Association of Depression, CD8+ T Lymphocytes, and Natural Killer Cell Activity: Implications for Morbidity and Mortality in Human Immunodeficiency Virus Disease

Dean G. Cruess, PhD, Steven D. Douglas, MD, John M. Petitto, MD, Jane Leserman, PhD, Thomas Ten Have, PhD, David Gettes, BS, Benoit Dubé, MD, and Dwight L. Evans, MD*

Address
*Department of Psychology, University of Pennsylvania, 3815 Walnut Street, Philadelphia, PA 19104, USA.
E-mail: dcruess@psych.upenn.edu

Current Psychiatry Reports 2003, **5:**445–450
Current Science Inc. ISSN 1523-3812

A heightened risk of mood disorders, such as major depression, and acute depressive symptoms has been observed among HIV-seropositive individuals since the start of the AIDS epidemic, and an accumulating body of data now shows that depression may have an impact on morbidity and mortality among individuals with HIV disease. Although the specific physiologic mechanisms involved in this process have not been delineated, there is some evidence to suggest that certain components of innate immunity, including killer lymphocytes such as CD8+ T lymphocytes and natural killer cells, may represent key pathways through which depression affects HIV disease progression. This paper reviews some of the main studies examining the effects of depression on immunity and HIV disease progression and discusses the potential role of killer lymphocytes as an underlying mechanism by which depression may impact morbidity and mortality.

Introduction

There is increasing evidence to suggest that certain psychologic factors, such as depression and stress, may influence the course of many diseases, including cardiovascular disease and cancer [1–6]. Psychosocial stress and depression in particular may downregulate key components of cell-mediated immunity [7–12] and also increase susceptibility to infectious diseases [13,14]. Although these types of psychologic factors also have been shown to impact on morbidity and mortality in HIV disease [15••,16••], the exact underlying mechanisms linking depression and HIV disease progression have not yet been determined.

The authors will review several published studies that examine associations between depression, immunity, and HIV disease progression and mortality. The authors will focus primarily on the relationship between depression and killer lymphocytes, specifically CD8+ T lymphocytes and natural killer (NK) cells, which are innate immune cells that possess the functional capacity to lyse HIV-infected cells and inhibit HIV infection by suppressing HIV entry and replication, and whose action has also been impaired during depression. The negative impact of depression on the number and function of circulating killer lymphocytes and subsequently HIV disease progression is just one potential mechanism through which psychosocial factors may impact morbidity and mortality in HIV disease.

Prevalence of Depression in Human Immunodeficiency Virus

Mood disorders, such as major depression, have been studied within the context of HIV disease since the start of the AIDS epidemic [17•], with most of the clinical studies focusing on HIV-seropositive (HIV+) men [18–22]. In an early study, the authors' group found that HIV+ homosexual men had a higher prevalence rate of major depression compared with overall rates of major depression among men of similar age in the general population, but this rate was no higher than HIV-seronegative (HIV-) men of comparable demographic status [21], a finding that has also been confirmed in other studies [22–24]. Overall, the majority of these studies have estimated that the preva-

lence of a major depression diagnosis among HIV+ men is roughly 5% to 10%.

The prevalence rates of major depression among HIV+ women have varied widely in existing studies of clinical and community samples [15••,25,26]. The authors' group recently conducted a clinical investigation of major depression among 155 women (93 HIV+, 62 HIV-) who were not active substance abusers, and found that the proportion of women with current major depression was four times higher in HIV+ women (19.4%) than in HIV- women (4.8%) [27]. In this study, mean depressive symptom scores on the Hamilton Rating Scale of Depression [28] were also significantly higher among HIV+ women compared with their HIV- counterparts. That nearly 20% of HIV+ women had a diagnosis of major depression is also consistent with a recent large-scale epidemiologic study documenting that 42% of 765 HIV+ women experience chronic depressive symptoms. More importantly, this epidemiologic study further reported that greater depressive symptoms are also associated with higher mortality rates among HIV+ women, which further underscores the need to examine the role of psychosocial factors, such as depression, on HIV disease progression [15••]. In sum, the vast majority of the psychiatric prevalence studies suggest that HIV+ men and women are at an increased risk of major depression or significant acute depressive symptoms throughout the course of the disease.

Depression, Immunity, and Human Immunodeficiency Virus Progression

There has been accumulating evidence that negative mood states, such as major depression and depressive symptoms, may have an adverse impact on immune system functioning of medically healthy individuals [9,29]. Severity of depression was associated with alterations in several in vitro measures of immune function (*eg*, lower CD8+ T lymphocytes and NK cell activity) in a large-scale meta-analysis among otherwise medically healthy persons [30]. There has also been some data to suggest that depression may result in a more acute phase response, which includes activation of some specific elements of cell-mediated immunity, including increased monocytic production of interleukins (interleukin-1-beta and interleukin-6) [31]. Thus, clinical studies of depression among patients without other medical illnesses have consistently demonstrated significant alterations in NK cells as well as CD8+ cells, which are two immune subpopulations that may play key roles in regulating HIV infection and disease progression.

A considerable body of evidence has also emerged from some longitudinal studies to suggest that depression is associated with HIV morbidity and mortality; the majority of the prospective studies with long-term follow-up demonstrate that depression (and stress) is associated with HIV disease progression [16••,32,33] and mortality [15••,34,35]. In the San Francisco Men's Health Study, a 9-year longitudinal study, median time to first AIDS diagnosis was 1.4 years shorter for depressed men compared with men not depressed at the initial assessment [34]. In addition, men with elevated depressive symptoms at each visit throughout this study had a 1.7 times greater risk of mortality compared with men without such consistent patterns of depression [32]. At 5-year follow-up, baseline depression was also associated with declines in CD4+ lymphocytes (-0.0285 × 10(9)/L per year), but not with progression to AIDS [33]. In another study, Ironson *et al.* [36] reported that men with more distress at HIV serostatus notification were at a greater risk for HIV-related clinical symptoms 2 years later. Bereavement, which has some inherent symptom overlap with depression, has also been associated with more rapid decline in CD4+ cell counts among HIV+ men during a 3- to 4-year follow-up [37], and traumatic stress has also been associated with lower CD4+/CD8+ cell ratios among HIV+ women [38].

However, not all studies have reported significant relationships between depression, immunity, and HIV disease progression. For example, no relationship was found between baseline depressive symptoms and progression to AIDS or decline in CD4+ lymphocytes in the Multicenter AIDS Cohort Study [39]. In addition, other major longitudinal studies with shorter follow-up periods (*eg*, 6 to 12 months) have also found no significant relationship between stressful events or depression and changes in CD4+ lymphocytes [40,41]. In a meta-analytic study, depressive symptoms (and not stressors) were related to symptoms of HIV infection, but neither was associated with decline in CD4+ lymphocytes [42]. Some of these conflicting findings may be because of, in part, methodologic differences, including measuring depression only at baseline rather than over time, the use of less specific assessments of cellular immunity that have excluded killer lymphocyte populations, and using a relatively short duration of follow-up assessments.

Coping, Health, and Illness Project Studies of Human Immunodeficiency Virus and Men

To address some of the methodologic problems outlined herewith, the authors' group conducted the Coping, Health, and Illness Project (CHIP) study, a 9-year longitudinal cohort study of HIV+ men. This study has found compelling evidence that psychosocial factors, such as stress and depression, influence key components of cellular immunity and also increase the likelihood of disease progression among HIV+ men [16••,43–47]. Severe stress is associated with lower levels of killer lymphocytes (CD8+ cytotoxic and suppressor cells; CD16+, CD56+, and CD57+ NK cell populations) at baseline assessment [43], and stress and depression were also associated with reductions in killer lymphocytes (CD8+ cells; CD56+ and CD16+ NK cells) among 66

HIV+ men during a 2-year follow-up [45]. The HIV+ men most likely to have decreases on these immune measures during the 2-year follow-up were those who scored greater than the median on stress and depressive symptoms. These findings are among the first prospective data demonstrating that stress and depressive symptoms, particularly when they co-occur, are associated with decreased numbers of NK cells and CD8+ T lymphocytes in HIV+ men. The authors also found a greater risk of early change in HIV disease status related to these same psychosocial factors among men studied for up to 3.5 years [44]. The clinical relevance of these initial findings has now been established in further longitudinal follow-up studies, demonstrating a significant relationship between several psychosocial factors, including stress and depressive symptoms, and disease progression among HIV+ men.

At a 5.5-year follow-up in the CHIP study, the authors' group examined the effects of depressive symptoms and stress on progression to AIDS among 82 HIV+ men who were without symptoms of AIDS at study entry [46]. Overall, 33% of the sample had progressed to AIDS (CD4+ cell count less than 200 or occurrence of an AIDS-related condition) during this follow-up period; those men with more cumulative average stress and depressive symptoms had more rapid progression to AIDS. Furthermore, men who developed AIDS were approximately two times more likely to have had a major depression before disease progression or at the end of the study (33.3%) than those without AIDS (16.4%). These findings are the first longitudinal evidence that depression and stress affect progression to AIDS among HIV+ men.

In the CHIP study, 37% of the 82 HIV+ men without AIDS at entry had progressed to AIDS at 7.5-year follow-up [47]. The authors then calculated the risk of AIDS associated with depressive symptoms and stress as well as several additional psychosocial variables. More stressful events, less support satisfaction, and greater use of denial coping were all significantly associated with progression to AIDS. There was also a trend for depressive symptoms and major depression diagnosis associated with HIV disease progression as well. Approximately 50% of the HIV+ men above the median in stress, use of denial coping, and depressive symptoms, and below the median in support, progressed to AIDS compared with approximately 25% of those below the median in stress, use of denial coping, and depressive symptom, and above the median in support.

At a 9-year follow-up in the CHIP study, the authors' group also examined the association of stressful life events, depressive symptoms, and other psychosocial measures, and specific cellular immune measures (*eg*, CD8+ T lymphocytes and NK cell numbers), with several indicators of HIV disease progression, including progression to Centers for Disease Control–defined AIDS, a clinical AIDS condition, and mortality [16••]. Higher cumulative average stressful life events and lower cumulative average social support predicted more rapid progression to the Centers for Disease Control AIDS classification and a clinical AIDS condition. Higher levels of anger and CD8+ cells were associated with faster progression to AIDS, and depressive symptoms were also associated with faster development of an AIDS clinical condition. These results suggest that depressed mood, stressful life events, and limited social support are associated with more rapid clinical progression in HIV infection. Overall, the results of the 9-year CHIP study suggest that specific psychosocial factors, such as stress and depressive symptoms, are associated with alterations in specific innate immune measures, such as CD8+ T lymphocytes and NK cells, especially in the early stages of HIV disease, and that stressful life events, depressive symptoms, and limited social support are associated with more rapid clinical progression in HIV infection.

Studies of Human Immunodeficiency Virus and Women

The authors have conducted similar types of investigations with HIV+ women, and now have some initial evidence that depression may also alter the function of killer lymphocytes among HIV+ women as well. The authors' group recently conducted a clinical study at two sites (Gainesville, FL and Philadelphia, PA) to determine if depression is associated with alterations in cellular immunity among 93 (63 HIV+, 30 HIV-) women [48•]. This study specifically focused on killer lymphocytes (NK and CD8+ T lymphocytes) based on the immunology literature suggesting a potential role for these lymphocytes in host defense against HIV infection and also on the psychiatric literature suggesting that depression is associated with alterations in these same lymphocyte subpopulations, including activation markers that have been associated with HIV disease progression. Although NK and CD8+ T lymphocyte populations have been studied in HIV+ men as possible mechanisms linking depression to HIV disease progression [43,45], to the authors' knowledge, no previous study has examined these specific cellular-immune mechanisms in HIV+ women.

In the authors' ongoing study of HIV+ women, those women with a diagnosis of major depression exhibited significant reductions in NK cell activity at baseline assessment. In addition, depressive symptoms and anxiety symptoms were associated with reductions in NK cell activity and increases in activated CD8+ lymphocyte (CD8+/CD38+/DR+) levels, as well as with increases in viral load. Because each of these physiologic outcome measures has been associated with HIV disease progression, these results provide further support that depression may also be associated with an increased likelihood of HIV disease progression as well. Moreover, these results also extend previous investigations of HIV+ men by demonstrating significant alterations in killer lymphocytes

among depressed HIV+ women. This finding, along with the growing interest in NK and CD8+ cell control of HIV infection, suggests that killer lymphocytes warrant further study as a potential mechanism whereby depression may influence the course of HIV disease.

Similar to the authors' earlier investigations with HIV+ men, all of the women in this study underwent comprehensive, structured interviews to assess psychiatric diagnoses, including mood disorders and other depressive symptoms. To more carefully address the effects of depression on cellular immunity, the authors excluded women with current alcohol or substance abuse or dependence to avoid the potential confounding effects of these substances to suppress immunity. The authors also focused on levels of specific killer lymphocyte subsets, NK and a marker of activated CD8+ cells (CD8+/CD38+/DR+), which are believed to play an important role in host resistance against HIV infection. This study also controlled the collection of the physiologic measures by performing phlebotomy at the same time of day, and after 1 hour of rest in a recumbent position, to avoid potential circadian effects on immunity and to avoid potential nonspecific methodologic factors [43,45,49]. In addition, all of the depression-immune analyses controlled for viral load, CD4+ cell count, and antiviral medication use. The authors also performed the depression analyses with the traditional 17-item Hamilton Rating Scale of Depression measure and also with an 11-item version that eliminates specific physical symptoms that may possibly overlap with symptoms of HIV disease progression. Overall, this high level of experimental control adds to the internal validity of the depression-immune association observed in this study.

To the authors' knowledge, the results of this study provide some of the first evidence that depression may alter the function of killer lymphocytes in HIV+ women. These findings suggest that depression may decrease NK cell activity and may also lead to an increase in activated CD8 lymphocytes and viral load. Thus, depression may have a negative impact on innate immunity, which suggests that an examination of killer lymphocytes may prove useful in assessing the potential relationship between depression, immunity, and HIV disease progression in women. The high rate of major depression observed among HIV+ women [27], paired with findings of the largest epidemiologic study to date indicating that depressive symptoms are associated with increased mortality in HIV+ women [15••], highlights the need for more controlled longitudinal studies to ascertain the mechanisms behind the association between major depression and depressive symptoms, immunity, and disease progression among HIV+ women.

Based on over a decade of research in this area, the authors have now proposed a model by which depression impacts on HIV disease progression through its effects on killer lymphocytes (Fig. 1).

As mentioned, depression may lead to significant alterations in NK cells as well as CD8+ cells, which are the two cellular immune populations that may play key roles in regulating HIV infection. More specifically, NK cells may be involved in natural resistance against viral infection and may thus have the capacity to lyse HIV-1 infected cells and also inhibit HIV entry and replication [50–53], although subsets of CD8+ cytolytic cells may serve similar functions as well, especially in the early stages of HIV disease [54–58]. In the authors' studies of HIV+ men, depression-associated alterations in NK cells and CD8+ T lymphocytes was also found [43,48•], which suggests that killer lymphocytes may potentially mediate the effects of depression during the earlier stages of HIV disease progression. CD8+ T lymphocytes may have a beneficial or perhaps an adverse effect in later stage infection, and a specific subpopulation of activated CD8+ cells (CD8+/CD38+/DR+ activated CD8+ cells) has been associated with cytotoxic activity and also with HIV disease progression [59–63]. Killer lymphocyte levels and activity among long-term non-progressors, and also HIV+ individuals with very low CD4+ cell counts, but who have prolonged asymptomatic periods, have also been examined. For example, Ironson *et al.* [64•] recently observed that NK cell number and function are preserved among patients with AIDS with low CD4+ cell counts. The authors of this paper observe that these immune factors may be important in maintaining the health and well being of these individuals. Overall, there is increasing evidence suggesting that killer lymphocytes may serve as a protective factor against HIV disease progression and perhaps influence health and survival.

The authors' research team is currently extending some initial observations regarding depression-associated alterations of NK and CD8+ cells in HIV+ women by conducting several specific ex vivo experiments to help categorize the functional capacity of these types of cells to suppress HIV activity in addition to their lytic activity. By focusing on the mechanisms of NK and CD8+ cell alterations in depression, coupled with evaluating certain novel and also mainstream pharmacologic agents for treating depression, these studies may provide further mechanistic insights into some fundamental relationships between depression, immunity, and HIV-disease progression. The goal of these current studies is to help clarify some of the potential mechanisms whereby depression may influence killer lymphocyte activity and HIV disease progression, and these types of well-controlled ex vivo experiments may perhaps form a scientific basis for future intervention studies of antidepressant therapies for HIV+ individuals.

Conclusions

Human immunodeficiency virus–seropositive individuals are at an increased risk of mood disorders, such as major

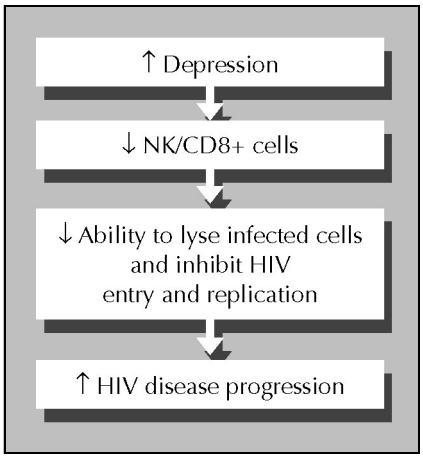

Figure 1. Human immunodeficiency virus (HIV) disease progression. NK—natural killer.

depression, and acute depressive symptoms, which may adversely affect morbidity and mortality. Although the specific immune mechanisms through which depression may impact HIV disease progression and mortality are unknown at this time, increasing evidence suggests that killer lymphocytes, such as CD8+ lymphocytes and NK cells, may play a key role. Clinical studies of depression among patients without other medical illness have consistently demonstrated significant alterations in NK cells and CD8+ lymphocytes, two immune subpopulations that may play vital roles in regulating HIV infection. There is increasing evidence that depression alters levels and functioning of killer lymphocytes in HIV disease, and there is also growing evidence that NK cells and CD8+ lymphocytes exert anti-HIV effects by classic killing activity as well as the production of HIV-suppressive factors. The negative effects of depression on number and function of circulating killer lymphocytes and, ultimately, HIV disease progression is just one potential mechanism through which depression may impact morbidity and mortality in HIV disease. Focused experiments that help to clarify these underlying mechanisms will perhaps form a scientific basis for future intervention studies of antidepressant therapies for HIV+ individuals.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Spiegel D, Kraemer HC, Bloom JR, Gottheil E: **Effect of psychosocial treatment on survival of patients with metastatic breast cancer.** *Lancet* 1989, **2:**888–891.
2. Frasure-Smith N, Lesperance F, Talajic M: **Depression following myocardial infarction: impact on 6-month survival.** *JAMA* 1993, **270:**1819–1825.
3. Frasure-Smith N, Lesperance F, Talajic M: **Depression and 18-month prognosis after myocardial infarction.** *Circulation* 1995, **91:**999–1005.
4. Fawzy FI, Fawzy NW, Hyun CS, *et al.*: **Malignant melanoma: effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later.** *Arch Gen Psych* 1993, **50:**681–689.
5. Musselman DL, Evans DL, Nemeroff CB: **The relationship of depression to cardiovascular disease: epidemiology, biology and treatment.** *Arch Gen Psych* 1998, **55:**580–592.
6. Faller H, Bulzebruck H, Drings P, Lang H: **Coping, distress, and survival among patients with lung cancer.** *Arch Gen Psych* 1999, **55:**756–762.
7. Cruess DG, Leserman J, Petitto JM, *et al.*: **Psychosocial-immune relationships in HIV disease.** *Semin Clin Neuropsychiatry* 2001, **6:**241–252.
8. Schleifer SJ, Keller SE, Bond RN, *et al.*: **Major depressive disorder and immunity.** *Arch Gen Psych* 1989, **46:**81–87.
9. Evans DL, Leserman J, Pedersen CA, *et al.*: **Immune correlates of stress and depression.** *Psychopharm Bull* 1989, **25:**319–324.
10. Stein M, Miller AH, Trestman RL: **Depression, the immune system and health and illness.** *Arch Gen Psych* 1991, **48:**171–177.
11. Reichlin S: **Mechanisms of disease: neuroendocrine-immune interactions.** *N Eng J Med* 1993, **329:**1246–1253.
12. Phillips MI, Evans DL: *Neuroimmunology: Methods in Neurosciences,* vol 24. San Diego: Academic Press Harcourt Brace Jovanovich; 1995.
13. Glaser R, Rabin B, Chesney M, *et al.*: **Stress-induced immunomodulation.** *JAMA* 1999, **281:**2268–2270.
14. Kiecolt-Glaser JK, Glaser R: **Depression and immune function: central pathways to morbidity and mortality.** *J Psychosom Res* 2002, **53:**873–876.
15. •• Ickovics JR, Hamburger ME, Vlahov D, *et al.*: **Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women.** *JAMA* 2001, **285:**1466–1474.

This large epidemiologic study documented elevated rates of psychologic symptoms among HIV+ women and also reported that greater depressive symptoms are associated with HIV disease progression among women.

16. •• Leserman J, Petitto JM, Gu H, *et al.*: **Progression to AIDS, a clinical AIDS condition and mortality: psychosocial and physiological predictors.** *Psychol Med* 2002, **32:**1059–1073.

This empiric study presents data from a 9-year study of HIV+ men and suggests that stressful life events, dysphoric mood, and limited social support are associated with more rapid clinical HIV disease progression among men.

17. • Evans DL, Mason K, Bauer R, *et al.*: **Neuropsychiatric manifestations of HIV-1 infection and AIDS.** In *Psychopharmacology: The Fifth Generation of Progress.* Edited by Charney D, Coyle J, Davis K, Nemeroff C. New York: Raven Press; 2002:1281–1299.

This is a comprehensive review of the neuropsychiatric symptoms and conditions experienced by HIV+ individuals.

18. Dickey WC, Dew MA, Becker JT, Kingsley L: **Combined effects of HIV-infection status and psychosocial vulnerability on mental health in homosexual men.** *Soc Psychiatry Psychiatric Epidemiol* 1999, **34:**4–11.
19. Griffin KW, Rabkin JG, Remien RH, Williams JB: **Disease severity, physical limitations and depression in HIV-infected men.** *J Psychosom Res* 1998, **44:**219–227.
20. Lyketsos CG, Hoover DR, Guccione M, *et al.*: **Changes in depressive symptoms as AIDS develops: the Multicenter AIDS Cohort Study.** *Am J Psychiatry* 1996, **153:**1430–1437.
21. Perkins DO, Stern RA, Golden RN, *et al.*: **Mood disorders in HIV infection: prevalence and risk factors in a non-epicenter of the AIDS epidemic.** *Am J Psychiatry* 1994, **151:**233–236.
22. Rabkin JG, Goetz RR, Remien RH, *et al.*: **Stability of mood despite HIV illness progression in a group of homosexual men.** *Am J Psychiatry* 1997, **154:**231–238.
23. Atkinson J, Grant I, Kennedy C, *et al.*: **Prevalence of psychiatric disorders among men infected with human immunodeficiency virus: a controlled study.** *Arch Gen Psychiatry* 1988, **45:**859–964.
24. Williams JBW, Rabkin JG, Remien RH, *et al.*: **Multidisciplinary baseline assessment of homosexual men with and without human immunodeficiency virus infection: standardized clinical assessment of current and lifetime psychopathology.** *Arch Gen Psychiatry* 1991, **48:**124–130.

25. Goggin K, Engelson ES, Rabkin JG, Kotler DP: **The relationship of mood, endocrine, and sexual disorders in human immunodeficiency virus positive (HIV+) women: an exploratory study.** *Psychosom Med* 1998, **60:**11–16.
26. Moore J, Schuman P, Schoenbaum E, *et al.*: **Severe adverse life events and depressive symptoms among women with, or at risk for, HIV infection in four cities in the United States of America.** *AIDS* 1999, **13:**2459–2468.
27. Morrison M, Petitto J, Ten Have T, *et al.*: **Depressive and anxiety disorders in women with HIV infection.** *Am J Psychiatry* 2002, **159:**789–796.
28. Hamilton M: **A rating scale for depression.** *J Neurol Neurosurg Psychiatry* 1960, **23:**56–62.
29. Evans DL, Folds JD, Pettito J, *et al.*: **Circulating natural killer cell phenotypes in males and females with major depression: relation to cytotoxic activity and severity of depression.** *Arch Gen Psych* 1992, **49:**388–395.
30. Herbert TB, Cohen S: **Depression and immunity: a meta-analytic review.** *Psychol Bull* 1993, **113:**472–486.
31. Maes M: **Evidence for an immune response in major depression: a review and hypothesis.** *Prog Neuropsychopharmacol Biol Psychiatry* 1995, **19:**11–38.
32. Page-Shafer K, Delorenze GN, Satariano W, Winkelstein W, Jr.: **Comorbidity and survival in HIV-infected men in the San Francisco Men's Health Survey.** *Ann Epidemiol* 1996, **6:**420–430.
33. Burack JH, Barrett DC, Stall RD, *et al.*: **Depressive symptoms and CD4 lymphocyte decline among HIV-infected men.** *JAMA* 1993, **270:**2568–2573.
34. Mayne TJ, Vittinghoff E, Chesney MA, *et al.*: **Depressive affect and survival among gay and bisexual men infected with HIV.** *Arch Int Med* 1996, **156:**2233–2238.
35. Patterson TL, Shaw WS, Semple SJ, *et al.*: **Relationship of psychosocial factors to HIV disease progression.** *Ann Behav Med* 1996, **18:**30–39.
36. Ironson G, Friedman A, Klimas N, *et al.*: **Distress, denial, and low adherence to behavioral interventions predict faster disease progression in gay men infected with human immunodeficiency virus.** *Int J Behav Med* 1994, **1:**90–105.
37. Kemeny ME, Dean L: **Effects of AIDS-related bereavement on HIV progression among New York City gay men.** *AIDS Educ Prev* 1995, **7:**36–47.
38. Kimerling R, Calhoun KS, Forehand R, *et al.*: **Traumatic stress in HIV-infected women.** *AIDS Educ Prev* 1999, **11:**321–330.
39. Lyketsos CG, Hoover DR, Guccione M, *et al.*: **Depressive symptoms as predictors of medical outcomes in HIV infection.** *JAMA* 1993, **270:**2563–2567.
40. Perry S, Fishman B, Jacobsberg L, Frances A: **Relationships over 1 year between lymphocyte subsets and psychosocial variables among adults with infection by human immunodeficiency virus.** *Arch Gen Psych* 1992, **49:**396–401.
41. Rabkin JG, Williams JB, Remien RH, *et al.*: **Depression, distress, lymphocyte subsets, and human immunodeficiency virus symptoms on two occasions in HIV-positive homosexual men.** *Arch Gen Psych* 1991, **48:**111–119.
42. Zorrilla EP, McKay JR, Luborsky L, Schmidt K: **Relation of stressors and depressive symptoms to clinical progression of viral illness.** *Am J Psych* 1996, **153:**626–635.
43. Evans DL, Leserman J, Perkins DO, *et al.*: **Stress-associated reductions of cytotoxic T lymphocytes and natural killer cells in asymptomatic HIV infection.** *Am J Psychiatry* 1995, **152:**543–550.
44. Evans DL, Leserman J, Perkins DO, *et al.*: **Severe life stress as a predictor of early disease progression in HIV infection.** *Am J Psychiatry* 1997, **154:**630–634.
45. Leserman J, Petitto JM, Perkins DO, *et al.*: **Severe stress, depressive symptoms, and changes in lymphocyte subsets in human immunodeficiency virus-infected men.** *Arch Gen Psych* 1997, **54:**279–285.
46. Leserman J, Jackson ED, Petitto JM, *et al.*: **Progression to AIDS: the effects of stress, depressive symptoms, and social support.** *Psychosom Med* 1999, **61:**397–406.
47. Leserman J, Petitto JM, Golden RN, *et al.*: **Impact of stressful life events, depression, social support, coping and cortisol on progression to AIDS.** *Am J Psychiatry* 2000, **157:**1221–1228.
48.• Evans DL, Ten Have T, Douglas SD, *et al.*: **Association of depression with viral load, CD8 T lymphocytes, and natural killer cells in women with HIV infection.** *Am J Psychiatry* 2002, **159:**1752–1759.

This is a recent empiric paper documenting an association between depression and killer lymphocyte number and function among HIV+ women.

49. Petitto JM, Folds JD, Ozer H, *et al.*: **Altered diurnal variation in natural killer cell phenotypes and cytotoxic activity in major depression.** *Am J Psychiatry* 1992, **148:**694–696.
50. Chehimi J, Starr SE, Frank I, *et al.*: **Natural killer (NK) cell stimulatory factor increases the cytotoxic activity of NK cells from both health donors and human immunodeficiency virus-infected patients.** *J Exp Med* 1992, **175:**789–796.
51. Whiteside TL, Herberman RB: **Role of human natural killer cells in health and disease.** *Clin Diagn Lab Immunol* 1994, **1:**125–133.
52. Levy JA: *HIV and the Pathogenesis of AIDS*. Washington, DC: American Society for Microbiology Press; 1998.
53. Oliva A, Kinter AL, Vaccarezza M, *et al.*: **Natural killer cells from human immunodeficiency virus (HIV)-infected individuals are an important source of CC-chemokines and suppress HIV-1 entry and replication in vitro.** *J Clin Invest* 1998, **102:**223–231.
54. Jassoy C, Harrer T, Rosenthal T, *et al.*: **Human immunodeficiency virus type 1-specific cytotoxic T lymphocytes release gamma interferon, tumor necrosis factor alpha, and TNF-beta when they encounter their target antigens.** *J Virol* 1993, **67:**2844–2852.
55. Ho HN, Hultin LE, Mitsuyasu RT, *et al.*: **Circulating HIV-specific CD8+ cytotoxic T cells express CD38 and HLA-DR antigens.** *J Immunol* 1993, **150:**3070–3079.
56. Fauci AS, Pantaleo G, Stanley S, Weissman D: **Immunopathogenic mechanisms of HIV infection.** *Ann Int Med* 1996, **124:**654–663.
57. Ferbas J: **Perspectives on the role of CD8+ cell suppressor factors and cytotoxic T lymphocytes during HIV infection.** *AIDS Res Hum Retroviruses* 1998, **14:**S153–S160.
58. Greenberg P, Riddell S: **Deficient cellular immunity: finding and fixing the defects.** *Science* 1999, **285:**546–551.
59. Famularo G, Moretti S, Marcellini S, *et al.*: **CD8 lymphocytes in HIV infection: helpful and harmful.** *J Clin Lab Immunol* 1997, **49:**15–32.
60. Perrit D, Sesok-Pizzini DA, Schretzenmair R, *et al.*: **C1.7 antigen expression on CD8+ T cells is activation dependent: increased proportion of C1.7+ CD8+ T cells in HIV-1 infected patients with progressing disease.** *J Immunol* 1999, **162:**7563–7568.
61. Gea-Banacloche JC, Migueles SA, Martino L, *et al.*: **Maintenance of large numbers of virus-specific CD8+ T cells in HIV-infected progressors and long-term non-progressors.** *J Immunol* 2000, **165:**1082–1092.
62. Gamberg JC, Bowmer MI, Trahey JC, *et al.*: **Functional and genetic integrity of the CD8 T-cell repertoire in advanced HIV infection.** *AIDS* 1999, **13:**2043–2053.
63. Levy JA: **The importance of the innate immune system in controlling HIV infection and disease.** *Trends Immunol* 2001, **22:**312–316.
64.• Ironson G, Balbin E, Solomon G, *et al.*: **Relative preservation of natural killer cytotoxicity and number in healthy AIDS patients with low CD4 cell counts.** *AIDS* 2001, **15:**2065–2073.

This is a recent empiric paper documenting the preservation of NK cell number and function among healthy individuals with AIDS with low CD4+ cell counts.