Psychological Risk Factors for HIV Pathogenesis: Mediation by the Autonomic Nervous System

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Background: *Epidemiologic studies have identified psychological risk factors for specific physical diseases, but the biological mechanisms mediating these relationships remain poorly defined.*

Methods: *Social inhibition and autonomic nervous system (ANS) activity were assessed on multiple occasions in 54 gay men with asymptomatic human immunodeficiency virus (HIV) infection. Following baseline ANS assessment, plasma HIV-1 viral load and CD4+ T cell levels were monitored for 12–18 months to assess relationships between ANS activity and HIV pathogenesis.*

Results: *We confirmed the previously reported relationship between socially inhibited temperament and vulnerability to viral pathology. Plasma viral load set-point was elevated eight-fold in socially inhibited individuals, and these individuals showed poorer virologic and immunologic response to initiation of highly active antiretroviral therapy (HAART). Effects were independent of duration of infection, HAART regimen, demographic characteristics, and health-relevant behavior. Neurophysiologic assessments documented elevated ANS activity in socially inhibited individuals, and mediational analyses showed that such differences could account for 64%–92% of the covariance between social inhibition and virologic parameters.*

Conclusions: *These data provide the first clinical evidence that differential neural activity mediates relationships between psychological risk factors and infectious disease pathogenesis. Such findings also suggest novel targets for adjunctive therapy in long-term control of HIV-1 disease.*
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Key Words: Temperament, autonomic nervous system, viral pathogenesis, human immunodeficiency virus, psychoneuroimmunology

Introduction

As far back as the second century AD, observant physicians noted that certain psychological characteristics seemed to be associated with increased vulnerability to physical illness (Kagan 1994; Solomon and Moos 1964). Contemporary epidemiologic studies have documented several such relationships, including a heightened risk of myocardial infarct among depressed individuals (Denollet et al 1996, 2000; Frasure-Smith et al 1993; Rozanski et al 1999) and an increased risk of all-cause mortality in chronically hostile people (Barefoot et al 1989; Everson et al 1997). Perhaps the earliest relationship between individual psychological characteristics and physical health was drawn by the Greek physician Galen, who noted that shy, sensitive, "melancholic" people seemed particularly prone to infectious diseases (Kagan 1994). Epidemiologic research has verified an increased prevalence of immunologically mediated diseases among socially inhibited individuals (Bell et al 1990; Gauci et al 1993; Kagan et al 1991; Pancheri et al 1982), and controlled viral challenge studies show a heightened vulnerability of introverts to upper respiratory infection (Broadbent et al 1984; Cohen et al 1997; Totman et al 1980) and accelerated progression of simian immunodeficiency virus infection among rhesus macaques low in sociability (Capitanio et al 1999). However, the physiologic processes that mediate such relationships remain poorly understood. Genetic differences in central nervous system (CNS) function are believed to contribute to inhibited social behavior (Gray 1991; Kagan 1994; Rothbart et al 1994), but the biological mechanisms linking CNS activity to peripheral infectious disease risk have not been identified. In fact, throughout the entire literature on psychological risk factors for physical disease, no neural or endocrine variable has ever been shown to simultaneously satisfy all three epidemiologic criteria for a mediator: 1) that the putative mediator be correlated with the risk factor; 2) that the putative mediator be correlated with disease pathogenesis; and 3) that variation in the putative mediator accounts for a significant portion of the correlation between risk factor and pathogenesis (Hoyle and Kenny 1999; Kemeny 1994).

Despite the incomplete evidence, neuroendocrine responses to psychological events are widely suspected to modulate host resistance to disease (Ader et al 1995; Glaser et al 1999; Sapolsky 1994). Such dynamics are well documented in animal models (Felten et al 1987; Sheridan et al 1994), and a variety of human studies have fulfilled the first criterion for mediation by linking psychological characteristics to individual differences in neuroendocrine activity, interferon production, and localized inflammatory responses (Block 1957; Broadbent et al 1984; Buck et al 1974; Cole et al 1999b; Field 1982; Jones 1935, 1950, 1960; Kagan et al 1988; Miller et al 1999). Socially inhibited individuals are known to show increased activity in the sympathetic division of the autonomic nervous system (ANS) (e.g., elevated plasma catecholamines, sympathetic reflex facilitation, and heightened skin conductance, heart rate, and blood pressure) (Block 1957; Buck et al 1974; Cole et al 1999b; Field 1982; Jones 1935, 1950, 1960; Kagan et al 1988; Miller et al 1999). However, it is unknown whether heightened sympathetic nervous system (SNS) activity plays a role in infectious disease in humans, or whether individual differences in SNS activity contribute to the disease risks associated with social inhibition.

In a 1996 cohort study of human immunodeficiency virus (HIV)-1 disease progression, we found that gay men who concealed their homosexual identity showed a 20%–40% acceleration in CD4+ T cell decline, and times to acquired immune deficiency syndrome (AIDS), and HIV-specific mortality (Cole et al 1996). Mediational studies ruled out explanations based on demographic, behavioral, or medical treatment differences. However, closeted participants did show several cardinal characteristics of socially inhibited temperament, including reduced emotional expressiveness, heightened sensitivity to others, and a tendency to withdraw in the face of threat or uncertainty (Cole et al 1997). Previous studies documenting elevated SNS activity in socially inhibited individuals (Block 1957; Buck et al 1974; Cole et al 1999b; Field 1982; Jones 1935, 1950, 1960; Kagan et al 1988; Miller et al 1999) led us to recruit a new sample of early-stage HIV patients to evaluate relationships between temperament, ANS activity, and HIV-1 disease progression (Cole et al 2001). The present analyses seek to determine whether social inhibition represents a psychological risk factor for intensified HIV pathogenesis, and whether individual differences in ANS activity mediate that relationship. Because progression to AIDS-defining clinical disease is fundamentally driven by HIV-1 replication, the present studies focus on individual differences in plasma viral load "set-point" as a primary indicator of clinical disease risk (Mellors et al 1996). To define the relevance of psychological risk factors in the era of effective antiretroviral therapies, we also examine the role of social inhibition and ANS activity in explaining the marked individual differences in virologic and immunologic response to initiation of highly active antiretroviral therapy (HAART) (Ramratnam et al 2000; Sharkey et al 2000; Zhang et al 1999).

Methods and Materials

Study Design

In a sample of 54 HIV seropositive homosexual men recruited from the western Los Angeles metropolitan area, psychological characteristics, ANS activity, HIV-1 plasma viral load, and CD4+ T lymphocyte levels were assessed on two occasions 7–14 days apart at baseline, and again 11–18 months later. Eleven HIV seronegative gay men were recruited in parallel to serve as healthy control subjects. Participants were screened to exclude individuals with recent seroconversion, current HIV-related symptomatology, history of AIDS-defining conditions (including 1993 CDC case definition Category B or C clinical conditions or peripheral blood CD4+ T cell level $< 200/mm^3$), medical conditions or drug regimens that might influence ANS activity, including alcoholism, heavy recreational drug use (nonprescribed opioids, amphetamines, tranquilizers, or hallucinogens more frequently than once a month), depression, anxiety, neuropathy or other neuropathologies, respiratory disease, glaucoma, cardiovascular disease/hypertension, and use of α- or β-blockers, antihistamines, or sympathomimetics. HIV-induced neuropsychological impairment was screened by computerized adaptive testing (Miller et al 1991). All participants gave informed consent and all procedures were conducted under institutional review by the University of California, Los Angeles School of Medicine and the West Los Angeles Department of Veterans Affairs Medical Center.

Behavioral, Treatment, and Psychological Assessment

Demographic, behavioral, and medical treatment variables were assessed by structured interviews and validated psychological instruments administered during each baseline and follow-up visit. Medical history variables and antiretroviral regimens were confirmed by chart review, and participants were interviewed during follow-up to gauge adherence to antiretroviral regimens (e.g., number of doses missed per week). No direct measure of inhibited temperament exists, so we assessed specific features of the syndrome using established instruments and combined scores on individual measures to produce a composite measure of social inhibition (see Appendix 1). Introversion was measured by (reverse-coded) scores on the Extraversion subscale of the NEO-60 Personality Inventory (McCrae 1991), social avoidance was measured by the Social Apprehensiveness and Intimacy Problems subscales of the Diagnostic Assessment of Personality and Psychopathology (omitting one item from the Intimacy Problems scale tapping loss of sexual interest) (Cole et al 1999b; Livesley et al 1992), and emotional inexpression was measured by the (reverse-coded) Emotional Expressiveness Questionnaire (King and Emmons 1990) and the Restricted Expression subscale

of the Diagnostic Assessment of Personality and Psychopathology. Standardized Z scores on each measure were averaged to create a single composite measure of social inhibition. Previous research suggests that cynical mistrust/irritability may contribute to relationships between social inhibition and disease (Allan and Gilbert 1997; Bagby et al 1999; Denollet et al 1996, 2000), so we assessed "hostility" by averaging Z scores on the Cook-Medley Hostility Inventory (Barefoot et al 1989), the (reverse-coded) Agreeableness subscale of the NEO-PI (Costa et al 1986), and the Irritability subscale of the Buss-Durkee Hostility Inventory (Coccaro 1992). Possible affective confounders were measured using the Center for Epidemiologic Studies Depression inventory (CESD) (Radloff 1977), the Bendig short form of the Taylor Manifest Anxiety Scale (TMAS) (Bendig 1956), and the Positive Affectivity/Negative Affectivity Scales (PANAS) (Watson et al 1988). Recreational drug use, alcohol consumption, cigarette smoking, and high-risk sexual practices (number of partners, incidence of unprotected anal-receptive intercourse) were assessed using established questionnaires (Kaslow et al 1987). Length of infection was quantified as the duration from estimated time of seroconversion (midpoint between last negative HIV serostatus report and the first HIV seropositive report) to the first ANS assessment. Personality assessment questionnaires took less than 30 min to complete, and no participant reported any difficulty completing the questionnaires. Stability of personality characteristics was gauged by reassessment at 1-year follow-up (to prevent spurious consistency due to practice/recall effects).

ANS Assessment

As previously described (Cole et al 2001), constitutive ANS activity levels were assessed at baseline on two occasions, 7–13 days apart by monitoring palmar skin conductance, brachial artery systolic blood pressure, electrocardiogram (EKG) interbeat interval (duration between R-spikes; IBI), finger photoplethysmograph pulse peak amplitude (FPA), and peripheral pulse transit time (duration from EKG R-spike to subsequent finger photoplethysmograph peak; PTT) during the final 60 sec of a 15-min resting baseline, during 90 sec of metronome-paced respiration (six respiration cycles min^{-1}), during 12-sec intervals surrounding eight auditory orienting stimuli (2-sec, 80-dB, 300-Hz tone at 30-sec intervals), during 60 sec of orthostasis after rising from a seated position, and during the final 60 sec of a 180-sec, verbal serial subtraction task (paced at 60 responses $minute^{-1}$). Autonomic nervous system activity was quantified as the SD of each indicator about its mean value under each assessment condition (Figure 1E), and measures from different indicators were standardized onto a common metric by Z-transformation (computed across subjects for each measurement condition and indicator). Individual ANS activity was quantified as the average of those individual-specific Z scores. This measure of total autonomic activity correlated .89 ($p < .0001$) with a comparable composite based on the mean level of activity (with signs reversed for IBI, FPA, and PTT to render all indicators positive for sympathetically mediated responses). Autonomic nervous system activity levels were normally distributed (normal scores test $r = .97$, no significant departure from normal, $p = .38$) and therefore treated as a continuous variable in primary statistical analyses. Individual differences in ANS activity were stable over time (test–retest $r = .79$, $p < 0001$).

HIV Pathogenesis

At both baseline visits and at follow-up, plasma HIV-1 viral load was quantified by Amplicor HN-1 Monitor (Roche Diagnostics, Indianapolis, IN), and CD4+ T cell levels were assessed by flow cytometry for CD3+/CD4+ lymphocytes. Parameters were assayed in a clinical reference laboratory blind to patient characteristics, and specimens were obtained under resting conditions before experimental procedures to avoid artifactual influence by ANS activity. HIV-1 viral load set-point was defined as the mean of all baseline plasma viral load measurements (log_{10}-transformed). To determine whether plasma viremia had reached a steady state set-point, the rate of change in plasma viral load was quantified by linear regression of log_{10}-transformed viral load on time (including follow-up over at least 12 months) in patients receiving no antiretroviral therapy. Virologic response to initiation of HAART was quantified by the change in plasma viral load from pretreatment baseline to follow-up. To determine whether differential virologic response to HAART stemmed from mutations conferring resistance to antiretroviral medications, viral reverse transcriptase and protease genes were sequenced (Trugene HIV-1, Bayer Diagnostics, Tarrytown, NY) in all patients with detectable plasma HIV-1 at follow-up. CD4+ T lymphocyte levels were measured in parallel and analyzed as a percent of total lymphocytes (similar results emerged from analyses of cells/mm^3). On all measurement occasions, recent physical health was assessed to ensure that intercurrent infections did not spuriously alter virologic or immunologic parameters. Three participants reported a recent mild illness (one during the second baseline and two at 1-year follow-up, all cold/flu-type upper respiratory infections), and were re-scheduled for assessment 2 weeks later, after symptoms had resolved.

Statistical Analyses

Relationships among indicators of social inhibition and hostility were analyzed by confirmatory factor analysis (CFA), with parameters estimated by maximum likelihood and models compared using likelihood ratio goodness-of-fit tests (Bollen 1989). CFA tests observed data for consistency with specified hypotheses, and analyses thus sought to identify models showing nonsignificant difference from the observed variance–covariance matrix among variables (i.e., the best-fitting model). Relationships between risk factors and viral load set-point were analyzed by linear regression, with subsequent multiple regression analyses controlling for potential confounders (e.g., demographic characteristics, duration of infection, prior antiretroviral treatment, or behavioral characteristics). Two sub-cohorts were defined for the set-point analyses: 1) the "antiretroviral naive cohort": 12 participants who had never taken antiretroviral medications and whose viral loads should thus represent an uncontaminated measure of viral load set-point; and 2) the "currently untreated cohort": 23 participants including all 12 members of the antiretroviral naive cohort and 11 individuals
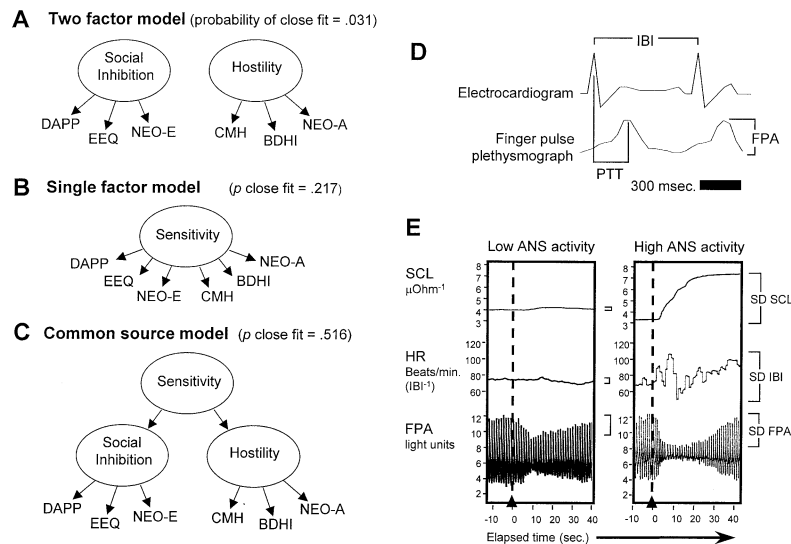
Figure 1. Quantification of social inhibition and autonomic nervous system (ANS) activity. Confirmatory factor analysis was used to analyze relationships between psychometric measures of social inhibition (DAPP, Diagnostic Assessment of Personality and Psychopathology scales measuring Social Apprehensiveness, Intimacy Problems, and Restricted Expression; EEQ, reverse-coded Emotional Expressiveness Questionnaire; NEO-E, reverse-coded NEO-Personality Inventory (NEO-PI) Extraversion) and measures of cynical hostility (CMH, Cook-Medley Hostility Inventory; BDHI, Irritability subscale of the Buss-Durkee Hostility Inventory; NEO-A, reverse-coded NEO-PI Agreeableness). Confirmatory factor analysis gauges the fit between a substantive hypothesis and an observed pattern of correlations among variables. Analysis thus seeks models showing *nonsignificant* deviation from the empirical data (i.e., good fit). Individual measures of social inhibition correlated as strongly with individual measures of hostility as they did with other indicators of social inhibition (mean r = .586 and .615, respectively, difference p = .758 by z-test), suggesting that inhibition and cynical hostility reflect a single common underlying syndrome (**A, B**). Confirmatory factor analysis supported this hypothesis by showing that a "single common factor" model (**B**) accounted for observed correlations among measures more accurately than did a "two independent factor" model (**A**) [probability of close fit for two-factor model = .031, likelihood ratio statistic testing departure of model predictions from observed data, $\chi^2(14)$ = 28.31, p = .0127, vs. the single factor model's probability of close fit = .217, with nonsignificant departure from observed data, $\chi^2(11)$ = 19.90, p = .133]. (**C**) The best-fitting model represented social inhibition and hostility as two distinct manifestations of a single common underlying syndrome [probability of close fit = .516, with nonsignificant departure from observed data, $\chi^2(11)$ = 11.39, p = .411]. Subsequent analyses of psychological risk factors for human immunodeficiency virus pathogenesis are thus based on a composite measure averaging measures of inhibition and hostility. (**D**) Autonomic nervous system activity levels were assessed on two occasions 7–13 days apart by monitoring palmar skin conductance (SCL), brachial artery systolic blood pressure (SBP), electrocardiogram (EKG) interbeat interval (duration between R-spikes; IBI), finger photoplethysmograph pulse peak amplitude (FPA), and peripheral pulse transit time (duration from EKG R-spike to subsequent finger photoplethysmograph peak; PTT) during the final 60 sec of a 15-min resting baseline, during 90 sec of metronome-paced respiration (six respiration cycles min^{-1}), during 12-sec intervals surrounding eight auditory orienting stimuli (2-sec, 80-dB, 300-Hz tone at 30-sec intervals), during 60 sec of orthostasis, and during the final 60 sec of a 180-sec verbal serial subtraction task (paced at 60 responses minute^{-1}). Autonomic nervous system activity was quantified as the SD of each indicator about its mean value under each assessment condition, and measures from different indicators were standardized onto a common metric by Z-transformation (computed across subjects and within measurement condition and indicator). Individual ANS activity was quantified as the average of individual-specific Z scores across measurement conditions and physiologic indicators. (**E**) The SCL, IBI, and FPA responses to an unexpected stimulus in individuals showing the lowest and highest overall ANS activity scores (at the time marked by the dashed line, a blood pressure cuff inflated on the arm contralateral to the SCL and FPA transducers). HR, heart rate.

who had previously taken one or more reverse transcriptase inhibitors (no protease inhibitors) and had ceased antiretroviral treatment more than 6 months before the first baseline assessment. Thirteen members of the currently untreated cohort subsequently began HAART (HAART-treated cohort), and their virologic and immunologic responses to therapy were analyzed in multiple regression of change in viral load (or CD4+ T cell level) on baseline viral load (or CD4 level) and psychological measures. Subsequent analyses controlled for potential con-

founders, such as duration of treatment and prior therapy with reverse transcriptase inhibitors. Relationships between psychological characteristics and ANS activity levels were quantified by linear regression. Mediational analyses were conducted as described (Hoyle and Kenny 1999), with SEs for the mediational path calculated by Goodman's approach (Goodman 1960). A risk factor's total relationship to HIV outcomes was quantified as the proportion of outcome variance attributable to its regression on the risk factor. The residual risk relationship, adjusted for the

influence of a mediator, was quantified as the same proportion from a multiple regression model including the putative mediator. The magnitude of mediation was quantified as (1 − [residual risk sum of squares/total risk sum of squares]) × 100%. To ensure that sampling variability did not attenuate estimates of the magnitude of mediation, analyses were repeated after correcting covariance estimates for measurement reliability using structural equation models (Hoyle and Kenny 1999). Analyses were carried out in SAS Release 6.12 for UNIX (SAS Institute, Cary, NC).

Results

Cohort Characteristics

A total of 54 HIV seropositive gay men met entry criteria for disease stage (CD4+ T cell levels > 200/mm^3, no history of AIDS, >6 months since seroconversion) and absence of ANS-relevant medications or illness (including peripheral neuropathy). Age ranged from 26 to 55 years (median 41), peripheral blood CD4+ T cells levels ranged from 243 to 1121 cells/mm^3 (median 558, constituting 12%–46% of total lymphocytes, median 27%), and plasma viral load ranged from <400 copies/mL to 422,321 copies/mL (median 43,524). Participants were well educated (94% high school graduate, 68% completing at least some college), predominately Caucasian (61%; 16% Hispanic, 16% Asian, 7% black), and had a median income in the range of $40,000–$60,000/year (21% < $20,000/year). Time since HIV seroconversion ranged from 7 to 158 months (median = 81), and all participants scored within the normal range on a computerized battery of cognitive tests identifying HIV-induced neuropsychological impairment (Miller et al 1991). At baseline, 29 patients were being treated with antiretroviral medications, and two had recently ceased treatment (currently treated cohort, n = 31). Analyses of viral load set-point were based on the remaining 23 patients (currently untreated cohort), none of whom had ever been treated with protease inhibitors. Twelve of these individuals had never taken any antiretrovirals (antiretroviral naive cohort), and 11 had been treated with reverse transcriptase inhibitors but ceased therapy more than 6 months before baseline. Thirteen members of the currently untreated cohort subsequently commenced HAART involving at least one protease inhibitor and two or more reverse transcriptase inhibitors (HAART-treated cohort). All members of the HAART-treated cohort received at least 3 months of uninterrupted therapy before follow-up (specific regimens summarized in Table 1).

Psychological Characteristics

Social inhibition was measured using multiple instruments assessing distinct features of the inhibited temperament syndrome (introversion, reduced emotional expression, and social avoidance). Previous studies of cardiovascular disease suggest that a syndrome of irritability/hostility may also be involved in inhibition-related health risk (Denollet et al 1996, 2000). To evaluate this hypothesis, we examined the correlation between measures of social inhibition and hostility/irritability (Figure 1). Canonical correlation analysis revealed substantial overlap between the two constructs (canonical r = .63, p = .004), and confirmatory factor analysis indicated that the most parsimonious account of the covariation among measures was given by a model in which inhibition and hostility represent different manifestations of a single common underlying syndrome (Figure 1). Subsequent risk-factor analyses thus utilized a composite measure averaging standardized scores on measures of both hostility and social inhibition. The resulting composite was internally consistent (Cronbach α = .81) and stable over 1 year (test–retest correlation = .76, p < .0001). Individual scores were normally distributed (departure from normality, p = .334), and did not differ as a function of age, ethnicity, prior antiretroviral use, or time since seroconversion (effect-size r ranging between .05 and .23 in magnitude, all p > .20). Social inhibition was uncorrelated with anxiety and generalized negative affectivity (TMAS, r = .22, p = .153; PANAS, r = .18, p = .179), but moderately correlated with symptoms of depression (CESD, r = .32, p = .019). No participant reported clinically significant depressive symptomatology (all CESD > 16).

Psychological Risk Factors for HIV Pathogenesis

Steady state HIV-1 viral load was measured by the mean of all baseline plasma viral load measurements. Regression analyses of currently untreated patients (antiretroviral naive or off therapy for more than 6 months) showed no significant change in plasma viral load over the subsequent 12 months, with change rates ranging between –5.8% and +.9% per month (all p > .05). The coefficient of variation (CV) in plasma viral load ranged between .4% and 3.6% for these patients (mean 2.0%). Similar values were observed in baseline data for patients who subsequently began HAART (mean CV = 2.4%, range = .3%–5.1%, difference from patients with >12 months of data, p = .444), indicating that all patients had reached a steady state level of viremia during the baseline set-point assessment period.

Socially inhibited individuals showed significantly elevated HIV-1 plasma viral load set-points relative to the remainder of the sample. Among antiretroviral naive individuals, those scoring in the upper half of the social inhibition distribution showed a median set-point of 102,329 HIV-1 copies/mL, compared with 13,283 copies/mL for individuals below the median (difference, p = .042 by Kruskal-Wallis rank analysis of variance

Table 1. Therapeutic Regimens and Virologic Characteristics for Patients Commencing HAART

Patient/Age (y)	Baseline				Follow-up	
	Viral Load[a]	CD4[b]	Prior RTI	Social Inhibition[c]	Duration[d]	HAART
037/34	422,321	699		1.36	4.8	SAQ, AZT, 3TC
042/44	40,331	328	AZT, ddI	1.28	4.5	SAQ, d4T, 3TC
062/36	102,632	650		1.21	10.9	RIT, SAQ, AZT, 3TC
027/29	16,561	446	AZT, 3TC	.69	10.5	IND, NEV, d4T
016/30	312,383	914	AZT	.61	3.0	SAQ, AZT, ddC
058/25	46,717	449		.46	3.0	SAQ, d4T, 3TC
039/35	1,646	640	AZT, 3TC	.03	4.0	IND, AZT, 3TC, ddC
014/54	276,316	297	AZT	−.54	3.0	SAQ, d4T, 3TC
060/44	65,567	259	AZT, 3TC	−.71	9.1	RIT, SAQ, d4T, ddI
043/37	4,948	697		−.72	10.9	NEL, d4T, 3TC
032/43	16,367	571	AZT, ddI	−.93	3.5	IND, d4T, 3TC
015/42	101,553	396		−1.35	3.0	IND, AZT, 3TC
024/42	13,115	316		−1.41	11.6	NEL, d4T, 3TC

HAART, highly active antiretroviral therapy; RTI, reverse transcriptase inhibitors; SAQ, saquinavir; AZT, zidovudine; 3TC, lamivudine; ddI, didanosine; d4T, stavudine; RIT, ritonavir; IND, indinavir; NEV, nevirapine; ddC, zalcitabine; NEL, nelfinavir.
[a]Mean plasma HIV-1 RNA copies/mm^3 during 2-week baseline.
[b]Mean peripheral blood CD3+/CD4+ lymphocytes/mm^3 during 2-week baseline.
[c]Social inhibition was measured as described in Figure 1, with values expressed as SD units relative to mean value (e.g., −1.0 = 1 SD below mean value).
[d]Duration of HAART at follow-up (months).

[ANOVA]). Regression analyses revealed a smooth linear relationship between social inhibition and viral load set-point ($r = .68$, $p = .014$, Figure 2). Comparable results emerged from multiple regression analyses controlling for age and time since seroconversion (both $p < .027$). Analyses including 11 individuals who had ceased antiretroviral treatment for more than 6 months before baseline verified the linear relationship between social inhibition and viral load set-point ($n = 23$ currently untreated, $r = .51$, $p = .013$, median viral load = 72,443 copes/mL for socially inhibited vs. 8709 copies/mL for uninhibited, difference $p = .017$, Figure 2). Viral load did not vary as a function of psychological characteristics such as depression (CESD, $r = -.32$, $p = .136$), anxiety (TMAS, $r = −.01$, $p = .935$), or generalized negative affectivity (PANAS, $r = −.18$, $p = .435$), and statistical control for these variables failed to attenuate relationships between inhibition and plasma HIV-1 set-point (partial $r = .52$, $p = .021$). Similar findings emerged in analyses controlling for demographic characteristics (ethnicity, income, education level), health-relevant behaviors (recreational drug use, alcohol consumption, cigarette smoking), and high-risk sexual activity (number of partners, rates of unprotected intercourse), all set-point/inhibition partial $r > .44$, $p < .05$.

Virologic response to HAART was quantified by the change in plasma HIV-1 viral load from baseline to follow-up 11–18 months later. Among patients with low levels of social inhibition, HIV-1 plasma viral load declined by an average of 162-fold following HAART, from a baseline median of 40,967 copies/mL to a posttreatment median of <400 ($p = .031$ by signed rank test of change over time). In contrast, plasma viral load declined by an average of only ~20-fold in socially inhibited patients, from a baseline median of 46,717 copies/mL to a post-treatment median of 2011 copies (difference from uninhibited patients' decline, $p = .003$ by Brown-Mood median test). Regression analyses revealed a smooth linear relationship between baseline social inhibition and HAART-induced suppression of plasma viral load ($r = .70$, $p = .008$, Figure 3C). Comparable results emerged from multiple regression analyses controlling for baseline viral load, prior antiretroviral monotherapy, and duration of HAART (partial $r = .75$, $p = .012$).

In multiple regression analyses controlling for demographic characteristics (age, ethnicity, income, education), health-relevant behaviors (recreational drug use, alcohol consumption, cigarette smoking), high-risk sexual behaviors (number of partners, unprotected intercourse), or potential affective confounders (anxiety, depression, negative affectivity), virologic response to HAART continued to show a significant linear decline with increasing levels of social inhibition (all partial $r < −.62$, $p < .05$). Viral genotyping revealed no evidence of mutations conferring resistance to protease inhibitors among patients with recoverable plasma HIV-1 at follow-up (data not shown). Mutations conferring resistance to reverse transcriptase inhibitors were identified in 50% of virus specimens recovered from the uninhibited group and 60% of those in the inhibited group (no difference, $p = .81$ by z-test). Multiple regression analyses controlling for the incidence of reverse transcriptase inhibitor–resistant viral genotypes continued to indicate a linear relationship between social inhibition and impaired virologic response to HAART (partial $r = .66$, $p = .021$). Similar findings emerged for HAART-treated patients who had never received any previous antiretroviral therapy (difference be-

A

$r = .68, p = .014$

Plasma viral load (copies / mL)

10^6
10^5
10^4
10^3

-2 -1   0 +1 +2

Social inhibition
(SD relative to mean)

B

$r = .51, p = .013$

Plasma viral load (copies / mL)

10^6
10^5
10^4
10^3

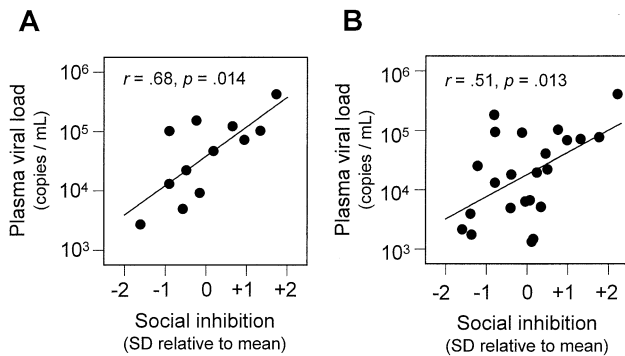-2 -1   0 +1 +2

Social inhibition
(SD relative to mean)

Figure 2. Relationship between social inhibition and human immunodeficiency virus (HIV)-1 viral load set point. Plasma HIV-1 ribonucleic acid levels were measured on multiple occasions, and linear regression was used to quantify the relationship between mean plasma viral load and individual differences in social inhibition (measured as described in Figure 1). Stable plasma viral load was verified in each patient before analysis (coefficient of variation of repeated measurements < 6%). Relationships were examined in both **(A)** the antiretroviral-naive cohort, and **(B)** the currently untreated cohort (including both antiretroviral-naive individuals and those who had previously received reverse transcriptase inhibitor treatment but had ceased therapy for >6 months).

tween high- and low-inhibition groups, $p = .025$; linear relationship, $p = .004$ controlling for baseline viral load and duration of therapy).

Socially inhibited individuals also showed poorer immunologic recovery following HAART (Figure 3B). Among uninhibited members of the HAART-treated cohort, CD4+ T cell levels increased from a baseline median of 360 cells/mm^3 (21% of total lymphocytes) to 558 cells/mm^3 (26% of lymphocytes) at follow-up ($p = .008$ by signed rank test). In contrast, CD4+ T cell levels failed to increase significantly in socially inhibited individuals (baseline median = 611 cells/mm^3, posttreatment median = 608, 23% vs. 22% of lymphocytes, $p = .352$). As a result, uninhibited individuals showed a significantly greater recovery in CD4+ T cell levels than did socially inhibited participants ($p = .002$ by Brown-Mood median test). Regression analyses revealed a linear relationship between social inhibition and the magnitude of CD4+ T cell recovery ($r = -.57, p = .021$, Figure 3D), and similar findings emerged in multiple regression analyses controlling for baseline CD4+ T cell level, prior reverse transcriptase inhibitor monotherapy, and duration of HAART (partial $r = -.61, p = .016$). Similar findings also emerged for the subset of HAART-treated patients who had never received any previous antiretroviral therapy (difference in CD4 recovery between groups, $p = .025$ by Brown-Mood median test).

Risk Factor Mediation by ANS Activity

Consistent with previous research in other samples (Block 1957; Buck et al 1974; Cole et al 1999b; Field 1982; Jones 1935, 1950, 1960; Kagan et al 1988; Miller et al 1999), socially inhibited members of this cohort showed elevated levels of ANS activity (Figure 4). Autonomic nervous system activity was quantified by the variability of heart rate, skin conductance, finger pulse amplitude, and peripheral pulse transit time at rest and in response to auditory orienting signals, paced respiration, orthostasis, and a pressured mental arithmetic stressor (Figure 1). Regression analyses documented significantly elevated ANS activity among socially inhibited individuals (for the sample as a whole, $r = .29, p = .038$; for the antiretroviral-naive cohort, $r = .65, p = .020$; and for the HAART-treated cohort, $r = .54, p = .050$). As in previous studies (Kagan 1994), group-based analysis showed significant elevations in ANS activity only in the upper third of the social inhibition distribution ($p = .001$ by Kruskal-Wallis rank ANOVA) (Figure 4A). Autonomic nervous system activity was unrelated to the duration of infection at the time of assessment ($r = -.17, p = .204$) and did not differ from the HIV-uninfected cohort recruited in parallel (mean difference < 0.01 within-group SD, $p = .883$).

Previous analyses of this cohort documented elevated plasma viral load and impaired response to HAART among individuals with high levels of ANS activity (relationship to viral load set-point, $r = .66, p = .020$; relationship to virologic response to HAART, $r = .70, p = .008$; relationship to CD4+ T cell recovery following HAART, $r = -.75, p = .004$) (Cole et al 2001). To determine whether individual differences in ANS activity might account for relationships between social inhibition and HIV pathogenesis, the composite measure of ANS activity was tested for its capacity to abrogate statistical relationships between social inhibition and HIV pathogenesis in multiple regression analyses (Figure 5). Individual differences in ANS activity accounted for 64% of the total covariance between social inhibition and viral load set-point in the antiretroviral-naive cohort (analysis controlling for duration of infection). Control for ANS activity levels rendered the direct relationship between social inhibition and viral load set-point nonsignificant ($p = .151$), but the indirect relationship mediated via differential ANS activity remained significant ($p = .047$). Parallel analyses of the HAART-treated cohort suggested that individual differences in ANS activity could account for 72% of social inhibition's relationship to virologic response and 92% of its relationship to CD4+ T cell recovery (controlling for duration of therapy and baseline viral load or CD4+ T cell level). For both outcomes,
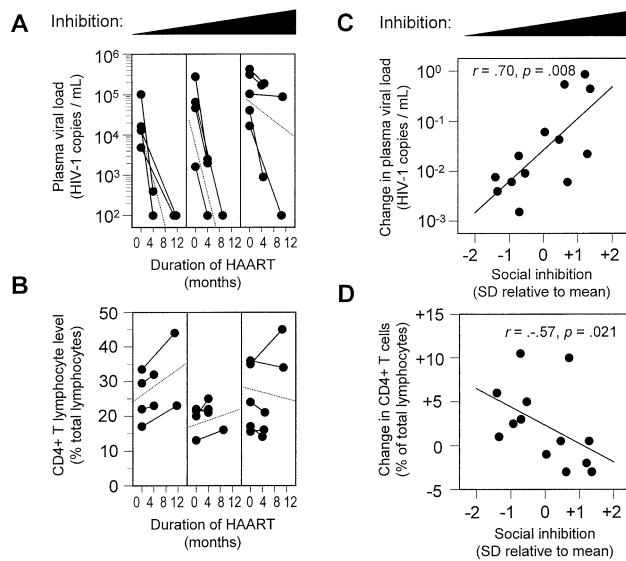
Figure 3. Relationship between social inhibition and response to highly active antiretroviral therapy (HAART). Among individuals untreated with antiretrovirals at baseline, 13 subsequently began combination antiretroviral therapy with at least one protease inhibitor in combination with two or more reverse transcriptase inhibitors (HAART; Table 1). **(A)** HAART-induced change in plasma HIV-1 viral load and **(B)** CD4+ T cell level were examined as a function of individual differences in social inhibition (measured as described in Figure 1). Dashed lines represent average slope within each tertile of the inhibition distribution. The decreased baseline CD4+ T cell level among individuals with intermediate levels of social inhibition (middle tertile of panel B) appears to reflect chance variation and was not statistically significant [$F(2,10) = .95$, $p = .418$]. Autonomic nervous system activity levels were normally distributed and thus treated a continuous linear predictor of HAART-induced changes in plasma HIV-1 viral load **(C)** and CD4+ T cell recovery **(D)**. Relationships were analyzed by linear regression, and dashed lines represent the 95% confidence interval for the regression line.

statistical control for ANS activity abrogated direct relationships between social inhibition and response to HAART (virologic response, $p = .128$; CD4 recovery, $p = .435$). Indirect pathways mediated via ANS activity remained statistically significant (virologic response, $p = .016$; CD4 recovery, $p = .003$).

Psychological Specificity of Risk Factors

As shown in Figure 1, the composite measure of social inhibition is composed of two highly correlated components measuring social withdrawal and hostility/irritability (Figure 1C). Both subcomponents showed significant independent correlations with plasma viral load set-point (e.g., in the antiretroviral-naive cohort, $r = .75$, $p = .008$

for social withdrawal, and $r = .58$, $p = .061$ for hostility/irritability). However, neither measure emerged as a significant predictor in multiple regression analyses including both variables simultaneously (both $p > .073$), implying that the most prognostic psychological characteristic is the variance shared by the two subcomponents (i.e., collinear regressors). This hypothesis was supported by the failure of the social inhibition composite to significantly predict plasma viral load when the covariance between measures was removed (e.g., residuals from the regression of social inhibition on hostility/irritability showed substantially weaker correlation with plasma HIV-1 viral load than did the composite measure including shared variance, $r = .48$, $p = .135$ vs. $r = .72$, $p = .009$, as did residuals from the regression of the social inhibition composite on the social withdrawal component, $r = -.01$, $p = .983$ vs. shared variance $r = .72$, $p = .009$). Comparable results emerged in analyses relating social inhibition to ANS activity (e.g., in the antiretroviral-naive cohort, shared variance composite $r = .66$, $p = .020$, composite excluding variance shared with hostility/irritability, $r = .12$, $p = .717$, composite excluding variance shared with social withdrawal, $r = .30$, $p = .363$).

To determine whether any single feature of the social inhibition composite might be predominately responsible for its statistical relationship to HIV plasma viral load, multiple regression analyses assessed relationships between viral load set-point and all six personality measures simultaneously (NEO Extraversion, Diagnostic Assessment of Personality and Psychopathology, Emotional Expressiveness Questionnaire, Cook-Medley, NEO Agreeableness, and Buss-Durkee Irritability). Again, no single personality variable showed significant predictive power beyond the variance shared by all measures (e.g., for the antiretroviral-naive cohort, $R^2 = .73$, but each individual predictor's partial $r < .30$, $p > .40$). These findings are consistent with the hypothesis that social inhibition represents a syndrome of multiple psychological and behavioral features, rather than a unidimensional characteristic (Kagan 1994).

Discussion

The present data document elevated HIV-1 plasma viral load set-point and impaired virologic and immunologic response to the initiation of antiretroviral therapy among socially inhibited individuals with asymptomatic HIV-1 infection. Socially inhibited patients showed plasma viral load set points 7.8-fold higher than uninhibited individuals and 8.1-fold poorer suppression of plasma viremia after 3–12 months of HAART. These results are consistent with
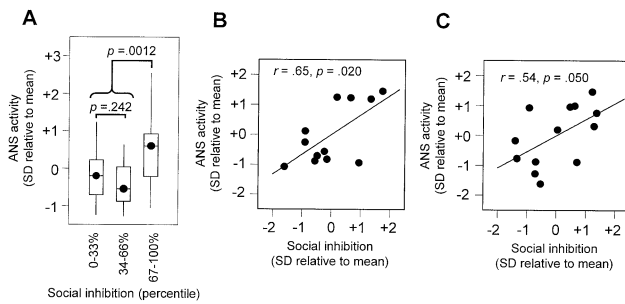
Figure 4. Relationship between social inhibition and autonomic nervous system (ANS) activity. Constitutive individual differences in ANS activity were measured by monitoring multiple physiologic indicators during several task periods on two occasions 7–14 days apart (as described in Figure 1). (A) Consistent with previous findings (Kagan 1994), individuals in the upper tertile of the social inhibition distribution showed significantly elevated ANS activity relative to those in the middle and lowest tertiles, who did not differ from one another (differences analyzed by Kruskal-Wallis rank analysis of variance). Boxes span the range of values between the 25th and 75th percentile, with whiskers extending from minimum to maximum and centerpoints indicating the median. Linear regression analyses revealed similar results ($r = .29, p = .038$, for the sample as a whole, data not shown) and comparable findings emerged for (B) the antiretroviral-naive cohort and (C) the highly active antiretroviral therapy (HAART)-treated cohort (who was not being treated with antiretrovirals at the time of baseline ANS assessment). Autonomic nervous system activity was unrelated to the duration of infection at the time of assessment ($r = -.17, p = .204$), and HIV-positive patients did not differ significantly from a cohort of HIV-negative individuals recruited in parallel on either ANS activity levels (mean difference $< .01$ population SD unit, $p = .883$) or social inhibition (mean difference $< .1$ population SD unit, $p = .740$). All individuals scored within the normal range on a battery of computerized adaptive tests assessing neuropsychological function (CalCAP, data not shown).

previous data identifying social inhibition as a risk factor for enhanced viral pathogenesis (Broadbent et al 1984; Capitanio et al 1999; Cohen et al 1997; Cole et al 1996; Totman et al 1980) and cardiovascular disease (Denollet et al 1996, 2000). Moreover, these results emerged despite statistical control for potential confounders, such as duration of infection, length of therapy, and baseline viral load and CD4+ T cell levels. Virologic parameters did not differ as a function of other psychological characteristics, such as depression, anxiety, or generalized negative affectivity, suggesting that social inhibition represents a psychologically specific risk factor. In multivariate analyses, social inhibition's effects were also independent of demographic and behavioral characteristics that could influence HIV disease progression (e.g., age, ethnicity, socioeconomic status, recreational drug use, and high-risk sexual activity).

Intensive neurophysiologic assessments documented elevated ANS activity among individuals showing high levels of social inhibition. Elevated ANS activity was also associated with heightened viral load set-point and impaired response to antiretroviral therapy, consistent with a possible role in mediating inhibition-related health risks. In multivariate analyses, individual differences in ANS activity accounted for 64%–92% of the association between social inhibition and virologic parameters. Social inhibition ceased to be a significant independent predictor of HIV pathogenesis after control for ANS activity, but its indirect relationship to pathogenesis *via* ANS activity remained significant in all analyses. To ensure that such results did not reflect any preexisting differences in disease status, analyses controlled for duration of infection, duration of antiretroviral therapy, and baseline viral load or CD4+ T cell level. In accounting for the majority of the statistical relationship between social inhibition and virologic parameters, ANS activity becomes the first neurophysiologic variable to meet established criteria for the mediation of a psychological risk factor's relationship to disease pathogenesis (Hoyle and Kenny 1999; Kemeny 1994). In nonstatistical terms, these data demonstrate that socially inhibited individuals have elevated levels of ANS activity, and this specific characteristic appears to place them at heightened risk for elevated HIV-1 plasma viral load and impaired response to antiretroviral therapy.

The clinical relationships observed here are consistent with in vitro studies showing that the ANS neurotransmitter norepinephrine can accelerate HIV-1 replication (Cole et al 1998). In response to stress or other stimuli, sympathetic neurons release micromolar quantities of norepinephrine into the parenchyma of all primary and secondary lymphoid organs (Felten et al 1987). Norepinephrine activates the leukocyte cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) signaling pathway via cellular β_2 adrenoreceptors, resulting in upregulated cell-surface expression of the HIV coreceptors CXCR4 and CCR5 (Cole et al 1999a, 2001), altered cytokine production profiles (Cole et al 1998), and enhanced HIV-1 gene expression (Cole et al 2001). Given the central role of ANS activity in physiologic stress responses, such dynamics may also play a role in stress-induced acceleration of simian immunodeficiency virus disease progression (Capitanio et al 1998, 1999). In conjunction with existing data on molecular mechanisms (Cole et al 1998, 1999a, 2001), the present findings also suggest that ANS function might represent a novel target for adjunctive therapy in the management of incompletely suppressed HIV-1 infection. The measure of ANS activity used in our study captures total variability in end-organ responses and likely reflects both sympathetic and parasympathetic components. This total variability measure correlated more strongly with
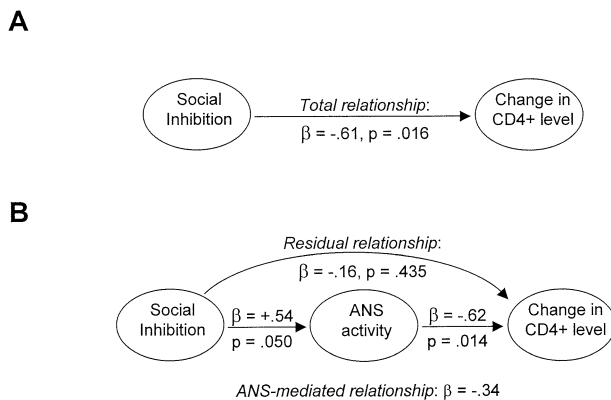
A

B

Figure 5. Mediation analysis. Multiple linear regression analysis was employed to quantify **(A)** the total covariation between social inhibition and human immunodeficiency virus (HIV) clinical parameters, and **(B)** the residual relationship remaining after controlling for individual differences in autonomic nervous system (ANS) activity (measured as described in Figure 1). β, standardized regression coefficient, with p values for coefficient t test. The magnitude of mediation was quantified by the change in analysis of variance sums of squares for the regression of HIV parameters on social inhibition before versus after statistical control for ANS activity. Statistical significance of the indirect ANS-mediated relationship was assessed by z test, with standard errors for the indirect path calculated as described (Goodman 1960; Hoyle and Kenny 1999). This figure gives results for CD4+ T cell recovery following highly active antiretroviral therapy (HAART) (controlling for pretreatment CD4+ T cell level and duration of therapy), with similar result reported in the text for analyses plasma viral load set point and response to HAART.

both social inhibition and HIV outcomes than did a similar composite based on mean levels of end-organ activity (data not shown); however, it is unclear whether such results imply a significant effect of parasympathetic activity on HIV pathogenesis or whether the total variance measure simply captured SNS-induced effects more efficiently than the mean level ANS composite.

Several limitations need to be considered in interpreting these data. Although the present correlational data are consistent with ANS mediation of relationships between social inhibition and HIV pathogenesis, definitive causal conclusions can only be drawn from studies that manipulate ANS activity (e.g., by pharmacologic blockade). Manipulation of catecholamine levels can accelerate HIV-1 replication in vitro (Cole et al 1998, 1999a; 2001), but it is unclear whether similar effects occur in vivo or whether pharmacologic manipulation of ANS activity would significantly impact disease progression. However, the present data suggest that such interventions merit testing because naturally occurring individual differences in ANS activity are associated with >100-fold variation in

plasma viral load. Given the correlational structure of the present study, these data cannot rule out the possibility that HIV pathology might be a cause rather than a consequence of differential ANS activity. Infection with HIV-1 can alter autonomic function (Brownley et al 2001; Gluck et al 2000; Kumar et al 1991; Scott et al 1990), but such effects are unlikely to account for the relationships observed here. Autonomic alterations generally occur only during advanced disease, whereas the present data come from clinically healthy, asymptomatic individuals with no history of AIDS and normal autonomic and neuropsychologic function (relative to both population norms and an HIV seronegative cohort accrued in parallel). Moreover, previous studies consistently report blunted ANS responses during late-stage infection, which would induce a negative association between ANS activity and HIV pathogenesis rather than the positive relationship observed here. Beyond the interpretive difficulties of correlational analysis, it is also unclear how the present findings might pertain to other populations of HIV-infected individuals (e.g., women, intravenous drug users, or people with other physical or psychiatric conditions that were excluded from this study). To overcome these limitations, future studies should focus on manipulating ANS activity in larger and more diverse samples.

Several theorists have proposed that underlying differences in CNS response to negative events predispose the development of both socially inhibited behavior and ANS reactivity (Gray 1991; Kagan 1994; Rothbart et al 1994). Such a mechanism would explain the empirical correlation between social inhibition and irritability/hostility observed here and elsewhere (Allan and Gilbert 1997; Bagby et al 1999; Denollet et al 1996, 2000). Both phenotypes may stem from an underlying CNS-level sensitivity that results in either hostile or withdrawn behavior, depending upon situational pressures, individual socialization, or other moderating influences. Multiple regression analyses indicated that it is the overlap between inhibition and hostility that is most strongly related to ANS activity and HIV pathogenesis. Aspects of social inhibition that were uncorrelated with hostility did not significantly predict HIV outcomes, and aspects of hostility that were uncorrelated with social inhibition were also poorly prognostic. As in studies of cardiovascular disease (Denollet et al 1996, 2000), the co-incidence of social inhibition and irritability seems to constitute a powerful psychological risk factor for HIV pathogenesis in vivo. This study also identifies the combination of social inhibition and irritability as a marker for stable elevations in ANS activity. To the extent that both social inhibition and ANS activity levels stem from common underlying differences in CNS function, interventions that alter central neural activity could conceivably impact host vulnerability to infectious disease.

Some evidence of such relationships already exists (Irwin et al 1988; Pellegrino and Bayer 2002; Reed and Glick 1991), and a more complete understanding of the CNS processes linking personality and ANS activity would provide an important advance in understanding psychological risk factors for virally mediated disease.

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Appendix 1. Representative Content of Social Inhibition Assessment Measures

DAPP–Intimacy Problems

I have difficulty with intimacy; I avoid getting too close or attached to anyone.

I avoid talking about myself, even to people I am close to.

DAPP–Social Apprehensiveness

I am shy and self-conscious in social situations.

I worry a lot about being hurt, embarrassed, or rejected by people.

I am very wary of people; I am always alert and on guard.

DAPP–Restricted Expression

I rarely show my feelings openly; it is hard for others to know what I am feeling.

I am uncomfortable openly expressing affection for others.

I almost never express angry feelings.

NEO–Extraversion (reverse-coded)

I like to have a lot of people around me.*

I usually prefer to do things alone.

DAPP, Diagnostic Assessment of Personality and Psychopathology; NEO, NEO Personality Inventory; EEQ, Emotional Expressiveness Questionnaire.

* reverse-coded.

I would rather go my own way than be a leader of others.

NEO–Agreeableness (reverse-coded)

I believe that most people will take advantage of you if you let them.

Some people think of me as cold and calculating.

If necessary, I am willing to manipulate people to get what I want.

EEQ (reverse-coded)

When I really like someone they know it.

People can tell from my facial expressions how I am feeling.

I laugh a lot.

Cook-Medley Hostility

I am likely not to speak to people until they speak to me.

I tend to be on guard with people who are somewhat more friendly than I had expected.

People often disappoint me.