus general).

Taken together, this review of the empirical research on psychoneuroimmunology and HIV/AIDS yields inconclusive and contradictory findings. The nature of human research on stress and health, with the inevitability of uncontrollable sources of variation, makes it unlikely that a perfect study will ever be implemented within the practical constraints of resources and time. Nevertheless, the design of the present research represents a significant advance over much of the existing research and the results further contribute to our understanding of psychosocial predictors of HIV disease progression.

METHOD

Subjects and Procedure

For the present analyses, the sample was comprised of 414 HIV-positive heterosexual and gay men who were participating in a longitudinal cohort study at the HIV Neurobehavioral Research Center (HNRC), University of California, San Diego. The sample was recruited from military personnel seen at the Naval Medical Center, San Diego, as well as from the civilian community in the greater San Diego area. Inclusionary criteria of the HNRC required that participants were male, residents of San Diego County with at least ten years of formal education, and willing to undergo extensive evaluations semi-annually for up to five years. Individuals were excluded if their medical history might confound interpretation of neurological or neuropsychological findings, such as a history of intravenous drug use, head injury with loss of consciousness exceeding 30 minutes, or a primary diagnosis of thought disorder. The present sample was selected from the HNRC main cohort based on three additional criteria: (a) availability of psychological variables from a baseline assessment; (b) participation in the study for at least one year; and (c) completion of at least two successive blood draws.

Demographic characteristics for the sample are shown in Table 1. The average participant was 33 years of age ($SD = 7.2$), had 14 years of formal education, and had known of his HIV-positive status for two years. The sample was largely Caucasian (79%), never married (74%), and of lower-middle-class socioeconomic background [a Hollingshead socioeconomic status (SES) rating of 4]. Participants with more severe HIV symptoms

TABLE 1
Demographic and Background Characteristics at Baseline by HIV Clinical Categories

Baseline Variable	(A) Asymptomatic, Acute (Primary) HIV or PGL			(B) Symptomatic, not (A) or (C) Conditions			(C) AIDS-indicator Conditions			Post-hoc Comparisons
	M	(SD)	Valid *N*	M	(SD)	Valid *N*	M	(SD)	Valid *N*	
Age*	31.9	(7.4)	243	34.3	(6.7)	99	35.7	(6.0)	52	A < B, C
Years education	13.9	(2.2)	252	14.3	(2.1)	106	14.4	(1.8)	56	
Hollingshead SES (1–5)	3.7	(0.9)	110	4.0	(1.3)	48	4.2	(1.2)	28	
Months HIV+*	22.8	(15.8)	148	33.1	(19.4)	31	39.9	(26.1)	4	A < B
CD4+ count*	546	(250)	248	349	(238)	106	104	(165)	55	A > B > C
Beta-2 microglobulin*	2.7	(1.4)	247	3.3	(1.4)	105	4.1	(2.0)	55	A < B < C
		%	*N*		%	*N*		%	*N*	
Ethnicity										
Caucasian		75.7	190		85.8	91		83.9	47	
African-American		15.5	39		2.8	3		10.7	6	
Latino		7.2	18		8.5	9		5.4	3	
Other		1.6	4		2.8	3		0.0	0	

* $p \leq .05$ (ANOVA).

were older, had known of their HIV-positive status longer, but were not different in background, education, ethnicity, and SES. As expected, differences in CD4+ cell count and serum $Beta_2$ microglobulin levels corresponded to the presence and severity of symptoms (see Table 1).

Stage of HIV infection was determined at baseline using the 1993 Revised Classification System for HIV Infection (26). As shown in Table 2, the majority of participants (61%) were asymptomatic at baseline (symptom category A). Using the bi-dimensional definition for an actual AIDS diagnosis (CD4+ less than 200/μL and/or AIDS-indicator opportunistic infections), 102 participants (25%) had reached these criteria prior to or concurrent with their baseline assessment. Of the total sample, 93 (23%) had CD4+ cell counts less than 200/μL. Only two participants had AIDS-indicator symptoms while maintaining a CD4+ cell count greater than 500/μL. The distribution of HIV severity in the sample might be described as somewhat bimodal: a large cluster of mostly asymptomatic cases with varying levels of immune function, and a smaller cluster of cases with an AIDS diagnosis and severely compromised immune function. All participants completed a two-hour psychosocial battery including measures of life stress, coping, social support, and depressive symptoms.

Psychosocial Predictor Measures

Depression, social support, coping, and life adversity were targeted as potential predictors of the course of HIV disease. These variables were assessed at the baseline assessment for all subjects regardless of initial HIV disease classification using the following measures.

Depressive Symptoms: The clinician-rated Hamilton Rating Scale for Depression (HRSD) is a 21-item clinical instrument for assessing depressive symptoms based on three- or five-point Likert scale responses. The HRSD has well-documented validity (27), and it has been used extensively in clinical trials of antidepressant drugs. Inter-rater reliability has been found to be in the range of 0.80 to 0.91 (28,29).

Negative Life Events: Data on life events were gathered through semi-structured interviews utilizing the Psychiatric Epidemiology Research Interview (PERI) (30). The PERI comprises a list of 136 stressful life experiences grouped into twelve major categories (e.g. love, work, finances). All events reported by the participants were self-rated for degree of desirability using a seven-point scale ranging from "extremely negative" to "extremely positive." Total number of negative life events was computed by counting only those events that were rated as mildly, moderately, or extremely negative.

Social Support: Social support was assessed using the Social Support Questionnaire, a five-item self-report measure developed by Schaefer, Coyne, and Lazarus (31). Participants identify individuals who provide support and rate them on a five-point Likert scale for the degree of useful information, reliable help,

TABLE 2
Sample Sizes at Baseline by CDC 1993 HIV Categories

CD4+ T-cell categories	(A) Asymptomatic, Acute (Primary) HIV or PGL		(B) Symptomatic, not (A) or (C) Conditions		(C) AIDS-indicator Conditions		Row Totals	
	N	%	*N*	%	*N*	%	*N*	%
(1) ≥ 500 /μL	130	31.4	22	5.3	2	0.5	154	37.2
(2) 200–499/μL	108	26.1	52	12.6	7	1.7	167	40.3
(3) < 200/μL	14	3.4	32	7.7	47	11.4	93	22.5
Column totals	252	61.0	106	26.0	56	13.5	414	100.0

TABLE 3
Means and Standard Deviations for Psychosocial Variables by HIV Clinical Categories

Variable Name	(A) Asymptomatic, Acute (Primary) HIV or PGL			(B) Symptomatic, not (A) or (C) Conditions			(C) AIDS-indicator Conditions			Post-hoc Comparison
	M	(SD)	Valid *N*	M	(SD)	Valid *N*	M	(SD)	Valid *N*	
Hamilton Depression*	5.0	(5.6)	241	7.2	(6.8)	104	7.5	(5.7)	51	A < B, C
Social Network Size*	10.0	(2.8)	237	9.6	(3.3)	101	8.5	(3.4)	51	A > C
Informational Support	2.7	(0.8)	237	2.7	(0.7)	101	2.8	(0.8)	51	
Emotional Support	3.6	(0.7)	237	3.6	(0.7)	101	3.7	(0.7)	51	
Approach Coping	7.5	(3.1)	240	7.4	(3.0)	102	8.1	(2.9)	50	
Avoidant Coping	6.0	(2.8)	240	6.6	(3.0)	101	6.3	(2.9)	53	
Negative Life Events*	3.1	(2.2)	243	3.6	(2.2)	104	2.8	(1.7)	54	B > AC (contrast)

* $p \leq .05$ (ANOVA).

emotional uplift, caring, and trust they receive from the individual. Mean ratings across relationship categories yielded summary scores for emotional and informational support. Social network size was calculated as the total number of all social support contacts listed. Test–retest reliability is 0.66 and internal consistency (alpha) is 0.95 (31).

Coping: The Ways of Coping Questionnaire–Revised (WOC–R) is a 67-item instrument that asks individuals to rate on a four-point scale the degree to which they use particular strategies in dealing with conflicts or stressful situations (32). Eight coping subscales were collapsed into two primary scales representing approach or avoidant coping (8).

Outcome Measures

HIV Disease Classifications: The 1993 Centers for Disease Control and Prevention (CDC) classification system for HIV infection (26) was used to classify subjects within the 3 × 3 matrix of CDC classifications ranging from A1 (asymptomatic, with CD4+ cell count greater than or equal to 500/μl) to C3 (AIDS-indicated symptoms, with CD4+ cell count less than 200/μl). From this classification system, three outcome measures were developed. The first was the time from baseline to a stage advance in HIV symptoms (from A to B or from B to C). The second was the time from baseline to a stage advance in CD4+ cell decline (from 1 to 2 or from 2 to 3). The third was a combined measure of the time from baseline to the time at which the expanded surveillance case definition for AIDS was met (any C or 3 classification). A fourth measure of disease outcome was survival time from baseline to death.

In the case of intermittent missing diagnostic data, CDC classifications from the last valid assessment were extended over the missing periods, but for no more than two assessments (a one-year period). In the case of dropouts, all valid assessment periods were included in the survival analyses. If changes in disease progression were not recorded at the time of dropout, then these cases remained in the analyses as "censored" cases (see Statistical Method section below).

Covariates

Because of the variable levels of HIV illness reported by our participants at baseline, we adopted three potential covariates for controlling for initial level of disease based on the 1993 CDC classification system: (a) baseline CD4+ cell count; (b) baseline symptom classification; and (c) an interaction term for baseline CD+ cell count x symptom classification. By testing the interaction term as a potential covariate, we were able to control for the possibility that low CD4+ cell counts may potentiate the effects of overt symptoms in predicting HIV disease progression.

Statistical Method

Statistical analyses were performed using the BMDP 2L computer program, Release 7 (33). Cox Proportional Hazards Models were used to test the influence of the psychosocial independent variables and various covariates on the time to reach each of the four outcome criteria. This method is one of a class of statistical procedures (survival analysis) designed to estimate odds/risk ratios for the time required to reach various criterion events. Both cases in which the criterion is met (uncensored cases) and continuing cases (censored cases) are included in the estimation of a survival function relating time to likelihood of the event occurring. Specifically, the Cox Proportional Hazards Model assumes that the influence of psychosocial variables and covariates is consistent across the duration of the survival function (i.e. that different individuals have hazard functions that are equally proportional to one another, regardless of time) (34).

The unique contribution of covariates and psychosocial variables to the proportional hazards function was tested using the maximum partial likelihood ratio (MPLR) method, producing both a global chi-square statistic and a chi-square statistic that assessed the change in the log-likelihood value from the previous step (34). Psychosocial variables were evaluated based on these statistical tests, as well as from physical plots of survival functions to estimate effect size.

RESULTS

Means and standard deviations for each of the psychosocial variables are shown in Table 3, stratified by A, B, or C classifications of HIV disease symptomatology. An analysis of variance (ANOVA) for each of the seven psychosocial variables indicated statistically significant group differences on depressive symptoms, $F(2,393) = 7.35$, $p < .05$, social support network size, $F(2,386) = 5.43$, $p < .05$, and number of negative life events reported, $F(2,398) = 3.12$, $p < .05$. Neuman-Keuls post-hoc pairwise comparisons revealed the following: (a) asymptomatic subjects were significantly less depressed than others, (b) asymptomatic individuals had larger social support networks than those with AIDS-indicator symptoms, and (c) subjects in

TABLE 4
HIV Survival Times for Outcomes Based on CDC 1993 Disease Classifications

Outcome Measure	Survival at 12 Months	Survival at 24 Months	Survival at 36 Months	Survival at 60 Months
Advance in symptoms				
Cases advancing	55 (16%)	103 (29%)	130 (37%)	143 (40%)
Cases censored	34 (10%)	102 (29%)	178 (50%)	211 (60%)
Cases remaining	265 (74%)	149 (42%)	46 (13%)	0 (0%)
Total cases	354 (100%)	354 (100%)	354 (100%)	354 (100%)
Advance in T-cell count				
Cases advancing	79 (25%)	130 (41%)	154 (48%)	161 (51%)
Cases censored	32 (10%)	79 (25%)	132 (42%)	157 (49%)
Cases remaining	207 (65%)	109 (34%)	32 (10%)	0 (0%)
Total cases	318 (100%)	318 (100%)	318 (100%)	318 (100%)
Advance to AIDS diagnosis				
Cases advancing	36 (12%)	68 (22%)	89 (28%)	94 (30%)
Cases censored	34 (11%)	101 (32%)	179 (57%)	219 (70%)
Cases remaining	243 (77%)	144 (46%)	45 (15%)	0 (0%)
Total cases	313 (100%)	313 (100%)	313 (100%)	313 (100%)
Mortality				
Cases not alive	13 (3%)	46 (11%)	73 (18%)	100 (24%)
Cases censored	35 (9%)	119 (29%)	229 (56%)	311 (76%)
Cases remaining	363 (78%)	246 (60%)	109 (26%)	0 (0%)
Total cases	411 (100%)	411 (100%)	411 (100%)	411 (100%)

clinical category B reported more negative life events than either asymptomatic subjects (clinical category A) or those with AIDS-indicator conditions (clinical category C).

A Cox Proportional Hazards Model for each of the four outcome measures (time until advance in T-cell decline, time until advance in symptoms classification, time until AIDS diagnosis, and time until death) was constructed hierarchically (see Tables 4 and 5). Baseline CDC classification was entered first to act as a covariate in evaluating the unique predictive strength of psychosocial variables entered later. CDC classification was entered in three steps. First, CD4+ cell count was entered as 1 (CD4+ count > 500/μL), 2 (CD4+ count between 200 and 499/μL), or 3 (CD4+ count < 200/μL). Second, symptoms classification was entered as 1 (asymptomatic, acute primary HIV or PGL), 2 (symptomatic, no AIDS-indicator conditions), or 3 (AIDS-indicator conditions). Third, a multiplicative interaction term (from 1 to 9) of CD4+ count and symptoms was tested as an additional covariate. All four outcome measures were significantly related to both CD4+ count and stage of symptoms. The interaction term was a statistically significant addition to only the model predicting time until death, $\chi^2(1,411) = 4.00$, $p < .05$.

Psychosocial variables were tested hierarchically as additional predictors of each of the four survival time outcomes, in the order shown in Table 5. The ordering of independent variables was based on the conceptual distinction between direct and mediating effects. Variables with hypothesized direct effects (depressive symptoms, life events) were entered before mediating variables (social support, coping) and interaction terms. For the three social support variables (network size, informational support, and emotional support), interactions between social support and symptoms (using A, B, or C CDC classifications) were tested in addition to main effects. Interaction terms were added after incorporating both root variables in the model to ensure that only the unique contribution of the interaction was assessed. The model results for each of the four outcome variables are summarized below.

Advance in Symptoms

The cases included in this analysis were all subjects in CDC symptom categories A or B at the baseline assessment (N = 354). Of this selected sample, 218 (40%) had advanced in symptom categories (from A to B or C, or from B to C). Therefore, the results for this Cox Proportional Hazards Model were based on observations of which 60% were censored data points (advance of symptoms did not occur). The results of the hierarchical testing of individual psychosocial variables are shown in Table 5. The Network Size × Symptom Classification interaction term was a significant predictor of time until advancement of symptoms, $\chi^2(1, N = 335) = 3.69$, $p = .05$. An examination of simple effects revealed an effect of network size only for those subjects who were asymptomatic (symptom category A) at baseline. Among this group, larger network size predicted a shorter symptom-free period. The survival function estimated that after 36 months, those who reported only three individuals in their network had a 64% chance of remaining symptom-free, whereas those who listed 16 individuals had only a 36% chance of remaining symptom-free. This estimate of the impact of network size assumes all other variables (covariates) in the model were equal (set to mean values).

After controlling for this significant interaction, a second psychosocial variable was also a significant predictor: the Informational Support × Symptom Classification interaction term, $\chi^2(1, N = 335) = 12.91$, $p = .0003$. An examination of simple effects revealed an effect of informational support ratings, this time for only those subjects who were symptomatic at baseline (symptom category B). Higher ratings of informational support, while controlling for network size, predicted a longer time until

TABLE 5
Results from Cox Proportional Hazards Models

Independent Variable	Advance in Symptoms			Advance in T-cell Count			Advance to AIDS Diagnosis			Time until Death		
	χ^2	N	p	χ^2	N	p	χ^2	N	p	χ^2	N	p
Baseline T-cell category	22.46*	354	<.001	18.16*	318	<.001	25.50*	313	<.001	101.39*	411	<.001
Baseline clinical category	5.09*	354	.02	16.41*	318	<.001	12.73*	313	<.001	37.88*	411	<.001
Category interaction term	2.88	354	.09	.01	318	.90	.60	313	.44	4.00*	411	.04
Hamilton depression	1.33	341	.25	.90	306	.34	.45	302	.50	5.56*	393	.02
Negative life events	.09	343	.77	.21	309	.64	.30	304	.59	.24	382	.63
Network size	.94	335	.33	.37	302	.54	.19	297	.66	9.57*	371	.002
Network × symptoms**	3.69*	335	.05	.03	302	.86	1.95	297	.16	1.32	371	.25
Informational support	.00	335	.96	.85	302	.36	1.18	297	.28	.47	371	.49
Informational support × symptoms**	12.91*	335	<.001	.35	302	.55	.04	297	.83	4.00*	371	.04
Emotional support	.08	335	.77	.01	302	.94	.04	297	.83	1.13	371	.29
Emotional support × symptoms**	.87	335	.35	.11	302	.74	.02	297	.88	.12	371	.73
Approach coping	.61	332	.44	1.02	305	.31	2.56	300	.11	.04	364	.85
Avoidant coping	.06	332	.80	1.94	305	.16	.44	300	.51	.88	366	.85

* $p \leq .05$ (Chi-square test).
** Root variables included in model when testing interaction terms.

the onset of an AIDS-defining opportunistic infection. The survival function estimated that after 36 months, those who rated their average informational support as 4.2 (on a scale of 1 to 5) had an 88% chance of remaining symptom-free, while those with an average rating of 1.2 had only a 16% chance of remaining symptom-free. This estimate of the impact of informational support assumes all other variables (covariates and predictors) in the model were equal (set to mean values). The final Cox Proportional Hazards Model predicting time until death, with three covariates and four independent variables, was statistically significant overall, $\chi^2(6, N = 335) = 41.97$, $p < .05$.

Advance in CD4+ Cell Count

A selected sample of 318 subjects had CD4+ cell counts greater than 200/μL at the baseline assessment. From this sample, 161 (51%) experienced CD4+ cell reductions in subsequent blood draws that resulted in CDC reclassification (from 1 to 2 or 3, or from 2 to 3). Therefore, the results for this Cox Proportional Hazards Model were based on observations of which 50% were censored data points (advance of CD4+ count did not occur). As shown in Table 5, none of the psychosocial variables were a significant predictor of the time until a marked reduction in CD4+ cell count, $p > .05$.

Advance to AIDS Diagnosis

This analysis included all subjects having a CD4+ cell count greater than 200/μL and having no AIDS-defining symptoms at the baseline assessment ($N = 313$). Of this sample, 94 (30%) advanced to an AIDS diagnosis (by either CD4+ or symptom definition) by the time of this analysis. Therefore, the results for this Cox Proportional Hazards Model were based on observations of which 70% were censored data points (AIDS diagnosis did not occur). As shown in Table 5, none of the psychosocial variables were a significant predictor of the time until an AIDS diagnosis, $p > .05$.

Time until Death

Of the total sample of 414 subjects, 411 were either living or had a documented date of death at the time of the analysis. Of this group, 100 (24%) were deceased. Therefore, the results for this Cox Proportional Hazards Model were based on observations of which 75% were censored data points (still alive). The results of the hierarchical testing of individual psychosocial variables are shown in Table 5. Hamilton depression was a significant predictor of time until death, $\chi^2(1, N = 393) = 5.56$, $p = .02$. A higher depression score was associated with a shorter time until death, as depicted in Figure 1, a plot of the survival function. After 48 months, those with a baseline rating of 0 on the Hamilton depression scale (the modal score) had a 72% chance of remaining alive, while those with a rating of 30 had only a 40% chance of remaining symptom-free. After controlling for depressive symptoms, network size was a second psychosocial predictor, $\chi^2(1, N = 371) = 9.57$, $p = .002$. A larger network was associated with a longer survival time. Those who reported sixteen individuals in their network had an 84% chance of remaining alive after 48 months, while those who listed only two individuals had a 44% chance.

In order to test the possibility that somatic items on the Hamilton depression score, rather than depressed mood, were responsible for predicting longevity (an instance of physical symptoms predicting physical symptoms), we repeated the previous analysis using a reduced form of the Hamilton depression scale that did not include items related to sleep, appetite, and lack of energy (scores ranged from 0 to 16, rather than 0 to 30 for the full scale). The resulting survival curves showed similar effects of depression on longevity (high scores predicted reduced longevity); however, these findings did not reach statistical significance, $\chi^2(1, N = 393) = 2.25$, $p = 0.13$. Therefore, inclusion of somatic items on the Hamilton depression scale were important in predicting longevity.

After controlling for both depressive symptoms and network size, a third psychosocial variable was also a significant predictor: the Informational Support × Symptom Classification interaction term, $\chi^2(1, N = 371) = 4.00$, $p = .04$. An examination of simple effects revealed an effect of informational support ratings for only those subjects who were at symptoms category B at baseline (symptomatic with no AIDS-defining opportunistic infections). In this group, higher ratings of informational support predicted a longer survival time while controlling for depressive symptoms and network size. The survival function estimated that after 36 months, those who rated their average informational support as 4.5 (on a scale of 1 to 5) had an 80%

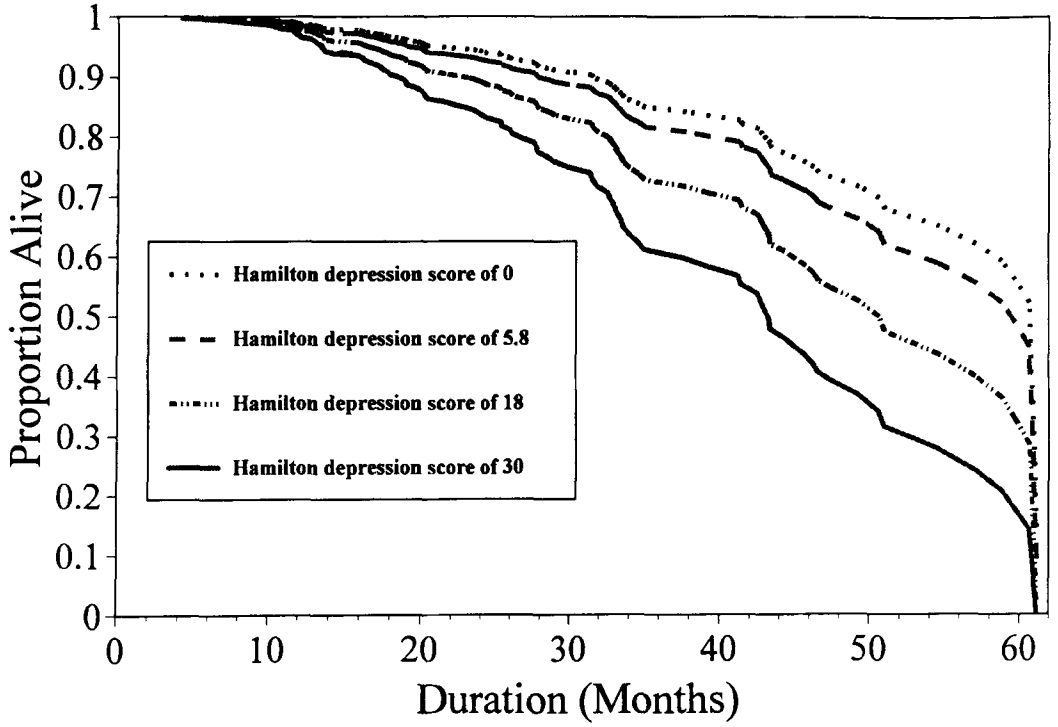

FIGURE 1: Survival curves depicting differential longevity based on baseline Hamilton depression ratings.

chance of remaining alive, whereas those with an average rating of 1.0 had only a 20% chance of remaining symptom-free. The final Cox Proportional Hazards Model predicting time until death, with three covariates and four independent variables, was significant overall, $\chi^2(7, N = 371) = 192.85$, $p < .05$.

DISCUSSION

In the present study, we found that depressive symptoms and social support were important predictors of both symptom onset and time until death in a sample of 414 HIV-positive men. This relationship existed after controlling for baseline disease severity. Unlike previous studies, this study utilized the 1993 CDC HIV Disease Classification System (26) for monitoring disease progression. Also, we assessed several psychosocial variables, including a more detailed and objective assessment of depressive symptoms than in earlier studies. Depressive symptoms predicted a more rapid disease progression, and social support played a mixed role depending on stage of illness. Coping and negative life events were not significant predictors. The present findings suggest a direction for controlled intervention research that might provide a more powerful test of the direct influence of psychosocial variables and mood states on HIV disease progression.

Depression is the psychological distress variable most often associated with HIV disease progression. In the present sample, depressive symptoms predicted time until death, but it did not predict either an advance to more severe symptoms or a clinically significant decline in CD4+ cell count. Depressive symptoms, therefore, may be more closely tied to HIV disease progression in the later stages of illness. Depression is hypothesized to affect HIV disease through two possible mechanisms: (a) neural influence on endocrine systems related to immunity (direct influence), and (b) manifestations of depression in poor health behaviors (indirect influence). Our data provide more support for the latter, because depressive symptoms did not predict CD4+ decline. Depression may limit the motivation of individuals to continue treatments or to provide self-care in the face of severe pain and disability. Future treatment studies might include interventions aimed at both reducing depressive symptoms and increasing positive health behaviors.

An important methodological issue when drawing conclusions about the influence of depression on physical health changes is the possible confound of baseline physical health symptoms. Depression scales typically contain somatic complaints (sleep disturbance, changes in diet, etc.) that overlap with physical health variables, and the Hamilton scale is no exception. In our study, removal of the somatic items (sleep, appetite, and lack of energy) from the Hamilton scale resulted in a "non-somatic" version of the scale that did not reach statistical significance ($p = 0.13$) as a predictor of longevity. Therefore, we were unable to rule out the possibility that the somatic items on the full Hamilton scale were reflecting HIV disease progression rather than actual mood-related symptoms. This occurred despite specific instructions to interviewers that HIV-related symptoms be discounted when scoring the Hamilton depression scale.

Because suitable reliability and validity studies of our non-somatic version of the Hamilton depression scale have not been performed and because this scale alteration substantially reduced the total variance in this measure, it was not surprising that the non-somatic variable did not reach statistical significance as a predictor. A stronger test would be to administer a mood measure (with suitable reliability and validity) rather than a syndromal depression measure. Evidence from other studies suggests that depressed mood alone is predictive of disease progression. For example, in the earlier study by Burack and associates (19), a mood-based subscale of the Centers for Epidemiological Studies–Depression (CES–D) measure found a greater effect on survival for depressed mood than the full-scale measure of depression including somatic complaints. The intertwining nature of HIV disease symptoms and depressed mood remains

a stumbling block in discriminating the effects of depression on HIV disease progression.

Our analyses reflected an influence of depressive symptoms on mortality similar to that reported by Burack (19) who compared the survival functions of depressed and non-depressed men. This replication is important because the finding withstood several differences between the two studies. Whereas the Burack study used the CES–D scale (a brief, self-report measure), the present study used the clinician-rated Hamilton depression scale. Another difference is that in the Burack study, the sample was dichotomized (depressed/not depressed) based on a clinically significant cutoff point. In our analyses, depression was tested as a continuous variable, providing more statistical power and allowing us to plot the relative changes in survival curve as a function of depressive symptoms. Because our computational procedure assumed changes in the survival function were proportional to changes in depression scores regardless of level, our positive findings suggest that individual differences in depressive symptoms may be important in HIV disease progression, regardless of whether the symptoms are clinically significant.

Depressive symptoms did not predict the time until significant CD4+ decline or time until AIDS diagnosis (consisting partly of a CD4+ criterion). Here, the CDC classification system based on CD4+ cell count may have been too gross and too arbitrary a measure to detect significant effects of the predictor variables that were tested. Conventional multiple regression techniques predicting changes in immune markers over time might be more powerful than the survival analysis techniques reported here. For example, Patterson and associates (8) found a relationship between depressive symptoms and major life adversity using multiple regression techniques to predict six-month decline in percent CD4+ lymphocytes among "dated seroconverters." The CD4+ cutoff points for disease classification in the 1993 CDC guidelines are considerably more arbitrary than the symptom-based classifications, which are based on the appearance of discrete symptoms. This might explain the selective nature of our findings by outcome measure.

In this sample, social support played a mixed role in predicting HIV disease progression depending on the chosen outcome measure. Based on the variable influence of social support observed in our sample, these findings may reflect merely chance relationships in our analyses. Further, this finding has not been reported elsewhere, and it deserves replication before any important conclusions can be drawn. Nevertheless, we endeavored to explain these findings based on the social support literature and knowledge of the experience of HIV disease. For those who were asymptomatic at baseline, a large network size predicted more immediate onset of early symptoms. This negative influence of network size on disease progression may be related to the stress of having to disclose HIV status (and possibly, sexual orientation) to a large group of friends, co-workers, and relatives. Large network size might also be reflective of a high level of sociability that is correlated with poor health habits (smoking, drinking, insufficient sleeping habits, etc.). A third explanation, suggested by findings among congestive heart failure patients (35), is that large social networks consist of friends and family members who are overprotective and overconcerned, resulting in more inactivity and less personal self-efficacy. This finding suggests that social activities and social adjustment related to HIV notification should be considered as primary targets for intervention early in HIV disease.

Our other social support findings supported the more widely-supported stress-buffering role of social support in coping with chronic illness. Among more advanced cases, longevity (time until death) was positively associated with both network size and informational support ratings. Among those who had intermediate symptoms but had no AIDS-defining opportunistic infections, informational ratings of support were associated with a slower onset of AIDS-defining symptoms. We did not find social support to be predictive of the time for significant drops in CD4+ cell count, as recently demonstrated among hemophiliac men (36). Here again, the absence of a statistically significant relationship in the present study may be related to our use of the 1993 CDC categories of CD4+ decline. These categories may be somewhat arbitrary and each encompasses a wide range of CD4+ cell count variation.

Social support has been associated with disease outcome in a wide variety of illness populations. One of the oldest and best known large-scale health studies, the Alameda County Study, demonstrated that, in a fairly representative sample of the general population, those who were more "socially connected" had significantly greater chances of survival than those who were less connected (37). This same study was also successful in showing relationships between social support and the frequency of specific health behaviors. Both pragmatic and intrapsychic explanations have been offered to explain this apparent positive influence of social support on health. Of our total sample, network size benefited late-stage HIV patients the most. This may reflect the aid of friends, neighbors, and relatives in accessing medical care or providing essential needs such as food and home care (i.e. the pragmatic functions of social support).

Neither negative life events nor coping emerged as a significant predictor of HIV disease progression in our sample after statistically controlling for disease classification at baseline. It is plausible that the absence of an effect for negative life events was a function of relating a baseline measure of stress to distal outcomes. Alternatively, negative life events may be appraised as less threatening by individuals who are faced with a terminal illness. Studies on HIV-positive populations have shown that assertive or active coping is associated with better cellular immunity (10,11), and there is some suggestion that such coping activities may be associated with lengthened survival (25). We were unable to replicate these findings. The methodology in previous studies has been cross-sectional, and coping has been assessed by fairly HIV disease-specific means. Perhaps the Ways of Coping–Revised measure is too general a measure to uncover effects of coping on HIV disease progression and longevity.

Several limitations of the present study deserve mention. First, the temporal distance between predictor variables and ultimate outcomes ranged from six months to eight years. Therefore, changes in predictor variables after baseline were not considered. Although this approach provides a more conservative estimate of predictor effects with less chance of confounding, it may miss important psychosocial events or changes in status that occur before the outcome criterion is reached. In particular, the negative life events and coping variables might experience large fluctuations over time. To remedy this, some statistical software packages are beginning to offer ways to include time-dependent covariates in survival analysis. However, this option has been introduced in the more popular statistical packages in only a very limited format, one that was not appropriate for our analyses.

Another limitation of this study is related to the representativeness of the sample. Our sample included mostly young, well-educated, Caucasian participants with plentiful access to health care resources and health information. Given the higher

prevalence of HIV among other subpopulations, including women, ethnic minorities, intravenous drug users, and hemophiliacs, there is a need for researchers to examine sociocultural background or risk status in predicting HIV disease progression. As in most longitudinal research, continued participation is difficult to maintain. We experience approximately 7% attrition at the HNRC each year. In survival analysis, however, attrition bias is a less serious threat to external validity because participants with partial data can be included up until their departure from the study as a censored data point. Therefore, inferences from our present analyses are much more impacted by a selection bias than by attrition bias.

The statistical power of our analyses was limited by the censoring of data points for whom individuals had not met our outcome endpoints of interest (from 50% to 75%). For this reason, we plan to repeat this set of analyses in the future, when a larger percentage of non-censored data could be included. Although we limited our covariates to baseline disease classification, there are many background characteristics and grouping variables that might be interesting covariates. Sexual orientation, demographic features, antiretroviral use, and type of coinfection have been suggested as additional covariates when examining the influence of psychosocial variables and mood states on HIV disease progression.

Although survival analyses provide a conservative approach for evaluating the relative influence of various factors on HIV disease progression, it remains difficult to eliminate all potential confounds, and the underlying statistical procedure remains largely correlational in nature. Indeed, experimentally-controlled intervention studies (38,39) may provide a more valid means of estimating the influence of psychosocial variables and affective states on HIV disease progression. Nevertheless, our findings suggest that depressive symptoms and social support may be predictive of the rate of HIV disease progression among men who are HIV positive. In our sample, asymptomatic individuals with large social networks experienced a more rapid onset of early symptoms (although we caution that this may be a chance finding). At later stages of HIV disease, social support had a positive influence on longevity, perhaps relating to increased instrumental support from family and friends. Depressive symptoms, although not related to the early progression of HIV disease, were a risk factor for rapid decline after AIDS diagnosis. Because the efficacy of known medical treatments for HIV disease remains relatively modest, psychosocial variables and mood status may be additional targets for health intervention. Future studies should focus on both depressive symptoms and social support in HIV disease, and on the possible variability of effects across levels of disease severity.

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