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Psychosocial Factors Predict CD4 and Viral Load Change in Men and Women With Human Immunodeficiency Virus in the Era of Highly Active Antiretroviral Treatment

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Abstract

Objective—Most previous longitudinal studies demonstrating relationships between psychosocial variables and human immunodeficiency virus (HIV) disease progression utilized samples of gay men accrued before the era of highly active antiretroviral treatment (HAART), without including viral load (VL) as an indicator of disease progression or assessing the impact of medication adherence. This study sought to determine whether psychosocial variables would predict both CD4 and VL changes in a diverse sample assessed entirely during the era of HAART and accounting for adherence effects.

Methods—This longitudinal study assessed a multiethnic HIV+ sample (n = 177) of men and women in the midrange of illness (CD4 number between 150 and 500; no previous acquired immunodeficiency syndrome [AIDS]–defining symptom) every 6 months for 2 years. Hierarchical linear modeling was used to model change in CD4 and VL controlling for sociodemographics (age, gender, ethnicity, education) and medical variables (baseline CD4/VL, antiretroviral medications at each time point, adherence).

Results—Baseline depression, hopelessness, and education predicted the slope of CD4 and VL. Avoidant coping and life event stress predicted VL change. Cumulative variables produced stronger relationships (depression, avoidant coping, and hopelessness with CD4/VL slope and life events stress with VL slope). High cumulative depression and avoidant coping were associated with approximately twice the rate of decline in CD4 as low scorers and greater relative increases in VL. Social support was not significantly related to CD4 or VL slope.

Conclusions—Psychosocial factors contribute significantly to the variance in HIV disease progression (assessed through CD4 number and VL) in a diverse sample, accounting for adherence and do so in the era of HAART.

Keywords

HIV/AIDS; disease progression; adherence; depression; coping; stress

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INTRODUCTION

Studies, primarily conducted on gay men before the availability of highly active antiretroviral therapy (HAART), suggest that psychosocial variables may predict disease progression in human immunodeficiency virus (HIV). Thus, depression has been related to faster CD4 decline (1), progression to acquired immunodeficiency syndrome (AIDS) (2–5), and mortality (6–8). Similarly, stress has predicted faster CD4 cell decline (9,10), clinical symptoms (11,12), and progression to AIDS (3,4). Longitudinal studies of coping found that denial predicts greater CD4 decline (11), progression to AIDS (11,13,14), and mortality (11). Conversely, active coping predicted decreased clinical progression (15), AIDS (16), and lower mortality (17). Mixed results have been found in the literature for social support, with some studies showing higher social support predicting slower disease progression to AIDS (4), less rapid decline in CD4 cells (18), slower symptom onset (4,14), and longer survival (7). However, others found either no relationship between social support and disease progression (19) or higher social support predicting faster decline in CD4 (20). Only 1 study of psychosocial predictors was undertaken during the time of HAART, and it reported that depression predicted CD4 decline and mortality (8). However, this study only examined depression in women, and the accrual period (1993–1995) was completed before the availability of protease inhibitors (PIs).

The present longitudinal study expands on the above findings by reporting on a diverse sample of men and women conducted entirely during a period of widespread HAART/PI availability, by examining several psychosocial predictors in addition to depression, and by predicting the change in both CD4 cells and viral load (VL) over time. VL was not available when most of the earlier studies were undertaken. In addition, since some studies suggested that cumulative measurement of psychosocial variables could be important (6,8,13), a compareison of baseline and cumulative measurement of these variables was undertaken. The intent was to determine if the psychosocial variables would predict above both traditional control variables (i.e., age, race, gender, socioeconomic status [SES]), as well as medically important behaviors (i.e., adherence, initial disease status, medications prescribed). This was accomplished using a statistical methodology, hierarchical linear modeling (HLM), that allowed for the control of medication changes at every time point. CD4 cell counts and VL were chosen because of their ability to predict clinical outcomes (21,22).

Adherence to antiretroviral medications prescribed for the treatment of HIV is central to the effective management of the disease (23–25). Poorer adherence to antiretroviral medications has been associated with more rapid HIV disease progression as measured by HIV-1 VL or CD4 cell counts (26–30) and has been associated with the emergence of viral mutations which can result in medication resistance (23,28,31).

The relationship between medication adherence in HIV and psychosocial factors is well established. Poorer adherence has been related to stressful life events, depression, hopelessness and anxiety, lower social support, lower levels of patient knowledge about HIV, as well as characteristics of the treatment and treatment setting (32–36). As medication adherence is of central importance to both HIV disease progression and sensitive to the psychosocial milieu of the patient, its relationship with the psychosocial predictors in this study and its relationship to the disease progression markers were also carefully considered.

METHODS

Subjects

Participants were a paid volunteer sample recruited through physician offices, specialty clinics, service organizations, and hospitals. Subjects were included in this study if they were HIV positive and had CD4 cells between 150 and 500 at study entry, thus capturing people in the

midrange of disease who we hypothesized would be most vulnerable to the possible impact of psychosocial factors on HIV disease. Subjects were excluded if they had ever experienced an AIDS-defining (Category C) symptom, ever had CD4 cells below 75, were under age 18, had other life-threatening illnesses (e.g., cancer), were actively psychotic or suicidal, had dementia or current alcohol or drug dependence or current IV use.

Design

This study used a longitudinal design where participants were assessed every 6 months for a period of 2 years. The accrual period lasted 2.5 years, and the study period was from 1997 to 2002.

Procedures

At baseline, subjects completed written informed consent, psychosocial questionnaires, a clinical assessment interview, and blood draw for CD4 and VL assay. Follow-up visits, repeated every 6 months, included the questionnaire battery, brief interview, and blood draw. Study procedures, including informed consent, were approved by the institutional review board.

Measures

Demographics and background medical information (see Table 1) were assessed by self-report. Prescribed medications and adherence were assessed through interviewer-administered AIDS Clinical Trials Group (ACTG) Adherence Measure (32). Adherence was calculated as the percentage of missed doses averaged over each assessment time point for which the subject was taking medications. Past drug/alcohol abuse and dependence and psychotic symptoms were assessed using the interviewer administered Structured Clinical Interview Diagnostic-Diagnostic and Statistical Manual-III-R.

Disease Progression Markers

CD4 lymphocyte count (CD3+CD4+) was determined by whole-blood 4-color direct immunofluorescence using a coulter XL-MCL flow cytometer. VL utilized the Roche Amplicor RT/PCR assay sensitive to 400 copies of plasma RNA.

Psychosocial Measures

Depression was assessed by the Beck Depression Inventory (BDI) (37), a 21-item scale of cognitive, affective, and behavioral symptoms of depression over the past week, which includes subscales for affective and somatic symptoms (38). Hopelessness was measured by the Beck Hopelessness Scale (BHS) (39), a 20-item true/false questionnaire that examines feelings about the future, loss of motivation, and expectations. Coping strategies were assessed using the COPE (40), a 24-item scale, modified for HIV populations, which assesses the endorsement of each of 12 cognitive and behavioral coping strategies. Two subscales, denial and behavioral disengagement, were combined for an avoidant coping composite because of previous work relating them to disease outcomes in HIV (4,11,14). Life event stress was assessed using the Sarason et al. (41) life events scale sum of the weighted (−3 to +3) negative life events excluding health related events. Social support was assessed using the ENRICHED Social Support Instrument (ESSI) (42), a 7-item scale assessing support over the past month, with 1 item asking if participants were married/partnered or not. Cumulative average psychosocial measures were calculated by averaging the patients' score from each of the first 4 assessment time points that were completed. This measure would be higher, for example, in patients who are chronically depressed rather than depressed at only baseline and provides a more reliable measure than single baseline assessment.

Statistical Methods

The main analyses used HLM (43,44) to model CD4 and VL change. HLM was chosen because it permits control for antiretroviral use at each time point, allows for prediction of slope, and the calculation of expected changes in CD4 and VL for each predictor. Variance in disease progression markers is separated into 2 levels: Level 1 represents a growth model for each individual capturing within-person change in CD4 and VL over repeated measurements. Level 2 represents a model of interindividual differences in parameters of individual change and uses between-person characteristics (e.g., depression) to predict change. Thus, systematic variability of the slopes and intercepts at level 1 are modeled by predictors at level 2.

Covariate Selection

Level 1 covariates included prescribed antiretroviral medication (as a time-dependent covariate), time since baseline (months), and the interactions of these terms. Time since baseline reflected the length of time each of the 5 repeated assessments were conducted relative to baseline and generated the structure of the latent slope and intercept. Antiretroviral medications were dummy coded at each time point, reflecting 3 levels: no medication, combination therapy, or HAART. The demographic variables of race (coded 1 = non-Hispanic Caucasian, 0 = other), gender (coded 1 = male, 0 = female), age, education level (coded 0 = less than high school, 1 = some high school, 2 = high school graduate, 3 = trade-school or some college, 4 = college graduate, 5 = graduate degree) were included as a priori covariates relevant to HIV (45,46). Education level was used as a relatively unbiased indicator of SES because income and employment may be affected by advancing HIV disease. Initial disease status was also controlled in the level 2 model using baseline CD4 number or VL $\log_{10}$ to account for the possibility that initial level of CD4 or VL may be related to change over time. The covariates were included, a priori, in the level 2 model at the slope (the outcome of interest) and remained in both CD4 and VL models for all subsequent analysis. All continuous variables in the model were centered, and all categorical variables were coded with zero as the lowest level. Because VL was skewed, it was transformed using a $\log_{10}$ transformation.

Medication Adherence

As only 77% of the sample were taking antiretroviral medication at study entry and only 90% of the sample were taking medications at any time during the study, medication adherence data were only available on a subset of the whole sample (n = 160). Because of the central role of adherence in optimal management of HIV, the main analyses were rerun to determine whether the significance of the psychosocial variables on disease progression was independent of adherence.

RESULTS

Description of the Sample

Demographic and medical information is presented in Table 1. Our sample (n = 177) was diverse in terms of gender, ethnicity, and sexual orientation. Most participants were of low to moderate SES, many were on disability or unemployed, and about one-third of the sample had a history of alcohol/drug abuse. At study entry, the average CD4 count was 297 and mean HIV VL was 44,861. Over 2 years of follow-up, 90% of patients had taken antiretroviral medications. Table 2 gives descriptive information for the psychosocial predictors.

Prediction to CD4 Change Over Time

Basic Model—Table 3 contains the basic equations (and explanation of terms) for the HLM model, and Table 4 includes the results and significance tests for the basic model for predicting CD4 change/slope controlling for antiretroviral medications and other covariates. There is a

significant linear decrease in CD4 over time (γ_{10}) controlling for covariates. The model indicates that average CD4 level at study entry is 285.52, and this decreased at a rate of 4.45 CD4 cells/month (about 53 cells/yr) above and beyond the effects of medications for minority women of low SES (i.e., categorical variables coded 0). There is also significant individual variation in CD4 change over time (χ^2 (170) = 415.48, p = < .001).

Covariates—At level 1 (see Table 4), there is a significant increase in CD4 attributable to changes in being on combination therapy or HAART (γ_{40} and γ_{50}). At level 2, higher education and higher baseline CD4 buffered CD4 decline.

The Contribution of Psychological Variables

Baseline Predictors—Faster CD4 decline was predicted from baseline depression (γ_{16}), hopelessness (γ_{16}), and social support (γ_{16}; trend) but not from avoidant coping or life event stress (Table 5a). Subsequent analysis restricting the BDI to the cognitive/affective subscale only showed a continued tendency toward significance (γ_{16} = −0.130, t(170) = −1.602, p = .11).

Relationship to Cumulative Variables—Cumulative depression, hopelessness, and avoidant coping were more strongly related to CD4 decline than baseline measures. The cognitive/affective subscale of the BDI was also significantly related to CD4 decline (γ_{16} = −0.189, t(170) = −1.936, p = .05), as were both denial (γ_{16} = −1.160, t(170) = −2.652, p = .009) and behavioral disengagement (γ_{16} = −1.12, t(170) = −2.127, p = .035). Cumulative life events stress and social support were not significantly related to CD4 change.

Clinical Translation—Decline ratios (DRs) were calculated to compare the impact of the high and low levels (75th and 25th percentile) of each psychological variable on CD4 and VL change (see Table 5a). The formula for the calculation of the DR is: DR = [γ_{10} + γ_{16} (75th percentile score − mean)]/[γ_{10} + γ_{16} (25th percentile score − mean)], where γ_{10} is the average rate of CD4 decline controlling for other covariates in the model and γ_{16} is the increment in CD4 decline for every point above or below the mean of the psychological variable. Cumulative depression provides an illustrative example. The rate of decline for those of average depression (γ_{10}) is −3.36 CD4 cells per month (run with BDI in the model), and the increment for each point from the mean of depression (γ_{16}) is −0.21. The 75th and 25th percentile scores in cumulative depression were 14.25 and 4.25, respectively, which were 4.20 and −5.80 points from the mean, respectively. The rate of CD4 cell decline for those at the 25th percentile in depression is given by (−3.36) + [(−0.21) (−5.80)] = 2.14 per month, or approximately 26 per year. The rate of CD4 cell decline for those at the 75th percentile in depression is given by (−3.36) + [(−0.21) (4.20)] = 4.24 cells per month, or approximately 51 per year. Thus those scoring at the 75th percentile in cumulative depression lose their CD4 cells at almost twice the rate compared with those at the 25th percentile, as indicated by DR = 1.96.[1] Increase ratios for VL log are calculated in a parellel fashion (Table 7a).

Other DRs for the significant psychosocial predictors are presented in Table 5a.

[1]An alternative method for assessing the impact of repeated measures of depressive symptomology on HIV disease progression markers utilized by Ickovics and colleagues (8) identified those with limited, intermittent, and chronic depression based upon the number of assessment points at which the participant had depression scores above a clinical cutoff score corresponding to the 80th percentile. Applying the same methodology within this sample yielded a trichotomous variable that was significantly associated with both CD4 (γ_{16} = −1.73, t(170) = −2.241, p = .026) and VL change (γ_{16} = -1.38×10^{-2}, t(170) = 3.391, p = .001) whereby those with chronic depression experienced a loss of CD4 cells at 2.02 times the rate and an increase in VL at 5.00 times the rate as those with limited or no depression. These results are consistent with the results of the main analyses.

Prediction to VL Change Over Time

Basic Model (Table 6)—VL significantly increased over time (γ_{10}), controlling for covariates. Patients had an average of 4.38 VL log units at study entry and increased 0.014 U/month (0.168 log units/yr). Individual variation around the slope of VL (change) was also significant (χ^2 (170) = 235.62, p = .001)

Covariates (Table 6)—Antiretroviral medications were significantly associated with lower levels of VL (γ_{20}, γ_{30}). Only education was significantly related to log VL slope (t(171) = −2.207, p = .029).

The Contribution of Psychological Variables

Prediction From Baseline Variables (Table 7a)—Higher baseline depression (BDI), hopelessness (BHS), negative life events, and avoidant coping (COPE) predicted greater VL increase. The cognitive/affective subscale of the BDI showed similar results ($\gamma_{16} = 0.1073 \times 10^{-2}$, t(170) = 2.325, p = .021), as did both denial ($\gamma_{16} = 0.433 \times 10^{-2}$, t(170) = 2.655, p = .009) and behavioral disengagement ($\gamma_{16} = 0.608 \times 10^{-2}$, t(170) = 3.298; p = .002). Baseline levels of social support were not significantly related to VL change over time.

Relationship to Cumulative Variables (Table 7a)—Cumulative depression, hopelessness, negative life events, and avoidant coping maintained their significant association with VL change. The COPE subscales of denial ($\gamma_{16} = 0.614 \times 10^{-2}$, t(170) = 2.293, p = .023) and behavioral disengagement ($\gamma_{16} = 0.896 \times 10^{-2}$, t(170) = 3.734, p = .001) were also significantly related to VL increase, as was the cognitive/affective subscale of the BDI ($\gamma_{16} = 0.150 \times 10^{-2}$, t(170) = 2.697, p = .008). Cumulative measures of social support were not significantly related to VL change.

Clinical Translation (Table 7a)—Those with high baseline depression scores (75th percentile) experienced close to a threefold increase in VL as compared with those with low scores (25th percentile). The largest baseline increase ratio (6.41) was observed for avoidant coping. The largest cumulative increase ratio was found for depression (7.44).

Medication Adherence—Cumulative self-reported medication adherence was significantly related to each of the psychosocial predictors, except social support (see Table 8). Medication adherence was significantly associated with slope of VL (γ_{16}=0.042, t(153)=2.539, p = .012) but not to CD4 change ($\gamma^{16} = -3.22$, t(153) = −0.979, p = .330). Controlling for medication adherence in these models did not alter the significance of any of the relationships found in the main analyses (see Table 5b and Table 7b), with the exception of life events stress, which had significantly predicted VL change but now showed only a trend (p = .055).

DISCUSSION

These results provide evidence that even in the era of powerful HAART medications, psychosocial variables still account for significant variation in CD4 cell number and do so for VL as well. The results provide valuable confirmation of earlier studies (6,11,13) that established these relationships for depression, negative life events, and coping before the availability of HAART. In addition to depression, our results establish that hopelessness and denial/avoidant coping have significant relationships with both CD4 and VL changes over time and extend findings to both men and women with access to HAART throughout the entire period of the study. This is the first study of which we are aware that establishes a prospective relationship between hopelessness, denial/avoidant coping, life event stress, and accelerated rate of increase in VL. (A prospective relationship between depression and VL has previously

been noted for women (8).) In fact, plasma VLs may be more sensitive to psychological influences than CD4, as indicated by higher increase and decline ratios.

Although many studies have found that depression and other psychological variables predict disease progression in HIV, none, to our knowledge, have controlled for adherence. This has become particularly important in the era of HAART as it has been estimated that adherence rates of up to 95% are required for achieving and maintaining viral suppression (26,27). It is interesting to note that in our study, medication adherence was significantly related to VL change, but not to CD4 change. Although the reason for this is not known, it raises the possibility that VL may be more immediately responsive to antiretroviral medications than CD4 cell reconstitution, which may require a longer period of time.

Our results provide information on the predictive relationships from both baseline and repeated measures of stress, distress, and coping. The presence of a significant relationship between cumulative avoidant coping with rate of CD4 change over time compared with the absence of a significant relationship with baseline supports the use of repeated assessments over time. The superior predictive power of repeated measures over baseline measures has been noted by others (5,6,8,13) and may help to explain some of the contrary findings relating depression to disease progression when depression was only measured at baseline (47).

Surprisingly, not only did no significant results emerge between social support and disease progression but a nonsignificant trend was observed whereby higher levels of baseline social support predicted more rapid CD4 decline. This puzzling result has some support in the existent literature (20) but is not consistent with results of several other studies which identified beneficial relationships (4,7). Subsequent analyses of our data revealed that higher levels of social support were associated with being sexually active ($r = 0.27$, $p < .001$) (assessed through interview) but were not associated with unsafe sex practices ($r = 0.00$, not significant). Notable aspects of this study that may be related to the absence of social support findings include the restriction of study participants to those in the midrange of disease, the exclusion of IV and dependent drug users, and the use of a measure that has items but not subscales for emotional, instrumental, and informational support.

Education was the only sociodemographic covariate significantly related both to rate of CD4 and VL change. The SES-health gradient is well established in the general literature (48), but this study is the first of which we are aware to predict changes in both biological markers of disease progression in HIV.

There are a number of plausible behavioral and biological mechanisms that have been suggested in explaining the link between depression/stress and disease progression (5,49). In this sample, adherence to medication does not explain the effect. Alterations in the hypothalamic-pituitary-adrenocortical system, including cortisol, have been demonstrated both in stress and depression, have been predictive of faster disease progression in HIV (4, 13), and may stimulate HIV replication (50). Similarly, products of the sympathetic nervous system (norepinephrine) become elevated during stress and have been shown to enhance HIV viral replication in vitro (51,52). Important immune variables, including cytotoxic T lymphocytes and natural killer cells, undergo change during depression in HIV patients and have been related to symptom onset and disease progression in HIV (53,54).

Limitations

Although psychosocial variables were related to important markers of disease progression (i.e., CD4, HIV VL) that are known to predict clinical outcomes (21,22), the relatively short follow-up time of this study precluded predicting to clinical symptoms or death. The longitudinal design allows for the statement of predictive but not necessarily causal relationships between

our baseline psychosocial variables and disease progression markers. Another limitation of the study was that the psychosocial (e.g., negative life events) and control (e.g., medication adherence) measures are based on self-reports and are vulnerable to the biases of that methodology. For example, it has been reported that life events stress measured by interview predicts CD4 change (3), whereas the present study using self-report assessment did not (although it did predict to VL). Finally, although changes in depression were carefully measured across assessments, the treatment of depression was not tracked and was not part of these analyses.

Conclusions and Future Directions

In summary, the present study demonstrated that several psychosocial factors contribute to the variance in HIV disease progression even in the present era of HAART medication. In particular, feelings of hopelessness, depressed mood, and avoidant coping predict an accelerated decline in CD4 cells and an increase in HIV VL. Pharmacologic (55,56) and behavioral treatments (57,58) have been shown to decrease depression in HIV patients. To the extent that these treatments may also attenuate both depressed affect and disease progression, large scale clinical intervention trials are needed to determine whether reducing distress and hopelessness, and improving adaptive coping skills in HIV infected individuals can decrease disease progression. Recent findings from a study of stress management in gay men with HIV (59) suggests that this may be the case, at least for VL.

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Glossary

HAART, highly active antiretroviral treatment
VL, viral load
HIV, human immunodeficiency virus
AIDS, acquired immunodeficiency syndrome
PI, protease inhibitor
HLM, hierarchical linear modeling
DR, decline ratio
SES, socioeconomic status
BDI, Beck Depression Inventory
BHS, Beck Hopelessness Scale
N/A, not applicable

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TABLE 1

Background and Medical Information

Demographics (n = 177), variable		Medical Information Variable	
Gender		Immune measures	
		CD4 (cells/mm^3).	
Male	70.1%	M	296.71
Female	29.9%	SD	102.45
Age		Viral load	
M	37.49	M	44,861.42
SD	8.88	SD	120,118.81
Ethnicity		Antiretroviral medication	
Non-Hispanic white	30.5%	None	23.2%
African American	36.2%	Combination therapy (non-HAART)	20.3%
Hispanic white	28.2%	HAART	56.5%
Other	5.1%	Past STDs	
Education		M	1.18
Some high school or less	18.1%	SD	1.18
High school graduate	13.7%		
Trade school/some college	40.7%	Medication adherence (average % of missed doses in past 3 days)	
College graduate	18.7%	M	0.099
		SD	0.173
Graduate degree	8.8%		
Employment		History of substance abuse or dependence	
Full time	18.6%	Alcohol	36.2%
		Sedatives	7.6%
Part time	13.6%	Cannabis	23.8%
Unemployed	15.3%	Cocaine	31.0%
Disability	42.2%	Opioids	5.7%
Other	10.2%	Hallucinogens	3.1%
Income		Other drugs	1.3%
Less than $5,000/yr	32.6%	Route of infection	
$5,000-$10,000/yr	29.0%	Gay/bisexual sex	50.6%
$10,000-$20,000/yr	19.4%	Heterosexual sex	38.1%
Greater than $20,000/yr	19.0%	IV drug use	4.5%
Sexual orientation		Multiple	3.4%
Homosexual/bisexual	54.8%	Other	3.4%
Heterosexual	45.2%	Sleep (hrs/night in past week)	
		M	7.00
		SD	1.71
		Exercise (hrs/week in past month)	
		M	4.51
		SD	5.39

TABLE 2

Means and Standard Deviations of Baseline and Cumulative Psychological Predictors of HIV Disease Progression Markers

Psychological Variable	Baseline		Cumulative Measures	
	Mean	SD	Mean	SD
Depression	11.13	8.87	10.05	7.29
Hopelessness	4.29	4.34	4.08	3.66
Avoidant coping	5.76	2.45	5.52	1.78
Life stress	−5.05	5.18	−3.13	2.58
Social support	24.54	6.79	24.40	5.91

TABLE 3

The Basic Equations for Predicting Changes (Slope) in CD4 or VL(Log)[a] With Explanation of Terms

Level 1	$Y_{ti} = \beta_{0i} + \beta_{1i}$ (months since baseline)$_{ti} + \beta_{2i}$ (antretroviral1)$_{ti} + \beta_{3i}$(antretroviral2)$_{ti} + \beta_{4i}$(antretroviral1 × time)$_{ti} + \beta_{5i}$(antretroviral2 × time)$_{ti} + e_{ti}$
Y_{ti}	CD4 count for participant i at time point t
β_{0i}	CD4 at entry to the study for the ith participant
β_{1i}	Slope representing linear change in CD4 for participant i
β_{2i}, β_{3i}, β_{4i}, β_{5i}	Slopes for the antiretrovirals (2 variables dummy coded) and the interaction of antiretrovirals and months since baseline. These terms control for increases in CD4 due to a particular antiretroviral therapy at a particular time point.
e_{ti}	Residual term for participant i at time t
To examine individual differences in level 1 change parameters, the level 2 equations are	
Level 2	β_{01} (intercept)=$\gamma_{00+} + u_0$ β_{1i} (slope) = $\gamma_{10} + \gamma_{11}$ (baseline CD4)$_i + \gamma_{12}$ (age)$_i + \gamma_{13}$ (gender)$_i + \gamma_{14}$ (ethnicity)$_i + \gamma_{15}$ (education)$_i + \gamma_{16}$ (psych variable)$_i + u_1$ $\beta_{2i,3i} = \gamma_{20}$, γ_{30} (antiretroviral 1 or 2), $\beta_{4i,5i} = \gamma_{40}$, γ_{50} (antiretroviral 1 or 2 × time)
γ_{00}	Group average initial CD4
γ_{10}	Average linear change in CD4 per month
γ_{20} and γ_{30}	Average effect on level of CD4 across patients from antiretroviral 1 or 2
γ_{40} and γ_{50}	Average effect on change in CD4 across patients from antiretroviral 1 or 2
γ_{11}–γ_{15}	Effect of the a priori covariates on change in CD4
γ_{16}	Effect of individual differences on CD4 slope (γ_{10}) attributable to putative psychological variables
The *u* terms represent unexplained individual variance associated with estimation of the γ coefficients. The *u* terms for the level 2 antiretroviral equations were not significant and were fixed at zero.	

[a] The HLM model used to predict VL(log) slope is identical in all respects to that used to predict CD4 except that baseline VL(log) replaces baseline CD4 and the interaction terms of time and antiretroviral medication (γ_{40}, γ_{50}) were not significant and were deleted from the VL(log) model.

TABLE 4

Basic Model Including Coefficients and Significance Tests for Level 1 and Level 2 Covariates in Prediction of CD4 Slope Over 2 Years

	Coefficient	Standard Error	*t* Ratio	*df*	*p*
Fixed effects					
CD4 intercept, β_0					
Average initial CD4, γ_{00}	285.52	14.627	19.521	176	<.001
CD4 slope (per month), β_1					
Average slope, γ_{10}	−4.445	1.629	−2.728	171	.007
Baseline CD4/mm^3 γ_{11}	0.012	0.005	2.298	171	.023
Age, γ_{12}	−0.001	0.063	−0.007	171	.994
Gender, γ_{13}	−1.187	1.135	−1.046	171	.298
Ethnicity, γ_{14}	−1.045	1.080	−0.967	171	.335
Education, γ_{15}	1.245	0.414	3.004	171	.004
Antiretroviral 1 increment, β_2					
Average increment, γ_{20}	45.472	18.895	2.407	719	.017
Antiretroviral 2 increment β_3					
Average increment γ_{30}	15.885	15.391	1.032	719	.303
Antiretroviral 1 increment over time, β_4					
Average increment over time, γ_{40}	3.211	1.493	2.151	719	.032
Antiretroviral 2 increment over time, β_5					
Average increment over time, γ_{50}	3.429	0.998	3.437	719	.001
Random effects	SD	Variance	*df*	χ^2	*p* Value
Intercept, U_0	86.282	7444.65	175	524.04	<.001
Slope, U_1	5.130	26.32	170	415.48	<.001
Error, R	72.792	5298.69			

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TABLE 5

Prediction From Baseline Psychosocial Variables and Association With Cumulative Psychosocial Variables to CD4 Slope (A) With Additional Control for Antiretroviral Medication Adherence (B)

Predictor	(A) Main Analyses (n = 177)				(B) Main Analyses With Additional Control for Medication Adherence (n = 160)		
	γ_{16} γ Coefficient	*t* Ratio	*p*	Decline Ratio	γ_{17} γ Coefficient	*t* Ratio	*p*
Baseline measures							
Depression	−0.127	−2.436	.016	1.41	−0.153	−2.712	.008
Hopelessness	−0.231	−2.373	.019	1.27	−0.265	−2.315	.022
Avoidant coping	−0.258	−1.240	.217	N/A	−0.284	−1.181	.240
Life events stress	−0.098	−0.843	.401	N/A	−0.118	−0.921	.359
Social support	−0.150	−1.910	.057	N/A	−0.151	−1.798	.074
Cumulative measures							
Depression	−0.207	−3.364	.011	1.96	−0.235	−3.303	.002
Hopelessness	−0.297	−2.772	.007	1.37	−0.302	−2.483	.014
Avoidant coping	−0.742	−2.655	.009	1.71	−0.739	−2.482	.014
Life events stress	−0.189	−0.876	.382	N/A	−0.192	−0.821	.413
Social support	−0.036	−0.362	.718	N/A	−0.025	−0.233	.816

TABLE 6

Basic Model Including Coefficients and Significance Tests for Level 1 and Level 2 Covariates in Prediction of Viral Load (Log) Slope Over 2 Years

	Coefficient	Standard Error	*t* Ratio	*df*	*p*
Fixed Effects					
VLlog intercept, β_0					
Intercept, γ_{00}	4.3791	0.0965	45.40	176	<.001
VLlog slope (per month), β_1					
Average slope, γ_{10}	0.01371	0.0069	1.974	171	.050
Baseline VLlog, γ_{11}	0.00089	0.0026	0.340	171	.734
Age, γ_{12}	0.00003	0.0003	0.075	171	.940
Gender, γ_{13}	0.00549	0.0065	0.846	171	.399
Ethnicity, γ_{14}	0.00821	0.0064	1.289	171	.199
Education, γ_{15}	−0.00533	0.0026	−2.207	171	.029
Antiretroviral 1 increment, β_2					
Average increment, γ_{20}	−1.03267	0.1212	−8.520	720	<.001
Antiretroviral 2 increment, β_{30}					
Average increment, γ_{30}	−1.04281	0.1112	−9.376	720	<.001
Random effects	SD	Variance	*df*	χ^2	*p* Value
Intercept, U_0	0.8787	0.7721	175	702.16	<.001
Slope, U_1	0.0193	0.0004	170	235.62	.001
Error, *R*	0.6192	0.383			

TABLE 7

Prediction From Baseline Psychosocial Variables and Association With Cumulative Psychosocial Variables of Log Viral Load Slope (A) With Additional Control for Antiretroviral Medication Adherence (B)

Predictor	(A) Main Analyses (n = 177)				(B) Main Analyses With Additional Control for Medication Adherence (n = 160)		
	γ_{16} γ Coefficient × 10^{-2}	*t* Ratio	*p*	Increase ratio	γ_{17} γ Coefficient × 10^{-2}	*t* Ratio	*p*
Baseline measures							
Depression	0.092	2.920	.004	2.95	0.098	3.012	.003
Hopelessness	0.185	2.922	.004	1.98	0.194	2.702	.008
Avoidant coping	0.354	3.713	<.001	6.41	0.366	3.448	.001
Life events stress	0.131	3.004	.004	2.23	0.127	2.736	.007
Social support	−0.005	−0.121	.904	N/A	−0.013	−0.281	.779
Cumulative measures							
Depression	0.126	3.329	.001	7.44	0.115	2.731	.007
Hopelessness	0.219	3.001	.004	2.31	0.193	2.414	.017
Avoidant coping	0.480	3.246	.002	5.75	0.450	2.975	.004
Life events stress	0.231	2.319	.022	1.82	0.202	1.934	.055
Social support	−0.510	−0.887	.377	N/A	−0.040	−0.671	.503

TABLE 8

The Interrelationship (Pearson Correlations) Between Self-Reported Antiretroviral Medication Adherence and Psychosocial Predictors (Depression, Hopelessness, Avoidant Coping, Life Event Stress, and Social Support)

Cumulative Measures	1	2	3	4	5	6
1. Adherence (ACTG) (n = 160)	—	0.37**	0.24**	0.23**	0.31**	−0.03
2. Depression (BDI)		—	0.69**	0.48**	0.41**	−0.44**
3. Hopelessness (BHS)			—	0.40**	0.35**	−0.45**
4. Avoidant coping (COPE)				—	0.20**	−0.19**
5. Life events stress (LES)					—	−0.29**
6. Social support (ESSI)						—