Published in final edited form as:

Int J Behav Med. 2008 ; 15(3): 221–226. doi:10.1080/10705500802219606.

Perceived Stress and Norepinephrine Predict the Effectiveness of Response to Protease Inhibitors in HIV

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Abstract

Background—In vitro evidence has suggested that increasing levels of norepinephrine (NE) can accelerate HIV replication; however, the importance in a clinical setting has not been tested.

Purpose—The purpose of this study was to determine if perceived stress as well as the stress hormones NE and cortisol would predict the response to starting a new protease inhibitor (PI) prospectively.

Method—Perceived stress, urinary cortisol and norepinephrine, CD4 and viral load (VL) were measured in people with HIV before starting a new PI and six months later (an average of three months after starting the new PI) in order to determine CD4 and VL response to the PI.

Results—Higher perceived stress significantly predicted lower effectiveness of the new PI in increasing CD4 and decreasing VL controlling for age, duration of new PI, baseline CD4/VL, sexually transmitted diseases (STDs), and gender/ethnic risk groups. Higher norepinephrine, but not cortisol, predicted worse VL response to PIs and, in fact, mediated the relationship between perceived stress and change in VL.

Conclusion—Perceived stress and high norepinephrine levels are prospectively associated with a poorer response to starting a new PI. Assessing stress and norepinephrine levels in patients starting on antiretroviral medications might be clinically useful.

Keywords

stress; HAART; protease inhibitors; norepinephrine; cortisol; HIV

Several studies have demonstrated that psychosocial factors predict faster disease progression in HIV (Leserman et al., 2002) even in the era of highly active antiretroviral therapy (HAART) (Ironson et al., 2005), and even after controlling for adherence (Ironson et

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al., 2005). However, the mechanism by which this occurs remains unknown (Kopnisky, Stoff, & Rausch, 2004). One of the major hypotheses of behavioral medicine is that stress hormones (cortisol, norepinephrine) may provide a link between psychological stress and health outcomes (Schneiderman, Ironson, & Siegel, 2005). Cortisol is one likely candidate as it enhances the ability of HIV to infect human lymphocytes (Markman, Salahuddin, Veren, Orndorff, & Gallo, 1986), is associated with down regulation of the immune system (Munck & Guyre, 1991), and it has been shown to predict disease progression in HIV (Leserman et al., 2000, 2002). Intriguing work by Cole, Korin, Fahey, and Zack (1998) has demonstrated that another stress-related hormone, norepinephrine, enhances HIV replication. However, that seminal study was done in vitro. More recently, the same group showed that HIV patients with high autonomic nervous system activity had poorer virologic and immunologic response to HAART (Cole et al., 2001; Cole, Kemeny, Fahey, Zack, & Naliboff, 2003); however, neither norepinephrine nor stress were directly measured. Thus, a study to directly test the prospective association between norepinephrine and stress with virologic response to PIs in a clinical setting appears warranted. The purpose of the current study was to determine whether stress would predict CD4 and viral load changes that occurred as patients were starting anti-HIV medications and to determine whether cortisol or norepinephrine might predict and/or mediate the effect in vivo.

Method

Design overview

The sample consisted of 55 people with HIV who were started on a new protease inhibitor (PI) during the course of a larger longitudinal study investigating psychological and immune predictors of disease progression in HIV (Ironson et al., 2005), in which subjects were seen every six months. Each subject in this sub-study had a pre- and post- new PI time point that were six months apart. Our HIV-positive patients were assessed before starting on protease inhibitors for perceived stress (Cohen, Kamarck, & Mermelstein's (1983) 10-item PSS scale) as well as urinary cortisol and norepinephrine (15 hours collected from 6 pm until first void of the next morning). CD4 and viral load were assessed as part of the longitudinal study before (pre) starting the new PI and six months later (post-PI time point).

Inclusion/exclusion criteria

To be included in the sub-study sample, the subject had to be starting on a new PI between two time points six months apart: pre-PI and post-PI, and not taking a protease inhibitor at the pre-time point. The larger longitudinal study consisted of 177 people with HIV who at study entry were in the mid-range of HIV disease (CD4 between 150 and 500, never had a clinical AIDS condition). Other inclusion criteria for the larger longitudinal study were: not on IV drugs, not substance dependent, no change in medication one month prior to baseline, no major stressful life event such as surgery within two months of entry, and no HIV dementia.

Measures

Perceived stress was measured by the perceived stress scale (PSS) originally developed by Cohen, Kamarck, and Mermelstein (1983), which measures "the degree to which situations in one's life are appraised as stressful." The 10-item version of this scale was used (Cohen & Williamson, 1988). For the purposes of this sub-study, perceived stress was measured at the pre-time point.

Adherence was measured by the AIDS Clinical Trials Group questionnaire (ACTG: Chesney et al., 2000), which asks about medications prescribed and missed doses. It has been used in at least nine clinical trials of combination therapy. For the purposes of this sub-

study, adherence was measured as the proportion of missed doses in the past three days at the post-time point, as we wanted it to reflect adherence during the trial of the new medication.

Collection of urinary stress hormones

At each 6-month visit, participants collected 15-hour urines. A 15-hour collection was used (from 6 pm until the first void the following morning) because one gets better compliance than with the 24-hour urine, it avoids a potential confound with working status (and almost half of our sample is unemployed), and because this period of time includes overnight, which is the period most sensitive to chronic stress (Mellman, Kumar, Kulick-Bell, Kumar, & Nolan, 1995). Participants collected their urine in a cup emptied into a container with 1 gram of sodium metabisulfite as a preservative. They were asked to keep their urine refrigerated. After they brought in the urine to the lab, the volume was noted. Volumes of less than 250 were excluded from analysis. Two samples were aliquoted in tubes (1 mL for cortisol and 10 mL for catecholamines, with 100 μ L concentrated hydrochloric acid (about 2 drops) added to the sample to be used for catecholamines. The vials were stored and frozen at -70°C . For the purposes of this study, the pre-time point was used.

Assay of urinary cortisol

Urinary cortisol was determined by radioimmunoassay kits obtained from the Diagnostic System Laboratories, Webster, Texas. This assay uses 50 μ L of a 500- μ L aliquot urine, which is extracted in 500 μ L of dichloromethane and the extract then evaporated to dryness under nitrogen. One milliliter I^{125} -labeled cortisol was added to tubes coated with antibodies, incubated for 45 minutes, decanted, and radioactivity quantified for 1 minute using a gamma counter calibrated for I^{125} . Levels of cortisol in the sample were calculated using a standard calibration curve. Cortisol levels are expressed as $\mu\text{g}/100\text{ mL}$ of urine. The intra-assay and inter-assay coefficient of variance were 8.2% and 9.3%, respectively.

Assay for urinary norepinephrine

High-performance liquid chromatography (HPLC) was used for the quantification of norepinephrine (Kumar, Kumar, Fernandez, Mellman, & Eisdorfer, 1991) using disposal columns filled with Biorex-70 resin (a cationic-exchange column). The catecholamines from the extract were separated on a HPLC-CoulArray system using reverse-phase C18, 5i column, and determined by coulometric system. The intra-assay and inter-assay coefficients of variation were 3.4% and 7.1%, respectively. The sample was smaller for catecholamines than for cortisol ($n = 31$ vs. 52), as catecholamines were measured at fewer time points for each participant in the larger longitudinal study due to budgetary constraints.

Disease progression markers

CD4 lymphocyte count ($\text{CD3}+\text{CD4}+$) was determined by whole-blood 4-color direct immunofluorescence using a XL-MCL flow cytometer (Beckman/Coulter, Miami, FL). In order to convert the percent of total lymphocyte values given by the flow cytometer to absolute count for each subset, the total lymphocyte count was determined using a MaxM electronic hematology analyzer (Beckman/Coulter). Serum viral load (VL) was measured by determining the number of HIV-1 virions per milliliter (ml) of peripheral blood plasma using the Cobas Amplicor HIV-1 Monitor RT/PCR assay (version 1.5, Roche Molecular Systems, Branchburg, NJ). The lower limit of sensitivity of this assay was 400 copies of HIV-1 RNA/ml of plasma.

Statistical methods, covariates

Hierarchical regression analysis was used, followed by tests of mediation suggested by Baron and Kenny (1986) and Mac Kinnon and Dwyer (1993). Covariates controlled for include age, duration of PI (time on PI prior to the post-time point), pre-time point CD4 or VL (log), number of STDs past and present combined, and ethnic/gender risk group using dummy coding (gay male, African-American female, heterosexual African-American male, other). The log transformation was used to normalize VL. Missing data was not replaced.

Results

The sample of 55 people with HIV was diverse with respect to gender (60% male, 40% female), ethnicity (53% African American, 26% Latino, 18% Caucasian, 4% other), and sexual orientation (gay 41%, heterosexual 56%, other 3%). Although there was a range of educational level and many had some college (17% less than high school grad, 26% high school grad, 44% some college, 13% college graduate), most of our participants were poor (71% with an income of less than \$10,000 per year), which is consistent with high unemployment (46%) and disability (24%). Most (82%) reported acquiring HIV through unprotected sex.

As noted in the methods section, in order to be included in the current sub-study of the larger longitudinal study, the participant had to have a pre-time point prior to the initiation of the new PI and a post-time point after initiation of new PI. In addition, they must not have been on a PI before. At the pre-time point, 18% had not been taking any antiretroviral medication prior to the new PI, 36% had been on antiretroviral treatment (but not HAART or PI), and 46% had been on HAART (but without a PI). Prior to starting a PI, the average CD4 was 255 ($SD = 127$) and the average VL was 129,123 copies/mL ($SD = 200,153$).

The average amount of time the participants were on the new PI for the immediate post-time point was 3.03 months ($SD = 2.51$). The average gain for CD4s after starting a PI was 17 cells/mm³, and the average decrease in viral load was 33,494 copies/mL. Non-compliance with the new regimen, measured by percent doses missed in the prior three days was 12% ($SD = .28$). Means and standard deviations of other study variables are noted in Table 1.

Prediction of Response to a New PI

Overall model

As noted in the methods section, the models predicting CD4 (or VL log) at the post-time point controlled for age, time since starting PI, pre-time point CD4 or VL log, sexually transmitted diseases (STDs past and present), and ethnic/gender risk group. The overall model predicting post CD4 after initiating a new PI (from pre CD4 and the other covariates) was significant, $F(7, 47) = 11.75, p = .000$. Similarly, the overall model predicting viral load (log) at the post-time point after initiating a new PI (from pre VL(log) and the covariates) was also significant, $F(7, 48) = 3.37, p = .005$. The models predicting CD4 and VL log with covariates are presented in Table 2 (block 1). The bottom of Table 2 shows the contributions of perceived stress and stress hormones (described below).

Perceived stress as a potential predictor of response to PI

Adding perceived stress into the model maintained the significance of the overall model for predicting CD4, $F(8, 46) = 13.64, p = .000$. Perceived stress significantly predicted the change in CD4 (post CD4 controlling for pre CD4 and other covariates) with a standardized β of $-.278, t = -3.23, p = .002$. The strength of the association can be estimated by the partial correlation between perceived stress and post CD4 controlling for pre CD4 and other

covariates of $-.43$, indicating that perceived stress accounted for approximately 18% of the variance in CD4 response to the new PI.

Perceived stress also significantly predicted the change in VL log (post VL log controlling for pre VL log and other covariates), $p = .003$. The overall significance of the model was maintained $F(8, 47) = 4.74$, $p = .000$. The strength of the association was estimated by the partial correlation (between perceived stress and post VL log controlling for pre VL log and other covariates) of $.42$, indicating that perceived stress accounted for about 18% of the variance in viral load response to the new PI (which is quite similar to the percent of variance accounted for by perceived stress in CD4 response).

Stress hormones as potential predictors of the CD4/viral load response to PI

Norepinephrine did not significantly predict the change in CD4 (post CD4 controlling for pre CD4 and other covariates), $p = .134$. The partial correlation was $-.315$. In contrast, NE did significantly predict the change in VL log (post VL log controlling for pre VL log and other covariates), $p = .024$. Including NE in the model maintained the significance of the overall model, $F(8, 22) = 4.065$, $p = .004$. The strength of the association can be estimated by the partial correlation between NE and post VL log controlling for pre VL log and other covariates of $.46$, indicating that perceived stress accounted for about 21% of the variance in VL response to the new PI. In order to determine whether the result was independent of adherence, the analysis was re-run controlling for adherence. With both adherence and NE in the model, NE maintained its significance ($t = 2.67$, $p = .015$). Not surprisingly, with both in the model, adherence (proportion of missed doses) was also significantly related to post VL log ($t = 2.46$, $p = .02$). As shown in Table 2, cortisol did not significantly predict the change in CD4, $p = .876$, or the change in VL log, $p = .24$.

Stress hormones as potential mediators of the perceived stress—CD4/viral load response to PIs

The first two criteria for mediational analyses were met for VL. Thus, as presented above, perceived stress and NE both predicted the change in VL, and NE was significantly related to perceived stress ($.47$, $p < .01$). The final step of mediational analysis was to set up a regression model (controlling for initial VL and other covariates), with perceived stress and NE as predictors. Since perceived stress was no longer significant when NE was added into the model (standardized $\beta = -.037$, $t = -.173$, ns), but NE maintained its significance ($\beta = .404$, $t = 2.152$, $p = .043$), then NE qualifies as a mediator of the relationship between perceived stress and VL change.

Discussion

The first result, that perceived stress prior to the initiation of a new PI predicts the biological response to PIs and is consistent with literature showing that stress is related to faster disease progression (Ironson et al., 2005; Kemeny & Dean, 1995; Leserman, 2003; Lesserman et al., 2000, 2002; Patterson et al., 1995); however, it is more specific in that it prospectively targets a time point at which a new medication is started, and uses a brief measure of perceived stress rather than a more extensive measure of life events. Furthermore, the data show that a product of the sympathetic nervous system, NE, mediates the effect of perceived stress on response of VL to a new PI. This is consistent with evidence of the effects of NE on VL provided in vitro by Cole et al. (1998) but extends the finding to HIV patients in vivo and underscores its potential clinical importance. It is also consistent with his other studies showing that people with high sympathetic arousal have a poorer response to HAART (Cole et al., 2001, 2003). It is interesting to note that we found NE predicted the VL response to the new PI but not the CD4 response. While it is unknown at this time why that occurred,

one possibility is that the VL decrease may take some time to be reflected in a CD4 increase if the rate of CD4 destruction is lowered when there is less virus to attack the CD4 cells. Another possibility to keep in mind is that the sample size was small and therefore this question was underpowered. This lack of power is suggested by the partial r of $-.315$ between NE and post CD4 controlling for pre CD4 and other covariates, $t = -1.56$, $p = .134$.

While some research has suggested the importance of cortisol as a predictor of disease progression in HIV (Leserman et al., 2000), as a factor in the pathophysiology of HIV entry (Markman et al., 1986), and as a mediator of immune down-regulation in general (Munck & Guyre, 1991), the current findings combined with Cole et al.'s (1998, 2001, 2003) findings suggest that the sympathetic nervous system deserves more attention as a potential predictor of disease progression in HIV. The inconsistent findings with the Leserman et al. (2000) study regarding the relationship between cortisol and disease progression need to be examined. Potential reasons for the discrepancy in findings that could be explored in future research are that Leserman et al. (2000, 2002) used plasma cortisol rather than urinary cortisol, their study was over a longer period of time with multiple time points and did not target initiation of treatment, those investigators had a larger sample size, our sample was on PIs while their sample predated the availability of PIs, and it is possible that cortisol may reflect disease progression rather than cause it.

Given the potential importance of perceived stress at the time of initiation of HAART, it is important to note that both pharmacologic and psychological approaches are available for stress management. Stress management, including relaxation techniques, stress awareness, cognitive reframing, coping, anger management, assertiveness training, and social support (Antoni, Ironson, & Schneiderman, 2007), has had a variety of beneficial psychological and biological effects in HIV (Antoni et al., 2006; Ironson et al., 2002). In particular, there is evidence to suggest that a variety of stress management techniques, including cognitive behavioral approaches incorporating relaxation practices (Antoni et al., 2000), as well as massage (Ironson et al., 1996), are related to lower NE levels. Furthermore, frequency of relaxation techniques in HIV has been related both to immune outcomes (Antoni et al., 1991) and lower mortality (Ironson et al., 1994), although the latter was with a small sample. In an animal model, Ben-Eliyahu's group (Benish et al., 2008) has found that administration of beta blockers (and anti-inflammatories) pre-surgery in rats is able to block the immune suppression associated with surgery.

Clinical implications

The findings of this study add to the growing number of factors that might be considered clinically important in maximizing the effectiveness of a new antiretroviral medication regimen. Consistent with our findings, adherence remains a critical component. Predictors of adherence have been noted elsewhere (Gordillo, Amo, Soriano, & Gonzalez-Lahoz, 1999) and include age, education, risk group, CD4 count, depression, and social support. One could also screen for stress, avoidant coping, and depression due to their relationship with faster disease progression (Mayne, Vittinghoff, Chesney, Barrett, & Coates, 1996; Leserman, 2003; Ironson et al., 2005; Ickovics et al., 2001). The current study suggests that a fairly short 10-item measure of perceived stress may identify people at risk for a poor outcome when starting new medication. Replication of the current study may lead to future consideration of screening for NE. Patients high in stress could be advised to practice a stress management technique for relaxation.

Acknowledgments

This research was funded by NIH (R01MH53791 and R01MH066697). Principal investigator: Gail Ironson and T32MH18917. Thanks go to Nathaniel Ezra Kieval for technical help with preparing the manuscript.

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Table 1

Mean and Standard Deviations (SDs) of Major Study Variables

	Before Starting PI	Post PI Initiation
Outcome variables		
Viral load (VL)	129,123 (200,153)	95,629 (187,318)
VL (log)	2.06 (1.07)	1.79 (1.27)
CD4	255 (127)	272 (155)
Predictors		
NE ($\mu\text{g/mL}$)	48.83 (35.35)	
Cortisol ($\mu\text{g/dL}$)	40.54 (38.46)	
Perceived stress	18.51 (7.82)	

Hierarchical Linear Regression Predicting CD4 or Viral Load (VL log) Post Initiation of Protease Inhibitors (PI)

Table 2

Covariate	Variables Predicting CD4			Variables Predicting VL (log)		
	β	t	p	β	t	p
Block 1: Control Variables						
Pre VL or CD4	.71	7.34	.000	.33	2.51	.016
STDs	-.02	-.17	.863	-.15	-1.13	.265
Risk group:						
AA female	.08	.64	.523	.28	1.60	.117
Gay male	-.24	-1.93	.059	.28	1.70	.095
AA male ²	-.13	-1.25	.217	.24	1.67	.102
Duration of PI	.06	.66	.516	-.19	-1.49	.142
Age	.19	1.88	.066	-.29	-2.25	.029
Block 2: Adds predictors (each alone) controlling for covariates above						
Predictors						
Cortisol	.02	-.16	.876	-.15	-1.20	.240
Norepinephrine	-.23	-1.56	.134	.39	2.43	.024
Perceived stress	-.28	-3.17	.003	.37	3.15	.003

Note. $n = 54-55$ for all models except those with cortisol ($n = 52$) or norepinephrine ($n = 31$), AA African American

¹ standardized beta

² if gay identified, included in gay male group.