Psychosocial Influences on HIV-1 Disease Progression: Neural, Endocrine, and Virologic Mechanisms

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This review surveys empirical research pertinent to the hypothesis that activity of the hypothalamus-pituitary-adrenal (HPA) axis and/or the sympathetic nervous system (SNS) might mediate biobehavioral influences on HIV-1 pathogenesis and disease progression. Data are considered based on causal effects of neuroeffector molecules on HIV-1 replication, prospective relationships between neural/endocrine parameters and HIV-relevant biological or clinical markers, and correlational data consistent with in vivo neural/endocrine mediation in human or animal studies. Results show that HPA and SNS effector molecules can enhance HIV-1 replication in cellular models via effects on viral infectivity, viral gene expression, and the innate immune response to infection. Animal models and human clinical studies both provide evidence consistent with SNS regulation of viral replication, but data on HPA mediation are less clear. Regulation of leukocyte biology by neuroeffector molecules provides a plausible biological mechanism by which psychosocial factors might influence HIV-1 pathogenesis, even in the era of effective antiretroviral therapy. As such, neural and endocrine parameters might provide useful biomarkers for gauging the promise of behavioral interventions and suggest novel adjunctive strategies for controlling HIV-1 disease progression. **Key words:** HIV-1, disease progression, sympathetic nervous system, HPA axis, neuroendocrine, catecholamine, norepinephrine, cortisol.

HPA = hypothalamus-pituitary-adrenal; **SNS** = sympathetic nervous system; **NE** = norepinephrine; **SIV** = Simian Immunodeficiency Virus; **ART** = antiretroviral therapy; **CTL** = cytotoxic T lymphocyte.

INTRODUCTION

A substantial body of evidence has documented relationships between psychosocial characteristics and differential progression of HIV-1 infection (1–5). Randomized controlled studies have shown that behavioral interventions can influence biological indicators of HIV-1 pathogenesis (e.g., $CD4^+$T lymphocyte levels and HIV-1 plasma viral load) (6,7), and experimental analyses of the closely related Simian Immunodeficiency Virus (SIV) model in rhesus macaques have demonstrated causal effects of social stress on viral replication and disease progression (8,9). This review analyzes the biological mechanisms that might mediate such relationships. Neural, endocrine, virologic, and immunologic processes are surveyed in the context of an integrative model (Figure 1) that focuses on two major questions: (1) which physiologic signaling pathways transmit psychosocial influences into the body? (the "biobehavioral signal transduction pathway"), and (2) which aspects of viral pathogenesis are modulated by those biobehavioral signals? (the "locus of impact on disease"). Our understanding of these pathways is incomplete, but the available evidence is most consistent with a theoretical model in which CNS-induced alterations in neural and endocrine activity (Figure 1A) regulate aspects of leukocyte biology that influence HIV-1 viral replication (Figure 1B), and thereby affect the pathogenesis of immunodeficiency-related disease (Figure 1C). Technical and ethical constraints prevent the experimental confirmation of the model as a whole, but individual links within the model have been empirically tested by experimental analysis in model systems (e.g., in vitro viral replication in human leukocytes or in vivo dynamics of the SIV animal model), and hypothesized systems of influence have been tested for consistency with observed associations in vivo using statistical mediation analyses (10). In this review, the theoretical model of Figure 1 is evaluated using three types of pertinent data: (1) experimental studies assessing causal effects of neural and endocrine factors on disease-related biology (e.g., viral replication in vitro, or in vivo viral load, $CD4^+$T lymphocyte levels, or clinical disease), (2) prospective relationships between neural/endocrine parameters and biological indicators of HIV-1 pathogenesis or disease progression in vivo, and (3) multivariate mediation analyses that simultaneously test transitive relationships among psychosocial risk factors, neural mediators, and HIV-related outcomes. Although the causal hypothesis moves from top to bottom in Figure 1, a mechanistic analysis is perhaps best focused by commencing at its ultimate target—the biological processes that drive HIV-1 disease.

The Neurobiological Interface to HIV Disease Progression

The progression of HIV-1 infection to clinical immunodeficiency and opportunistic disease is driven fundamentally by viral replication in activated $CD4^+$T lymphocytes and macrophages (11–14). HIV-1 replicates primarily in secondary lymphoid organs (e.g., lymph nodes and spleen) (15), which house more than 90% of the body's total complement of leukocytes. From a mechanistic standpoint, understanding how psychosocial factors such as stress, depression, or temperament might influence HIV-1 disease progression essentially involves determining how CNS perceptual, interpretive, and coping processes might affect the biology of viral replication in leukocytes residing within secondary lymphoid tissues.

Two major physiologic signaling pathways are most often studied as possible mediators of biobehavioral influences on HIV-1 pathogenesis—the hypothalamic-pituitary-adrenal (HPA) axis, which could potentially affect HIV-1-infected leukocytes through the blood-borne glucocorticoid, cortisol, and the sym-

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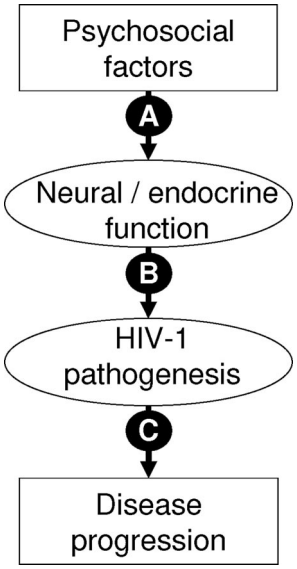

Figure 1. Theoretical model of biobehavioral influences on HIV-1 disease progression. Psychosocial factors = stress, depression, coping, social support, temperament, and other CNS-mediated influences on neural and endocrine activity, (**A**) CNS-mediated effects of psychosocial factors on neural/endocrine activity, (**B**) neural/endocrine influences on HIV-1 replication, (**C**) effects of HIV-1 replication on clinical disease progression.

pathetic division of the autonomic nervous system (SNS), which would affect HIV-1-infected leukocytes via the catecholamines, epinephrine, and norepinephrine (NE) (16,17). Both the HPA/cortisol and SNS/catecholamine systems are activated by stress (16,17), and both have also been linked to other psychological or social risk factors for HIV-1 disease progression such as depression, social support, psychological inhibition, and social temperament (reviewed in Refs. (4,5)). Activity of these signaling pathways has also been linked to biological indicators of HIV-1 pathogenesis in clinical natural history studies (18–23), experimental animal models (8,9), and pharmacologic intervention studies (24–29). Other physiologic signaling pathways examined as potential mediators include hormones from the growth and gonadal axes and peptide neurotransmitters such as substance P (30,31). However, much less is known about how those factors might affect HIV-1 replication and disease pathogenesis. As a result, this review focuses primarily on HPA and SNS regulation, and readers are referred to more comprehensive reviews for consideration of other potential mediators (5,32).

Both cortisol from the HPA axis and epinephrine from the SNS can reach HIV-1-infected leukocytes via blood plasma perfusion of secondary lymphoid organs, and during leukocyte recirculation through the vasculature. NE spillover from SNS innervation of the vasculature can also signal leukocytes in both of those compartments, but this catecholamine can also reach virally infected leukocytes via SNS innervation of secondary lymphoid organs (33,34). T lymphocytes and macrophages harbor receptors for both glucocorticoids and catecholamines, and those signaling molecules are known to affect several aspects of leukocyte function, including cellular activation, cytokine production, cell trafficking and chemotaxis, and immune effector responses (35,36). Effects of neural mediators on cell localization are particularly pertinent because two key receptors for chemotactic molecules, CCR5 and CXCR4, also facilitate entry of HIV-1 viral particles into human cells (37–39) and show relationships to biobehavioral risk factors and signaling pathways (3,21,40–44). Understanding how HPA and SNS activity might affect HIV-1 disease progression thus involves understanding how the net effect of these multiple host cell factors, the ability of the virus to complete its full replication cycle and disseminate infection to other cells.

Cortisol and the HPA Axis

Several studies have documented relationships between psychological factors and circulating cortisol levels in HIV+ individuals (6,45–47; reviewed in 4,5,32), and cross-sectional studies have linked elevated cortisol levels to HIV-1 disease progression (48,49). One longitudinal natural history study has found elevated cortisol levels to predict subsequent onset of AIDS (18,19). However, it is unclear whether these associations reflect HPA axis mediation of psychosocial influences, or whether elevated cortisol levels instead represent a neuroendocrine response to underlying disease progression (i.e., independent of psychological influences). Consistent with the later hypothesis, several studies have shown that progressing HIV-1 infection can activate the HPA axis and alter the adrenal gland (5,49). In the most comprehensive study of HPA relationships to HIV-1 disease progression, high cortisol levels were found to be an additional risk factor for AIDS onset that was independent of psychosocial risk factors (e.g., depression) (18,19). However, studies experimentally manipulating glucocorticoid levels have not identified any consequent increase in HIV-1 plasma viral load, $CD4^+$T lymphocyte loss, or clinical disease onset (25,27,28,50,51). In fact, several of those studies have shown that glucocorticoid elevation can actually reduce plasma HIV-1 viral load and $CD4^+$T lymphocyte loss (25,27,28). One nonrandomized observational study has suggested that administration of pharmacologic glucocorticoids to late-stage HIV-1 patients may precipitate the onset of full-blown AIDS (likely due to the immunosuppressive effect of glucocorticoids) (52). No prospective study of HIV-1 disease progression has found HPA axis activity to be a plausible mediator of biobehavioral risk in multivariate statistical analysis, although one cross-sectional result is consistent with that hypothesis (20). A decisive demonstration of HPA axis mediation would require experimental control of cortisol levels to abrogate the risk of disease progression associated with a known psychosocial risk factor. In the absence of such data, and in light of experimental studies documenting a suppressive effect of glucocorticoids on markers of HIV-1 pathogenesis, it remains unclear whether correlations between endogenous cortisol levels and HIV-1 disease progression reflect HPA axis mediation of stress effects or simply serve as a neuroendocrine marker of underlying disease progression.

Experimental studies in cellular models have identified several molecular mechanisms by which glucocorticoids

might potentially influence HIV-1 replication, including altered expression of the CXCR4 chemokine receptor that mediates cellular vulnerability to infection by some strains of HIV-1 (40,42–44), arrest of the cell cycle in the G_2 phase favoring viral gene expression (53), and impaired activation of the Type I interferon system, which represents a key innate immune response to viral replication (54). However, most in vitro virology studies have shown minimal impact of glucocorticoids on overall viral replication rates (55–58). This is likely because, in addition to whatever stimulatory effects glucocorticoids have on specific elements of the HIV-1 replication cycle, they also profoundly inhibit the basic leukocyte activation signals required for productive viral gene expression (e.g., the NF-κB transcription factor) (58). Such suppressive effects on lymphocyte activation are consistent with clinical effects of glucocorticoids in suppressing HIV-1 viral load and $CD4^+$T lymphocyte declines (25,27,28).

In vitro viral replication models do not capture the effects of adaptive immune responses to HIV-1 (e.g., cytotoxic T lymphocyte responses), which are believed to play a central role in establishing equilibrium rates of viral replication in vivo. One experimental system that does capture both basic viral replication dynamics and adaptive immune responses is the rhesus macaque model of SIV infection. Studies in this system have shown that experimentally imposed social stress can increase SIV replication and accelerate the onset of clinical immunodeficiency (8,9). However, this system also showed reduced glucocorticoid levels in stressed animals, suggesting that stress-induced acceleration of SIV progression stemmed from some mechanism other than chronically elevated glucocorticoid levels.

The present research literature provides mixed evidence regarding glucocorticoid regulation of HIV-1 replication in vitro, and no in vivo data currently support the hypothesis that increased HPA axis activity mediates observed relationships between psychosocial risk factors and HIV-1 (or SIV) disease progression in vivo.

Catecholamines and the SNS

Studies have more consistently linked increased SNS activity to HIV-1 pathogenesis. Initial research in this area was motivated by data showing accelerated disease progression in people with socially inhibited personality characteristics (59,60), which have been linked to elevated SNS activity in previous research (61). Subsequent studies directly assessed autonomic nervous system activity in HIV+ individuals, and found those with constitutively high levels of SNS activity to show elevated plasma viral load set-points and impaired virologic response to the initiation of combination antiretroviral therapy (ART) (21,23). Multivariate statistical analyses also supported the hypothesis that individual differences in SNS activity might account for much of the relationship between stress or temperament-related risk factors and individual differences in virologic or immunologic indicators of HIV-1 pathogenesis (22,23). Those findings are also consistent with data from experimental pharmacologic studies that (inadvertently) activated the cAMP/PKA signaling pathway which mediates catecholamine response and found a consequent increase in HIV-1 plasma viral load (24,26). Thus, both natural history studies and pharmacologic manipulation studies support the hypothesis that SNS activity may mediate some biobehavioral influences on HIV-1 pathogenesis.

In vitro studies have shown that catecholamines can significantly enhance HIV-1 replication (21,62). Several molecular mechanisms of this effect have been identified, including up-regulated cell surface expression of the viral coreceptors, CXCR4 and CCR5 (21,41), enhanced transcription of HIV-1 genes by cellular transcription factors (21), and catecholamine-mediated suppression of Type I interferon responses to infection (54). Signal transduction analyses identified beta adrenergic receptor activation of the cAMP/PKA signaling pathway as the key mediator of catecholamine effects on HIV-1 replication, and showed that pharmacologic blockade of beta adrenergic receptors can abrogate those effects (62).

Analyses of lymph nodes from the rhesus macaque model of SIV infection have revealed a key role of SNS neurons in regulating viral replication in secondary lymphoid tissue. Initial studies found increased SIV replication adjacent to the SNS neural varicosities that release catecholamines within the lymph node parenchyma (34). Subsequent studies showed a surprising degree of behaviorally induced plasticity in the SNS innervation of lymphoid organs. Macaques subject to experimentally imposed social stress showed elevated density of catecholaminergic varicosities within the lymph node parenchyma (9). Stress also enhanced SIV replication, and that effect was attributable specifically to the increased density of catecholaminergic varicosities. Consistent with in vitro cellular models, interferon-beta gene expression was also suppressed in stressed animals, suggesting that impairment in innate antiviral responses might play a key role in the relationship between SNS innervation and viral replication. A recent study has also shown that pharmacologically induced enhancement of SNS innervation density is associated with increased SIV gene expression in macaque lymph nodes (29), providing an experimental link between modulation of the sympathetic nervous system and viral replication in vivo. Figure 2 provides a theoretical model that integrates existing results from human clinical studies relating SNS activity to indicators of HIV-1 pathogenesis (21,23), in vitro analyses of catecholamine effects on HIV-1 replication (21,41,54,62), and experimental analyses of the SIV lymphoid tissue model in vivo (9,29,34). In this system, SNS activity is hypothesized to enhance viral replication by inhibiting the activity of Type I interferons (9,54), which increases viral replication through multiple mechanisms including impaired resistance to viral gene expression (via inhibition of the interferon-mediated antiviral state) (54) and enhanced cellular vulnerability to infection (via disinhibited expression of the viral coreceptors CCR5 and CXCR4, which occurs under physiologic conditions (63–66), but not in artificially stimulated cells (67)). In conjunction with immune activation (e.g., via proinflammatory cytokines or ligation of the T cell receptor), these factors

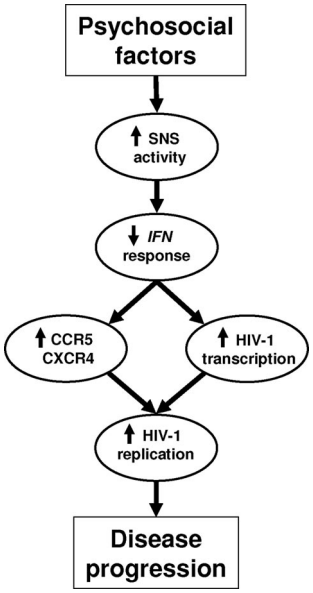

Figure 2. Theoretical model of SNS mediation of psychosocial influences on HIV-1 disease progression. SNS = sympathetic nervous system, IFN = Type I interferon. CCR5 and CXCR4 = cell surface expression of cellular coreceptors that complement CD4 as mediators of HIV-1 infection.

facilitate viral replication and thereby accelerate disease pathogenesis.

Summary and Implications

Current empirical data are generally consistent with the hypothesis that SNS activity might mediate biobehavioral influences on HIV-1 pathogenesis, but the role of the HPA axis is less clear. In vitro model systems have shown catecholamine effects on cellular vulnerability to infection (CCR5 and CXCR4 expression), viral gene expression (transcription factor activation), and innate antiviral responses (Type I interferons). Statistical mediation analyses from clinical natural history studies find that variations in SNS activity are plausible mediators of relationships between psychosocial risk factors and HIV-1 replication (22,23), and experimental analyses of the SIV model identify a key role for stress-induced remodeling of SNS innervation in lymphoid tissues as an influence on viral replication (9,29,34). In terms of Figure 1, existing data support the both the individual binary relationships A (22,23) and B (21,54,62), and their simultaneous transitive relationship linking psychosocial risk factors to indicators of HIV-1 pathogenesis (22,23).

Data regarding HPA mediation are less consistent. In vitro analyses suggest that glucocorticoids can influence selected molecular processes involved in viral replication, but glucocorticoids have not been found to substantially enhance overall viral replication rates either in vitro or in the SIV animal model in vivo. In fact, glucocorticoid elevation has been linked to reduced viral replication in both of those systems (8,52). Similarly mixed results emerge from human clinical studies. Some observational natural history analyses have linked high cortisol levels to subsequent AIDS onset (18,19), but several studies have also shown that experimental elevation of glucocorticoid levels can reduce viral load and $CD4^+$T cell loss (25,27,28). No corelational mediation analyses currently support the hypothesis that variations in HPA activity serve as biological intermediates between psychosocial risk factors and long-term individual differences in HIV-1 disease progression. It is conceivable that such mediating relationships do exist, but are obscured by sampling limitations or failure to assess glucocorticoid activity at the postreceptor level. In the absence of positive empirical support, however, the role of HPA activity as a mediator of psychosocial influences on HIV-1-related disease remains uncertain. Some evidence supports the binary relationship A in Figure 1 (6,45–47; as reviewed in 4,5,32), but data relevant to the B relationship are contradictory, and no prospective data currently support a transitive influence through A and B simultaneously.

To the extent that data continue to support a role for SNS activity in driving HIV-1 pathogenesis, catecholamine signaling could constitute an appealing target for behavioral or pharmacologic interventions. SNS activity may also serve as a functional neural biomarker to assess the impact of potential behavioral interventions on HIV-1 biology. This could provide for rapid assessment of intervention impact, and rational selection of psychosocial or pharmacologic interventions to protect HIV+ individuals from the detrimental effects of stress on disease progression. A similar case might be made for suppressing HPA activity based on natural history data, but results from clinical pharmacologic interventions and the SIV animal model raise the possibility that such suppression might instead enhance disease pathogenesis.

Several potential mechanisms of neural influence on HIV-1 pathogenesis are not considered in the current research literature, and might constitute productive targets for future research. No published data are available on potential effects of the parasympathetic nervous system on HIV-1 disease pathogenesis or progression (i.e., no prospective clinical analyses, and no experimental studies assessing effects of the parasympathetic neurotransmitter acetylcholine on viral replication). A great deal also remains to be learned about the interface between neural/endocrine activity and the adaptive immune response to HIV-1. The studies outlined above suggest that neural dynamics can directly regulate viral replication and the innate antiviral response, but little information is available regarding their impact on the adaptive immune response to HIV-1. Cytotoxic T lymphocyte (CTL) responses are believed to play a key role in regulating long-term viral replication set-points (68), but no published research has examined the relationship between psychosocial characteristics or neural/endocrine parameters and HIV-specific CTL activity (ascertained through PubMed in May 2007). Activated $CD8^+$T lymphocytes can also inhibit HIV-1 replication via a soluble "CD8 antiviral factor" (69), but no biobehavioral studies have examined this parameter as a potential mechanism of differential disease progression. Another immune parameter that has received little attention in the HIV biobehavioral literature, but looms large (and, unfortunately, still distant) on the

public health horizon, is the vaccine-induced immune response. Current efforts to develop a prophylactic vaccine to HIV-1 are hampered by difficulties in eliciting durable CTL responses in the absence of viral replication, and by difficulties in identifying specific antibodies that neutralize a broad range of viral strains. However, the development of an HIV vaccine may represent the most effective means for controlling the global pandemic (68,70). Given the inhibitory effects of stress and social isolation on other vaccine-induced immune responses (71–76), it is critical that mechanisms of those effects be elucidated to help optimize the efficacy of HIV vaccine candidates.

A great deal has been discovered in the past 25 years about the mechanisms by which psychosocial factors might potentially influence the basic biology of HIV infection. We now understand much about how HIV-1 causes disease, and it is increasingly clear how biobehavioral processes might affect those processes. What remains to be accomplished is the translation of these basic insights into effective clinical interventions that can suppress viral pathogenesis over the long periods of time necessary to preserve the health and well-being of HIV+ individuals. Antiretroviral medications slow, but do not stop, HIV-1 replication (77). Studies carried out in the context of ART suggest that biobehavioral dynamics continue to influence underlying viral replication rates as well as virologic and immunologic response to treatment (21,23). As the other articles in this special issue emphasize (1–3), a broad array of psychosocial factors could potentially influence HIV-1 disease progression. Modulation of HIV-1 replication by the neuroendocrine system and by penetrating innervation of lymphoid tissue provides new insights into biobehavioral regulation of infectious disease, and may suggest novel targets for health-protective intervention.

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REFERENCES

1. Ironson G, Hayward H. Do positive psychosocial factors predict disease progression in HIV? A review of the evidence. Psychosom Med 2008; 70:546–54.
2. Leserman J. Role of depression, stress, and trauma in HIV disease progression. Psychosom Med 2008;70:539–45.
3. Temoshok L, Wald RL, Synowski S, Garzino-Demo A. Coping as a multisystem construct that influences pathways mediating HIV-relevant immune function and disease progression. Psychosom Med 2008;70:555–61.
4. Leserman J. HIV disease progression: depression, stress, and possible mechanisms. Biol Psychiatry 2003;54:295–306.
5. Sloan EK, Collado-Hidalgo A, Cole S. Psychobiology of HIV infection. In: Ader R, editor. Psychoneuroimmunology, 4th ed. Vol. 2. Burlington, MA: Elsevier Academic Press; 2007:1053–76.
6. Goodkin K, Feaster DJ, Asthana D, Blaney NT, Kumar M, Baldewicz T, Tuttle RS, Maher KJ, Baum MK, Shapshak P, Fletcher MA. A bereavement support group intervention is longitudinally associated with salutary effects on the CD4 cell count and number of physician visits. Clin Diagn Lab Immunol 1998;5:382–91.
7. Petrie KJ, Fontanilla I, Thomas MG, Booth RJ, Pennebaker JW. Effect of written emotional expression on immune function in patients with human immunodeficiency virus infection: a randomized trial. Psychosom Med 2004;66:272–5.
8. Capitanio JP, Mendoza SP, Lerche NW, Mason WA. Social stress results in altered glucocorticoid regulation and shorter survival in simian acquired immune deficiency syndrome. Proc National Acad Sci USA 1998;95:4714–9.
9. Sloan EK, Capitanio JP, Tarara RP, Mendoza SP, Mason WA, Cole SW. Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis. J Neurosci 2007;27: 8857–65.
10. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173–82.
11. Levy JA. Pathogenesis of human immunodeficiency virus infection. Microbiol Rev 1993;57:183–289.
12. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995;373:123–6.
13. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996;272:1167–70.
14. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science 1996;271:1582–6.
15. Hasse AT, Henry K, Zupancic M, Sedgewick G, Faust RA, Melroe H, Cavert W, Gebhard K, Staskus K, Zhang Z, Dailey PJ, Balfour HH, Erice A, Perelson AS. Quantitative image analysis of HIV-1 infection in lymphoid tissue. Science 1996;274:985.
16. Sapolsky RM. Why Zebras Don't Get Ulcers: A Guide to Stress, Stress-Related Diseases, and Coping. New York: Freeman; 1994.
17. Weiner H. Perturbing the Organism: The Biology of Stressful Experience. Chicago: University of Chicago Press; 1992.
18. Leserman J, Petitto JM, Golden RN, Gaynes BN, Gu H, Perkins DO, Silva SG, Folds JD, Evans DL. The impact of stressful life events, depression, social support, coping and cortisol on progression to AIDS. Am J Psychiatry 2000;157:1221–8.
19. Leserman J, Petitto JM, Gu H, Gaynes BN, Barroso J, Golden RN, Perkins DO, Folds JD, Evans DL. Progression to AIDS, a clinical AIDS condition and mortality: psychosocial and physiological predictors. Psychol Med 2002;32:1059–73.
20. Ironson G, Solomon GF, Balbin EG, O'Cleirigh C, George A, Kumar M, Larson D, Woods TE. The Ironson-woods Spirituality/Religiousness Index is associated with long survival, health behaviors, less distress, and low cortisol in people with HIV/AIDS. Ann Behav Med 2002;24:34–48.
21. Cole SW, Naliboff BD, Kemeny ME, Griswold MP, Fahey JL, Zack JA. Impaired response to HAART in HIV-infected individuals with high autonomic nervous system activity. Proc National Acad Sci USA 2001; 98:12695–700.
22. Cole SW, Kemeny ME, Fahey JL, Zack JA, Naliboff BD. Psychological risk factors for HIV pathogenesis: Mediation by the autonomic nervous system. Biol Psychiatry 2003;54:1444–56.
23. Ironson G, Balbin EG, Stieren E, Detz K, Fletcher MA, Schneiderman N, Kumar M. Perceived stress and norepinephrine predict the effectiveness of response to protease inhibitors in HIV. Int J Behav Med. In press.
24. Hofmann B, Afzelius P, Iverson J, Kronborg G, Aabech P, Benfield T, Dybkjaer E, Nielsen JO. Buspirone, a serotonin receptor agonist, increases CD4 T-cell counts and modulates the immune system in HIV-seropositive subjects. AIDS 1996;10:1339–47.
25. Kilby JM, Tabereaux PB, Mulanovich V, Shaw GM, Bucy RP, Saag MS. Effects of tapering doses of oral prednisone on viral load among HIV-infected patients with unexplained weight loss. AIDS Res Hum Retroviruses 1997;13:1533–7.
26. Eugen-Olsen J, Benfield T, Axen TE, Parner J, Iversen J, Pedersen C, Nielsen JO. Effect of the serotonin receptor agonist, buspirone, on immune function in HIV-infected individuals: a six-month randomized, double-blind, placebo-controlled trial. HIV Clin Trials 2000;1: 20–6.
27. Ulmer A, Muller M, Bertisch-Mollenhoff B, Frietsch B. Low-dose prednisolone has a CD4-stabilizing effect in pre-treated HIV-patients during structured therapy interruptions (STI). Eur J Med Res 2005; 10:227–32.
28. Ulmer A, Muller M, Bertisch-Mollenhoff B, Frietsch B. Low dose prednisolone reduces CD4+ T cell loss in therapy-naive HIV-patients without antiretroviral therapy. Eur J Med Res 2005;10:105–9.
29. Sloan EK, Cox BF, Tarara RP, Capitanio JP, Mason WA, Cole SW. Beta-blockers for SIV infection: Impact on lymph node innervation and viral replication. Brain Behav Immunity 2007;21:e37.

30. Douglas SD, Ho WZ, Gettes DR, Cnaan A, Zhao H, Leserman J, Petitto JM, Golden RN, Evans DL. Elevated substance P levels in HIV-infected men. Aids 2001;15:2043–5.
31. Ho WZ, Douglas SD. Substance P and neurokinin-1 receptor modulation of HIV. J Neuroimmunol 2004;157:48–55.
32. Cole SW, Kemeny ME. Psychosocial influences on the progression of HIV infection. In: Ader R, Felten DL, Cohen N, editors. Psychoneuroimmunology, Vol. 2. San Diego: Academic Press; 2001:583–612.
33. Bellinger DL, Lorton D, Lubahn C, Felten DL. Innervation of lymphoid organs. In: Ader R, Felten DL, Cohen N, editors. Psychoneuroimmunology, 3rd ed. San Diego, CA: Academic Press; 2001.
34. Sloan EK, Tarara RP, Capitanio JP, Cole SW. Enhanced replication of simian immunodeficiency virus adjacent to catecholaminergic varicosities in primate lymph nodes. J Virol 2006;80:4326–35.
35. Onard JL, Schoenveld M, Cidlowski JA. Glucocorticoids and Immunity: Mechanisms of Regulation. In: Ader R, editor. Psychoneuroimmunology. 4th ed. Vol. 1. Burlington, MA: Elsevier Academic Press; 2007:45–62.
36. Sanders VM, Kavelaars A. Adrenergic Regulation of Immunity. In: Ader R, editor. Psychoneuroimmunology. 4th ed. Vol. 1. Burlington, MA: Elsevier Academic Press; 2007:63–84.
37. Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 entry cofactor: Functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. Science 1996;272:872–7.
38. Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, Cayanan C, Maddon PJ, Koup RA, Moore JP, Paxton WA. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Nature 1996;381:667–73.
39. Deng H, Liu R, Ellmeier W, Choe S, Unutmaz D, Burkhart M, Di Marzio P, Marmon S, Sutton RE, Hill CM, Davis CB, Peiper SC, Schall TJ, Littman DR, Landau NR. Identification of a major co-receptor for primary isolates of HIV-1. Nature 1996;381:661–6.
40. Wang J, Harada A, Matsushita S, Matsumi S, Zhang Y, Shioda T, Nagai Y, Matsushima K. IL-4 and a glucocorticoid up-regulate CXCR4 expression on human CD4+ T lymphocytes and enhance HIV-1 replication. J Leukoc Biol 1998;64:642–9.
41. Cole SW, Jamieson BD, Zack JA. cAMP externalizes lymphocyte CXCR4: Implications for chemotaxis and HIV infection. J Immunol 1999;162:1392–400.
42. Caulfield J, Fernandez M, Snetkov V, Lee T, Hawrylowicz C. CXCR4 expression on monocytes is up-regulated by dexamethasone and is modulated by autologous CD3+ T cells. Immunology 2002;105:155–62.
43. Curnow SJ, Wloka K, Faint JM, Amft N, Cheung CM, Savant V, Lord J, Akbar AN, Buckley CD, Murray PI, Salmon M. Topical glucocorticoid therapy directly induces up-regulation of functional CXCR4 on primed T lymphocytes in the aqueous humor of patients with uveitis. J Immunol 2004;172:7154–61.
44. Okutsu M, Ishii K, Niu KJ, Nagatomi R. Cortisol-induced CXCR4 augmentation mobilizes T lymphocytes after acute physical stress. Am J Physiol Regul Integr Comp Physiol 2005;288:R591–9.
45. Gorman JM, Kertzner R, Cooper T, Goetz RR, Lagomasino I, Novacenko H, Williams JB, Stern Y, Mayeux R, Ehrhardt AA. Glucocorticoid level and neuropsychiatric symptoms in homosexual men with HIV infection. Am J Psychiatry 1991;148:41–5.
46. Cruess DG, Antoni MH, Kumar M, Schneiderman N. Reductions in salivary cortisol are associated with mood improvement during relaxation training among HIV-seropositive men. J Behav Med 2000;23:107–22.
47. Antoni MH, Cruess S, Cruess DG, Kumar M, Lutgendorf S, Ironson G, Dettmer E, Williams J, Klimas N, Fletcher MA, Schneiderman N. Cognitive-behavioral stress management reduces distress and 24-hour urinary free cortisol output among symptomatic HIV-infected gay men. Ann Behav Med 2000;22:29–37.
48. Christeff N, Gherbi N, Mammes O, Dalle MT, Gharakhanian S, Lortholary O, Melchior JC, Nunez EA. Serum cortisol and DHEA concentrations during HIV infection. Psychoneuroendocrinology. 1997;22:S11–8.
49. Kumar M, Kumar AM, Waldrop D, Antoni MH, Schneiderman N, Eisdorfer C. The HPA axis in HIV-1 infection. J Acquir Immune Defic Syndr 2002;31:S89–93.
50. McComsey GA, Whalen CC, Mawhorter SD, Asaad R, Valdez H, Patki AH, Klaumunzner J, Gopalakrishna KV, Calabrese LH, Lederman MM. Placebo-controlled trial of prednisone in advanced HIV-1 infection. AIDS 2001;15:321–7.
51. Andrieu JM, Lu W. Long-term clinical, immunologic and virologic impact of glucocorticoids on the chronic phase of HIV infection. BMC Med 2004;2:17.
52. Shafer RW, Offit K, Macris NT, Horbar GM, Ancona L, Hoffman IR. Possible risk of steroid administration in patients at risk for AIDS. Lancet 1985;1:934–5.
53. Ayyavoo V, Mahalingam S, Rafaeli Y, Kudchodkar S, Chang D, Nagashunmugam T, Williams WV, Weiner DB. HIV-1 viral protein R (Vpr) regulates viral replication and cellular proliferation in T cells and monocytoid cells in vitro. J Leukoc Biol 1997;62:93–9.
54. Collado-Hidalgo A, Sung C, Cole S. Adrenergic inhibition of innate anti-viral response: PKA blockade of Type I interferon gene transcription mediates catecholamine support for HIV-1 replication. Brain Behav Immun 2006;20:552–63.
55. Markham PD, Salahuddin SZ, Veren K, Orndorff S, Gallo RC. Hydrocortisone and some other hormones enhance the expression of HTLV-III. Int J Cancer 1986;37:67.
56. Laurence J, Sellers MB, Sikder SK. Effect of glucocorticoids on chronic human immunodeficiency virus (HIV) infection and HIV promoter-mediated transcription. Blood 1989;74:291–7.
57. Mitra D, Sikder SK, Laurence J. Role of glucocorticoid receptor binding sites in the human immunodeficiency virus type 1 long terminal repeat in steroid-mediated suppression of HIV gene expression. Virology 1995;214:512–21.
58. Kino T, Kopp JB, Chrousos GP. Glucocorticoids suppress human immunodeficiency virus type-1 long terminal repeat activity in a cell type-specific, glucocorticoid receptor-mediated fashion: direct protective effects at variance with clinical phenomenology. J Steroid Biochem Mol Biol 2000;75:283–90.
59. Cole SW, Kemeny ME, Taylor SE. Social identity and physical health: Accelerated HIV progression in rejection-sensitive gay men. J Pers Soc Psychol 1997;72:320–36.
60. Cole SW, Kemeny ME, Taylor SE, Visscher BR, Fahey JL. Accelerated course of Human Immunodeficiency Virus infection in gay men who conceal their homosexual identity. Psychosom Med 1996;58:219–31.
61. Kagan J, Reznick JS, Snidman N. Biological bases of childhood shyness. Science 1988;240:167–71.
62. Cole SW, Korin YD, Fahey JL, Zack JA. Norepinephrine accelerates HIV replication via protein kinase A-dependent effects on cytokine production. J Immunol 1998;161:610–6.
63. Zang YC, Halder JB, Samanta AK, Hong J, Rivera VM, Zhang JZ. Regulation of chemokine receptor CCR5 and production of RANTES and MIP-1alpha by interferon-beta. J Neuroimmunol 2001;112:174–80.
64. Shirazi Y, Pitha PM. Interferon downregulates CXCR4 (fusin) gene expression in peripheral blood mononuclear cells. J Hum Virol 1998;1:69–76.
65. Cremer I, Vieillard V, De Maeyer E. Interferon-beta-induced human immunodeficiency virus resistance in CD34(+) human hematopoietic progenitor cells: correlation with a down-regulation of CCR-5 expression. Virology 1999;253:241–9.
66. Cremer I, Vieillard V, De Maeyer E. Retrovirally mediated IFN-beta transduction of macrophages induces resistance to HIV, correlated with up-regulation of RANTES production and down-regulation of C-C chemokine receptor-5 expression. J Immunol 2000;164:1582–7.
67. Yang Y-F, Tomura M, Iwasaki M, Ono S, Zou J-P, Uno K, Shearer GM, Fujiwara H, Hamaoka T. IFN-alpha acts on T-cell receptor-triggered human peripheral leukocytes to up-regulate CCR5 expression on CD4+ and CD8+ T cells. J Clin Immunol 2001;21:402–9.
68. Girard MP, Osmanov SK, Kieny MP. A review of vaccine research and development: the human immunodeficiency virus (HIV). Vaccine 2006;24:4062–81.
69. Levy JA. The search for the CD8+ cell anti-HIV factor (CAF). Trends Immunol 2003;24:628–32.
70. Garber DA, Silvestri G, Feinberg MB. Prospects for an AIDS vaccine: three big questions, no easy answers. Lancet Infect Dis 2004;4:397–413.
71. Glaser R, Kiecolt-Glaser JK, Bonneau RH, Malarkey W, Kennedy S, Hughes J. Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. Psychosom Med 1992;54:22–9.
72. Jabaaij L, Grosheide PM, Heijtink RA, Duivenvoorden HJ, Ballieux RE, Vingerhoets AJ. Influence of perceived psychological stress and distress

on antibody response to low dose rDNA hepatitis B vaccine. J Psychosom Res 1993;37:361–9.
73. Jabaaij L, van Hattum J, Vingerhoets JJ, Oostveen FG, Duivenvoorden HJ, Ballieux RE. Modulation of immune response to rDNA hepatitis B vaccination by psychological stress. J Psychosom Res 1996;41:129–37.
74. Marsland AL, Cohen S, Rabin BS, Manuck SB. Associations between stress, trait negative affect, acute immune reactivity, and antibody response to hepatitis B injection in healthy young adults. Health Psychol 2001;20:4–11.
75. Pressman SD, Cohen S, Miller GE, Barkin A, Rabin BS, Treanor JJ. Loneliness, social network size, and immune response to influenza vaccination in college freshmen. Health Psychol 2005;24:297–306.
76. Miller GE, Cohen S, Pressman S, Barkin A, Rabin BS, Treanor JJ. Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? Psychosom Med 2004;66:215–23.
77. Ramratnam B, Mittler JE, Zhang L, Boden D, Hurley A, Fang F, Macken CA, Perelson AS, Markowitz M, Ho DD. The decay of the latent reservoir of replication-competent HIV-1 is inversely correlated with the extent of residual viral replication during prolonged anti-retroviral therapy. Nat Med 2000;6:82–5.