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# Two-Year Prospective Study of Major Depressive Disorder in HIV-Infected Men

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## Abstract

**Objective—**The risks and factors contributing to major depressive episodes in HIV infection remain unclear. This 2-year prospective study compared cumulative rates and predictors of a major depressive episode in HIV-infected (HIV+) men (N=297) and uninfected (HIV−) risk-group controls (N=90).

**Method—**By design participants at entry were without current major depression, substance dependence or major anxiety disorder. Standardized neuromedical, neuropsychological, neuroimaging, life events, and psychiatric assessments (Structured Clinical Interview for DSM III-R) were conducted semi-annually for those with AIDS, and annually for all others.

**Results—**Lifetime prevalence of major depression or other psychiatric disorder did not differ at baseline between HIV+ men and controls. On 2-year follow up those with symptomatic HIV disease were significantly more likely to experience a major depressive episode than were asymptomatic HIV+ individuals and HIV− controls ($p<0.05$). Episodes were as likely to be first onset as recurrent depression. After baseline disease stage and medical variables associated with HIV infection were controlled, a lifetime history of major depression, or of lifetime psychiatric co-morbidity (two or more psychiatric disorders), predicted subsequent major depressive episode ($p <0.05$). Neither HIV disease progression during follow-up, nor the baseline presence of neurocognitive impairment, clinical brain imaging abnormality, or marked life adversity predicted a later major depressive episode.

**Limitations—**Research cohort of men examined before era of widespread use of advanced anti-HIV therapies.

**Conclusions—**Symptomatic HIV disease, but not HIV infection itself, increases intermediate-term risk of major depression. Prior psychiatric history most strongly predicted future vulnerability.

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## 1. INTRODUCTION

The prevalence of major depression is elevated in HIV-infected men compared to the general population, but the reasons for this are uncertain (Atkinson et al., 1988; Perry et al., 1990; Williams et al., 1991; Perkins et al., 1994; Rabkin, 1996; Maj et al., 1994; Bing et al., 2001; Evans et al., 2002; Dew et al., 1997; Pugh et al., 1994; Rabkin et al., 1997, a, b). Populations at highest risk for HIV have of a high prevalence of primary (pre-HIV) mood disorder (Atkinson et al., 1988; Perkins et al., 1994; Rabkin, 1996), making it possible that any excess in post-infection major depression reflects recurrence of a pre-exisiting mood disorder. Since HIV enters the CNS early in the course of infection, other proposed explanations include direct effects of HIV on the CNS, or indirect effects mediated by HIV-associated neurocognitive impairment (Evans et al., 2002). The impact of multi-system medical disease, or the severe life adversity of living with HIV may also increase risk of mood disorder (Perry et al., 1990; Williams et al., 1991; Perkins et al., 1994; Rabkin, 1996; Bing et al., 2001; Evans et al., 2002). Since advances in antiretroviral and other therapies now allow longer life, even in those with histories of AIDS-defining illness, identifying risk of depressive episodes has become increasingly important, but questions about predictors of depression remain unanswered. In terms of the risks associated with HIV involvement of the CNS, cross-sectional and short-term prospective studies have not detected higher rates of depressive disorder in those having HIV-associated neurocognitive impairment (Perry et al., 1990; Perkins et al., 1994) but longer term studies are not available. Regarding systemic medical disease, a meta-analysis of cross-sectional studies concluded that whereas HIV infection increased likelihood of a major depressive disorder (Ciesla and Roberts, 2001), medically asymptomatic and symptomatic individuals did not differ in risk. Few studies, however, obtained detailed staging of HIV disease. Additionally reliance on cross-sectional designs may be inherently unreliable, since risk of major depression may vary over the course of HIV infection, and may increase with onset of frank AIDS (Lyketsos et al., 1996). Finally, an extensive literature relates increased depression symptoms to stressful life events and diminished social support within the context of HIV infection (Evans et al., 1997; Leserman et al., 2002, Ironson et al., 2005), but whether this bears on risk of major depressive episodes is not known. Although past psychiatric history, HIV systemic and CNS disease, and life adversity are thought to be intertwined, they customarily have been studied separately rather than together. Prospective research considering potential contributing variables could help sort out their unique predictive power.

This 2-year prospective study examined occurrence and correlated predictors of major depression in HIV-seronegative (HIV−) risk-group controls, and HIV-infected HIV+) men, using standardized psychiatric, neuromedical, neuropsychological, and neuroimaging evaluations as well as interviews for life events and difficulties to determine contextual stressors. Considered as predictors of a major depressive episode on follow-up were lifetime psychiatric history, neurocognitive, neurologic, and neuroimaging abnormality, and marked life adversity at baseline. HIV disease progression over the follow up period was also evaluated as a predictor.

## 2. METHODS

Data were obtained from participants enrolled in the HIV Neurobehavioral Research Center (HNRC) at the University of California San Diego (UCSD). This longitudinal cohort study of neuromedical, psychiatric, neuroimaging, and psychosocial factors in HIV has been described elsewhere (Heaton et al., 1995). Individuals who did not meet criteria for current DSM III-R major depressive disorder or other major psychiatric disorder at baseline, and who completed 2 years of follow-up, are the basis of this report.

## 2.1 Participants

HIV+ men aged 21–55 years, and HIV-− controls matched for age, education, and social position, were recruited from clinics and the San Diego community through advertisement and word-of-mouth. HIV status was determined by enzyme-linked immunoabsorbent assay and confirmed by Western blot. Sexual exposure (men who have sex with men) was the reported route of acquisition of HIV. Because the parent study focused on HIV-related CNS disease, those with histories of injection drug use were excluded. Additional exclusion criteria were: 1) chronic pre-existing non-HIV medical illness (e.g., diabetes mellitus, hypertension), 2) non-HIV related neurological disorder (e.g., epilepsy), 3) psychotic or bipolar mood disorder preceding HIV-infection, 4) current psychoactive substance use disorder, and 5) presence at entry of HIV-associated dementia or current (one-month) major depression, major anxiety disorder, or substance use disorder. After complete description of the study to the subjects, written informed consent was obtained. This study was approved by the institutional review board of the University of California, San Diego.

The initial longitudinal cohort (N=533) consisted of seropositive and seronegative men, of whom 146 (N=121 HIV+ and N=25 HIV− controls) did not complete two years on study; of these non-completers 118 either missed a required visit or were lost to follow-up; 28 HIV+ men died.

## 2.2 Procedures

All assessments (e.g., medical, psychiatric, neuropsychological, life event, and neuroimaging) generally were completed within a 4-week window. Participants with AIDS at entry were re-examined semi-annually while all other HIV+ individuals and controls were seen annually.

## 2.3 Measures

**2.3.1 Structured Clinical Interview for DSM III-R Non-Patient Version (SCID)—**At baseline the SCID (Spitzer et al., 1992) was administered by trained clinicians to establish lifetime DSM III-R diagnoses (those with current [1-month] disorders were excluded). Six diagnoses were sought: major depression, alcohol and non-alcohol use disorders, generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder. At each follow-up visit during the 2-year study an interim version of the measure was used to determine whether an episode of major depression was current at the time of the interview, or had occurred within the preceding six or twelve months, depending upon the frequency of follow-up visits. Lifetime history at baseline of any of the six major diagnoses being evaluated were considered possible risk factors for an episode of major depression during follow-up.

**2.3.2 HIV Disease Status—**HIV disease staging at each visit was established according to 1993 Centers for Disease Control criteria (Centers for Disease Control and Prevention, 1992). Laboratory assessments included white blood cell count (WBC); markers of immune suppression (CD4+ lymphocyte count); HIV viral burden (HIV RNA, copies/mL) in plasma and, for volunteers who separately consented to a research lumbar puncture, WBC and HIV RNA also in CSF (Amplicor, San Diego, CA). Pleocytosis was defined as WBC > 4 cells/mL in CSF. Independently a neurologist, who was unaware of the results from other assessments (eg, SCID, neuropsychological, neuroimaging) conducted a neurological examination using previously described procedures (Heaton et al., 1995; Mehta et al., 1996) to globally rate the presence of any HIV-associated central or peripheral nervous system abnormality (present or absent).

**2.3.3 Neuropsychological Evaluation—**Neuropsychological (NP) testing consisted of an expanded Halstead-Reitan Battery, the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), and additional tests of attention and speed of information processing,

language skills, verbal and non-verbal learning and retention, and motor skills, previously described elsewhere (Heaton et al., 1995). Each subject's NP protocol was then subjected to clinical ratings by an experienced neuropsychologist (RKH) blind to the participants' HIV or treatment status. Before the clinical rating process, raw scores on tests were converted to demographically corrected standard scores based upon large normative data sets. The clinician assigned ratings of global neuropsychological performance using a 9-point scale (1=above average, 5=definite mild impairment, and 9=severe impairment). A global rating of abnormal performance required a rating of at least 5 on at least two of the eight ability areas surveyed. The rationale, nature, reliability, and validity of these ratings have been described (Heaton et al., 1995).

**2.3.4 Brain Imaging—**Magnetic Resonance Imaging (MRI) was performed with a 1.5-Tesla Superconducting Magnet (General Electric, Milwaukee, WI). Brain scans were independently reviewed by two neuroradiologists, blind to participants' serostatus and diagnoses, who assigned a rating (0=normal, 1=borderline abnormal, 2=mild abnormality, 3=moderate abnormality, 4=severe abnormality) using established procedures (Dohrenwend et al., 1978) to each of the following areas: cortical brain volume, central brain volume, right hemisphere parenchyma and left hemisphere parenchyma. An overall rating was computed as an average of the four ratings. Overall baseline ratings $\geq 1$ were considered abnormal for purposes of prediction.

**2.3.5 Life Adversity—**Data on life events and difficulties in the six months preceding baseline were gathered through a modified Psychiatric Epidemiology Research Interview (Dohrenwend et al., 1978; Brown and Harris, 1978). Using previously established procedures life events were assigned levels of severity of threat (1 = most severe threat; 2 = moderate; 3 = mild; 4 = minimal threat); life difficulties were also graded on a 6-point scale (from 1 = most severe to 6 = trivial). Persons experiencing substantial life events (levels 1 or 2) or difficulties (levels 1, 2, 3) were classified as having marked adversity during the period in question (Grant et al., 1989). The presence of "marked" life adversity within six months before baseline was used to predict subsequent psychiatric disorder.

### 2.4 Statistical Analysis

Participants who did and did not complete the two years of follow-up were compared on baseline parameters. Demographic and medical information of the participants who completed two years of follow-up was summarized. The proportion of individuals with a major depressive episode during the two-year follow-up was compared between HIV+ and HIV− controls, between those who did and did not progress to AIDS, and among CDC disease stages, using chi square. Sets of logistic regression analyses were conducted to evaluate the following as baseline predictors of the occurrence of a major depressive episode on follow-up: lifetime history of major depression; history of two or more major psychiatric disorders other than major depression; presence of marked life adversity; presence of impaired neurocognitive performance short of dementia (a global rating of $\geq 5$, but without meeting the dual criteria of $\geq 7$ and severe interference with everyday functioning); global rating of "abnormality" on brain magnetic resonance imaging; and global rating of an "abnormal" neurological examination. Age, baseline CDC classification, and CD4+ lymphocyte count were included as controlling covariates. Odds ratios and 95% confidence intervals (CIs) were calculated for each predictor variable to describe its relative contribution to risk of an episode of depression, apart from the risk associated with HIV disease and other predictors. Kaplan-Meier estimates (Kaplan and Meier, 1958) of time to the onset of major depression were developed for the groups who did or did not progress to AIDS, and a logrank test was used to examine for equality between the two cohorts. A Cox proportional hazards model was developed, using age as a covariate, and progression to AIDS was tested for significance. Exploratory analyses also examined the

relationship between groups which did or did not develop a major depressive episode on follow-up and repeated measures slopes for changes in key medical variables: change in WBC count, in CD4+ lymphocyte count, and in viral burden (HIV RNA) in plasma (N = 226) and CSF (N = 189). For these analyses root and log transformations were done as needed to symmetrize the distributions (square-root transformed CD4+, fourth-root transformed WBC, log transformed plasma and CSF viral load). Additionally depressed and not depressed groups were compared for presence of CSF pleocytosis (ever/never) during follow up. Data were analyzed using S-Plus Statistical Software (Statistical Sciences: S-Plus. Seattle, WA). All p values are for two-tailed tests of significance.

## 3. RESULTS

### 3.1 Participants

Participants who completed two years (N=387) did not differ from those who did not in mean age, years of education, ethnicity, serostatus, proportion with AIDS at entry, and lifetime prevalence of major depression, alcohol or other psychoactive substance use disorder, or generalized anxiety disorder (all p-values > 0.1).

Participants were predominantly white (78%), young (mean age=31.9 years, SD=7.0), and well-educated (mean =14.2 years of education, SD=2.1). HIV-infected men were somewhat younger than uninfected controls (mean age=31.5 years, SD=6.6 years vs. 33.6 years, SD=8.0 years, t = 2.5, p = .013), and were slightly less well-educated (14.0 years, SD=2.0 vs. 14.9 years, SD=2.1, t = 3.6, p = .0004). These men were classified into four groups: HIV-negative at risk controls (N=90) and three stages of HIV infection, defined using criteria established by the Centers for Disease Controls (Centers for Disease Control and Prevention, 1992). Those in CDC stage A (N=213) were medically asymptomatic. Those in stage B (N=66) had experienced minor opportunistic infections or constitutional symptoms, and those in stage C (N=18) had a history of an AIDS-defining condition. As expected men in CDC group C had markedly lower CD4+ lymphocyte counts (142, SD=211) compared to those in group B (379, SD=246), group A (534, SD=247) or controls (867, SD=289) (F= 6.4, p = .0001).

### 3.2 Baseline Psychiatric, Neuromedical, Neuropsychological and Life Event Status

At baseline the most prevalent lifetime diagnoses were major depression and psychoactive substance use disorders (see Table 1). Lifetime prevalence for any psychiatric disorder did not differ between HIV-infected men and risk-group controls; rates also were similar in controls and infected men at each disease stage. Psychiatric “multiple comorbidity” was defined as lifetime prevalence of two or more major psychiatric disorders (including major depression). The maximum number of lifetime diagnoses in this sample was 4. The overall proportion of those with comorbidity, as well as the pattern, did not differ significantly between HIV+ and HIV− men or across CDC disease classifications (all p-values not significant). Comorbidity was present in 20.5% (N=61) of the pooled HIV-infected men and 23% (N=21) of controls. The most frequent combinations of comorbidity were major depression and alcohol use disorder (30% of all participants with multiple comorbidity) and major depression, alcohol, and substance use disorders (21% of all with multiple comorbidity). Regarding other baseline characteristics evaluated as predictors of subsequent psychiatric disorder, prevalence of neurocognitive impairment was significantly ($p < 0.05$) higher in HIV-infected individuals compared to controls, ranging from 16% in HIV controls to 61% in AIDS. Similarly, the prevalence of neurological examination abnormality was higher in infected individuals compared to controls ($p<0.05$), with AIDS patients having the highest likelihood of abnormal neurological (72%) findings. Ratings of a gross (clinically apparent) neuroimaging abnormality did not differ between HIV-infected and HIV-negative groups, but was significantly higher ($p<0.05$) in AIDS (28%) compared to other CDC disease stages and controls. Finally, the

proportion of those with marked life adversity in the 6 months preceding baseline was higher in HIV-infected persons compared to controls ($p<0.05$), and differed significantly ($p<0.05$) across all groups, with AIDS (61%) having the highest likelihood of severe stress,

### 3.3 Associations Between HIV Disease and Incident Major Depression

**3.3.1 Relationship to Stable HIV Disease Stage—**To relate HIV disease to psychopathology, we first examined occurrence of major depressive episodes in medically symptomatic and asymptomatic men whose CDC disease stage did not change throughout the 2-years on study (see Table 3). On follow-up a higher proportion of those with stable symptomatic stage B and C disease reported a depressive disorder than did those with medically asymptomatic HIV infection (chi square = 10.62, df = 2, p = .005), who did not differ from HIV- controls.

**3.3.2 Relationship to Disease Progression—**Progression to AIDS during two-year follow-up was not associated with diagnosis of a major depressive episode during follow-up (see Table 3). Cumulative two-year rates of a major depressive episode were similar in those who progressed to AIDS, in other HIV-positive men, and in controls, with approximately one of every four individuals in each group being affected (chi square = 1.02, df = 2, p = 0.600). Because disease progression might be more subtly reflected by rate of change (decline) in immune function, or change (increase) in HIV viral burden, we conducted exploratory analyses to determine if longitudinal change of CD4+ lymphocyte count, plasma and CSF HIV RNA, or WBC count were associated with development of a major depressive episode. Likewise we examined whether detection of CSF pleocytosis (an expression of HIV involvement of the CNS) was associated with a depressive episode. The only significant difference was that decline of CD4+ count was steeper in those who had a major depressive episode during follow-up ($t = -1.969$, $p = 0.05$). When baseline CDC stage was added in follow-on ANOVAs, the overall significance did not change.

To determine if the first onset of major depression or another psychiatric disorder might be associated with or triggered by HIV disease or its progression we compared proportions of those reporting first episodes of major depression across groups. During two-year follow-up there was no significant difference in the proportion experiencing first onset major depression between controls (33%, N=7 of 21 participants), non-progressing HIV disease (47%, N=28 of 59), and disease progressors (33%, N=6 of 18). Results were similar when disease stage was examined within HIV non-progressors (A: 42% [N=14 of 33]; B: 50% [N=9 of 18], C: 62% [N=5 of 8]).

**3.3.3 Do Major Depressive Episodes Precede or Follow Medical Transitions?—**Since symptoms of depression may herald onset of AIDS (Lyketsos et al., 1996), we compared the number of individuals who reported a major depressive episode in the 12 months preceding versus following a diagnosis of AIDS. Time of AIDS diagnosis was defined as date of the research visit at which the person first met criteria for AIDS. Eighteen individuals reported a major depressive episode in a 12-month epoch preceding or following AIDS diagnosis. Major depression clearly preceded AIDS diagnosis in six cases, followed AIDS diagnosis in three, and was coincident (both psychiatric and medical diagnoses made at the research visit) in the remaining nine cases (Wilcoxon signed rank test $z = -1.30$, $p = .192$). We also assessed whether incident major depressive episodes were related to worsening of disease stage apart from progression to AIDS (i.e., transition from asymptomatic to symptomatic disease). There was no significant relationship (Wilcoxon signed rank test $z = .823$, $p = .410$).

We also constructed Kaplan-Meier survival curves (Kaplan and Meier, 1958) and used Cox proportional hazards modeling to examine for differences in time from baseline to incident

major depressive episode in men whose disease did or did not progress to AIDS. Age at baseline was included as a covariate in the Cox model. Progression to AIDS after baseline was not a significant estimator of time to depression (chi-square=0.5, df=1, p=0.499; adjusted for age, z=0.49, p=0.625).

### 3.4 Predicting Major Depressive Disorder in HIV-Infected Men

Using multiple logistic regression, we examined the independent contributions of psychiatric, neurological, and neurocognitive factors to predicting an episode of major depression in HIV-infected men. In each regression analysis presence versus absence of an interval major depressive episode was the outcome variable. Each regression contained three predictor variables. Two of the variables were covariates controlling for nonspecific HIV-related decline: baseline CD4+ lymphocyte count and baseline binary CDC classification--asymptomatic (stage A) or symptomatic-advanced (stages B and C). These two variables were used in each of the logistic regressions. The third variable in each regression was the predictor of interest present at baseline examination. The following predictors were considered: lifetime history of major depression at baseline, lifetime history of alcohol use disorder, comorbidity (presence of two or more lifetime psychiatric disorders), marked life adversity within the six months preceding baseline, presence of neurocognitive impairment, abnormal rating on brain neuroimaging, and HIV-related abnormality on neurological evaluation. Lifetime multiple psychiatric comorbidity was the most potent predictor, heightening the risk of a major depressive episode on follow–up almost five-fold (t=5.29; p <.00001; odds ratio = 5.2; CI= 2.8–9.7). Past history of major depression increased the risk almost four-fold (t=4.69; p=.0001; odds ratio = 3.9; CI=2.2−6.8); and alcohol dependence doubled the likelihood of intercurrent mood disorder (t=2.55, p=.01; odds ratio = 2.2; CI=1.2−3.9). A rating of marked life adversity at baseline was not predictive (t=0.40, p=.693). Likewise baseline rating of impaired performance on neuropsychological testing (t=0.49, p=0.622), clinician judgment of overall abnormality on neurological examination (t = −1.28, p = 0.202), and a global clinical rating of abnormal magnetic resonance imaging of brain (t = 0.50; p = .615) failed to predict major depression during follow-up.

## 4. DISCUSSION

In this study individuals with more advanced HIV disease were at higher risk of experiencing a major depressive episode during two-year follow-up than were men in earlier stage HIV disease and uninfected controls. Also, background psychiatric factors, especially the lifetime presence of two or more psychiatric disorders (multiple comorbidity) strongly predicted incident depression.

The two-year cumulative rate of a major depressive episode, ranging from 40% in those with stable symptomatic-advanced illness to about 20% for asymptomatic individuals and in controls, were higher than the cross sectional and prospective 12-month rates described in epidemiologic community surveys, which range from 4 to 10% (Robins et al., 1991; Kessler et al., 1994; Regier et al., 1993). Methodological differences make direct comparisons with other HIV research less straightforward. Three prior prospective studies reported rates of major depression for seropositive men in the aggregate without reference to disease staging. One noted that 9% met criteria at some point during six-month follow-up (Perkins et al., 1994), another 37% on one-year follow-up (Dew et al., 1997). This latter rate may reflect sampling of injection drug users, a group which we excluded from our study by design, but one vulnerable to psychiatric comorbidity (Lipsitz et al., 1994). A third carefully controlled 12-month prospective study (Rabkin et al., 1997) found current (one month) rates of mood (8 %) and other disorders were comparable in HIV-infected men and controls, despite progressive decline in immune function and increased medical symptoms. By contrast the present study evaluated

for any episode of a psychiatric disorder during the follow-up period, rather than current rates at a specific end-point, and did not aggregate all HIV-infected individuals. Indeed, when we considered seropositive individuals as group, we too observed rates similar to that found in our seronegative group. A recent meta-analyses of cross-sectional studies found rates of current major depression were comparable in medically asymptomatic and symptomatic infected men, but noted that simple dichotomizing of HIV stage might be inadequate for representing the experience of disease over time. The present study attempts to address that limitation. Finally, the rates we report are in the range of those calculated by a large prospective cohort study using cut-scores from self-report mood scales, rather than psychodiagnostic examination, which suggested 12% of men at early stage disease and 23% of those in later stage illness would meet criteria for syndromic major depression (Lyketsos et al., 1996). Both studies suggest risk of mood disorder may vary over time.

Many cases of major depression represented recurrence of mood disorder in those with positive lifetime histories, but in an almost equal number this was the first onset. A six-month prospective study likewise has reported that cases of incident depressive episodes were roughly equally distributed between recurrent and first onset cases (Williams et al., 1991). The likelihood of first onset depression varied from 33% of episodes in seronegatives to almost 50% of cases in those with stable symptomatic disease. Further work is needed to determine whether elevated rates of major depression in symptomatic illness partly result from triggering episodes in men previously resistant to mood disorder.

Although currently active substance abusers and injection drug users were excluded, lifetime prevalence of psychoactive substance use disorders was elevated in both HIV-infected and risk group controls, as expected (Atkinson et al., 1988; Williams et al., 1991; Rabkin, 1996). Lifetime generalized anxiety disorder rates were comparable in HIV-infected men and male controls, and to reports in the general population (1–2%) (Robins et al., 1991; Kessler et al., 1994) and in HIV cross-sectional studies (Williams et al., 1991; Dew et al., 1997), but are lower than in women (Morrison et al., 2002). Prior history of psychiatric disorder was the most potent predictor of a major depressive episode. Among these was the impact of multiple psychiatric comorbidity which, while not emphasized in HIV studies, is in general psychiatric research thought to be associated with greater symptom severity, more role impairment, and treatment resistance (Kessler et al., 1994).

Effects of HIV disease progression were less clear. Although there is some evidence progression to AIDS precipitates depressive episodes (Lyketsos et al., 1996), we did not observe significantly heightened vulnerability, perhaps due to relatively few cases upon which to base our judgments. On the other hand our finding a higher risk of major depression in patients with symptomatic disease short of AIDS is consistent with evidence of increase in depressive symptoms as disease progresses (Lyketsos et al., 1996). The finding that incident major depressive episode was associated with more rapid decline in immune function (CD4+ lymphocyte count) is consistent with evidence that depressive symptoms are associated with more rapid progression of HIV disease (Ironson et al., 2005).

Other factors also had less detectable impact than anticipated. Consistent with a six-month follow-up study (Perkins et al., 1994), neither impaired performance on neuropsychological testing nor rating of abnormal neuroimaging was associated with an interval episode of major depression. Failure of prediction could be due to insufficient power, the relapsing and remitting pattern of milder forms of HIV-related neurocognitive impairment, the limited period of observation, or insensitivity of clinical ratings of neuroimaging abnormality. That marked life adversity at entry did not predict subsequent psychiatric episodes may reflect on the resilience of a rather well-educated cohort of research volunteers.

### 4.l Limitations

Important limitations of the study include the relatively small sample size in some HIV categories (eg, CDC Stage C), so that differences in classifying a few cases could alter considerably the rates of mood disorder between medically asymptomatic and symptomatic men. The structured clinical interview we employed is not designed to elicit the full range of bipolar spectrum diagnoses, nor were interviewers trained to seek these conditions. This is an important omission since bipolar spectrum disorders, and disturbances of temperament, may be prevalent in HIV risk groups, and indeed may themselves be risks for acquisition and transmission of HIV (Moore et al., 2005; Perretta et al., 1998) Research volunteerism may limit generalizability, but it is unclear whether this is associated with bias towards emotional health, or psychopathology. The sample was mostly white, of high overall social position, who were recruited using strict exclusion criteria, further reducing the generalizability of the results. Even though baseline medical and psychiatric factors did not distinguish those who did and did not complete two full years on study, there is an inherent bias in examining study completers. There is overlap of some symptoms of HIV illness and treatment with criterion items for major depression (eg, weight loss, fatigue, insomnia). It is possible that interviewers (or participants) attributed somatic symptoms of HIV disease as counting toward a diagnosis of major depression. In practice making this distinction is generally straightforward, particularly in ambulatory populations. Moreover, interviewers were specifically trained to assess for change in mood and interest, and other depression criteria, as distinct from change in medical status. Finally, interviewers cannot be reliably blinded to serostatus, or symptomatic disease, raising the possibility of diagnostic bias.

### 4.2. Clinical Implications

The results suggests that surveillance for major depression in symptomatic HIV disease is particularly warranted, that psychiatric history provides a cue to increased risk, and advancing illness may also contribute to vulnerability.

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## REFERENCES

Atkinson JH, Grant I, Kennedy CJ, Richman DD, Spector SA, McCutchan JA. Prevalence of psychiatric disorders among men infected with human immunodeficiency virus: A controlled study. Arch. Gen. Psychiatry 1988;45:859–864. [PubMed: 3415427]

Atkinson JH, Grant I. Natural history of neuropsychiatric manifestations of HIV disease. Psychiatr. Clin. North Am 1994;17:17–33. [PubMed: 8190664]

Bing EG, Burnam MA, Longshort D, Fleishman JA, Sherbourne CD, London AS, Turner BJ, Eggan F, Beckman R, Vitiello B, Morton SC, Orlando M, Bozzette SA, Ortiz-Barron L, Shapiro M. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch. Gen. Psychiatry 2001;58:721–728. [PubMed: 11483137]

Brown, GW.; Harris, T. Social Origins of Depression: A Study of Psychiatric Disorder in Women. New York, NY: Free Press; 1978.

Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. Morbidity Mortality Weekly Report 1992;41:1–19.

Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. Am. J. Psychiatry 2001;158:725–730. [PubMed: 11329393]

Dew MA, Becker JT, Sanchez J, Caldararo R, Lopez OL, Wess J, Dorst SK, Banks G. Prevalence and predictors of depressive, anxiety and substance use disorders in HIV-infected and uninfected men: a longitudinal evaluation. Psychol. Med 1997;27:395–409. [PubMed: 9089832]

Dohrenwend BS, Krasnoff L, Askenasy AR, Dohrenwend BP. Exemplification of a method for scaling life events: the PERI Life Events Scale. J. Health Soc. Behav 1978;19:205–229. [PubMed: 681735]

Leserman J, Petitto JM, Gu H, Gaynes BN, Barroso J, Golden RN, Perkins DO, Folds JD, Evans DL. Progression to AIDS, a cliical AIDS condition and mortality: psychosocial and physiological predictors. Psychol. Med 2002;32:1059–1073. [PubMed: 12214787]

Evans, DL.; Mason, K.; Bauer, R.; Leserman, J.; Petitto, J. Neuropsychiatric manifestations of HIV-1 infection and AIDS. In: Charney, D.; Coyle, J.; Davis, K.; Nemeroff, C., editors. Psychopharmacology: The Fifth Generation of Progress. New York, NY: Raven Press; 2002. p. 1281-1300.

Grant I, Brown GW, Harris T, McDonald WI, Patterson TL. Severely threatening events and marked life difficulties preceding onset or exacerbation of multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 1989;52:8–13. [PubMed: 2709039]

Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, McCutchan JA, Taylor MJ, Kelly MD, Ellis RJ, Wolfson T, Velin R, Marcotte TK, Hesselink JR, Jernigan TL, Chandler J, Wallace M, Abramson I. HNRC Group. The HNRC 500—Neuropsychology of HIV infection at different disease stages. J. Internatl. Neuropsych. Soc 1995;1:231–251.

Ironson G, O'Cleirigh C, Fletcher MA, Laurenceau JP, Balbin E, Kilmas N, Schneiderman N, Solomon G. Psychosocial factors predict CD$ and viral load change in men and women with human immunodeficiency virus in the era of highly active antiretroviral treatment. Psychom. Med 2005;67:1013–1021.

Jarvik JG, Hesselink JR, Kennedy C, Teschke R, Wiley C, Spector S, Richman D, McCutchan JA. Acquired immunodeficiency syndrome. Magnetic resonance patterns of brain involvement with pathologic correlation. Arch. Neurol 1988;45:731–736. [PubMed: 3390027]

Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J. Am. Statistical Assn 1958;53:281–224.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch. Gen. Psychiatry 1994;51:8–19. [PubMed: 8279933]

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;32:1059–1073. [PubMed: 12214787]

Lipsitz JD, Williams JW, Rabkin JG, Remien RH, Bradbury M, el Sadr W, Goetz R, Sorrell S, Gorman JM. Psychopathology in male and female intravenous drug users with and without HIV infection. Am J Psychiatry 1994;151:1662–1668. [PubMed: 7943458]

Lyketsos CG, Hoover DR, Guccione M, Dew MA, Wesch JE, Bing EG, Treisman GJ. Changes in depressive symptoms as AIDS develops. Am. J. Psychiatry 1996;153:1430–1437. [PubMed: 8890676]

Maj M, Janssen R, Starace F, Zaudig M, Satz P, Sughondhabirom B, Luabeya M, Reidel R, Ndetei D, Calil HM, Bing EG, St Lojuis M, Sartorius N. WHO neuropsychiatric AIDS study, cross-sectional Phase I: Study design and psychiatric findings. Arch. Gen. Psychiatry 1994;51:39–49. [PubMed: 8279928]

Perkins DO, Stern RA, Golden RN, Murphy C, Nafolowitz D, Evans DL. Mood disorder in HIV infection prevalence and risk factors in a nonepicenter of the AIDS epidemic. Am. J. Psychiatry 1994;151:233–236. [PubMed: 8296895]

Mehta P, Gulevich SJ, Thal LJ, Jin H, Olichney JM, McCutchan JA, Heaton RK, Kirson D, Kaplanski G, Nelson J, Atkinson JH, Wallace MR, Grant I. HNRC Group. Neurological Symptoms, Not Signs, Are Common in Early HIV Infection. J. Neuro-AIDS 1996;1:67–85.

Moore D, Atkinson JH, Gonzalez BA, Wolfson T, Akiskal HS, Grant I. Temperament and risky behaviors: a pathway to HIV? J. Affect. Disord 2005;85:191–200. [PubMed: 15780689]

Morrison MF, Petilto JM, Ten Have T, Getter DR, Chiallin MS, Weber AL, Brinker-Spence P, Bauer RM, Douglas SD, Evans DL. Depressive and anxiety disorders in women with HIV infection. Am J Psychiatry 2002;159:789–796. [PubMed: 11986133]

Perretta P, Akiskal HS, Nisita C, Lorenzetti C, Zaccagnini E, Della Santa M, Cassano GB. The high prevalence of bipolar II and associated cyclothymic and hyperthymic temperaments in HIV-patients. J. Affect. Disord 1998;50:215–224. [PubMed: 9858080]

Perry S, Jacobsberg LR, Fishman B, Frances A, Bobo J, Jacobsberg BK. Psychiatric diagnosis before serological testing for the human immunodeficiency virus. Am J Psychiatry 1990;147:89–93. [PubMed: 2293794]

Pugh K, Riccio M, Jadresic D, Burgess AP, Baldeweg T, Catalan J, Lovett E, Hawkins DA, Gruzelier J, Thompson C. A longitudinal study of the neuropsychiatric consequences of HIV-1 infection in gay men. II. Psychological and health status at baseline and a 12-month follow-up. Psychol Med 1994;24:894–904.

Rabkin J. Prevalence of psychiatric disorders in HIV illness. Int Rev Psychiatry 1996;8:157–166.

Rabkin JG, Goetz RR, Remien RH, Williams JBW, Todak G, Gorman JM. Stability of mood despite HIV illness progression in a group of homosexual men. Am J Psychiatry 1997a;154:231–238. [PubMed: 9016273]

Rabkin JG, Johnson J, Lin SH, Lipsitz JD, Remien RH, Williams JBW, Gorman JM. Psychopathology in male and female HIV-positive and negative injecting drug users: longitudinal course over 3 years. AIDS 1997b;11:507–515. [PubMed: 9084799]

Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto US mental and addictive disorders service system: Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85–94. [PubMed: 8427558]

Robins, LN.; Locke, BZ.; Regier, DA. An overview of psychiatric disorders in America. In: Robins, LN.; Regier, DA., editors. Psychiatric Disorders in America. New York, NY: Free Press; 1991. p. 328-366.

Spitzer RL, Williams JBW, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID) I: history, rationale and description. Arch Gen Psychiatry 1992;49:624–629. [PubMed: 1637252]

Wechsler, D. Wechsler Adult Intelligence Scale-Revised (WAIS-R). New York: Psychological Corporation; 1981.

Williams JB, Rabkin JG, Remien RH, Gorman JM, Ehrhardt AA. Multidisciplinary baseline assessment of homosexual men with and without human immunodeficiency virus infection. Arch Gen Psychiatry 1991;48:124–130. [PubMed: 1671198]

**Table 1**

Lifetime Prevalence at Baseline of DSM-III R Disorders in HIV-Infected Men (N=297) and HIV-Negative Controls (N=90)[a]

| Disorder | CDC Group[b], No. (%) of Participants | | | |
|---|---|---|---|---|
| | A (n=213) | B (N=66) | C (N=18) | HIV− (N=90) |
| P | | | | |
| Major Depression | 58(27) | 22(33) | 6(33) | 30(33) |
| Alcohol Use Disorder[c] | 46(22) | 20(31) | 5(26) | 27(30) |
| Other Substance Use Disorder[c] | 35(16) | 11(17) | 4(21) | 10(11) |
| Generalized Anxiety Disorder | 7(3) | 5(8) | 0(0) | 6(7) |
| Panic Disorder | 5(2) | 0(0) | 0(0) | 0(0) |
| Obsessive Compulsive Disorder | 2(1) | 0(0) | 0(0) | 0(0) |
| Lifetime Multiple Comorbidity[d] | 39(18) | 21(32) | 4(21) | 22(24) |

[a] There were no significant differences in lifetime prevalence of psychiatric disorders across groups. Psychiatric diagnostic categories are not mutually exclusive

[b] CDC A= medically asymptomatic; B=minor opportunitstic infections or constitutional symptoms; C=AIDS

[c] Abuse or dependence

[d] Defined as lifetime presence of two or more of the psychiatric diagnoses described above

**Table 2**

Baseline Neuromedical and Life Adversity Characteristics of HIV Infected Men (N=297) and HIV-Negative Controls (N=90)

| Characteristics[a] | CDC Group[b], No. (%) of Participants | | | |
|---|---|---|---|---|
| | (1)A (n=213) | (2)B (N=66) | (3)C (N=18) | (4)HIV− (N=90) |
| Neurocognitive Impairment | 68(32) | 28(42) | 11(61) | 14(16) |
| Neurological Abnormality | 40(19) | 18(27) | 13(72) | 8(9) |
| Neuroimaging Abnormality | 16(7.5) | 6(9) | 5(28) | 7(8) |
| Marked Life Adversity | 100(47) | 26(39) | 11(61) | 13(14) |

[a] CDC A= medically asymptomatic; B=minor opportunitstic infections or constitutional symptoms; C=AIDS

[b] See text for description of criteria for ratings

**Table 3**

Two-Year Occurrence of Psychiatric Disorder in HIV-Negative Controls and HIV-Infected Men Who Did or Did Not Progress to AIDS After Baseline

| Disorder | Group, No. (%) of Participants | | | | | P[a] |
|---|---|---|---|---|---|---|
| | Non-Progressors | | | Progressors | Controls | |
| | (1) A (N=171) | (2) B (N=48) | (3) C (N=18) | (4) To AIDS (N=60) | (5) HIV− (N=90) | |
| Major Depression | 33(19) | 18(38) | 8(44) | 18(30) | 21(23) | 2,3 >1, 5 |
| Alcohol Use Disorder | 12(7) | 8(17) | 2(11) | 9(15) | 11(12) | NS |
| Other Substance Use Disorder | 11(6) | 6(13) | 0(0) | 4(7) | 4(4) | NS |
| Generalized Anxiety Disorder | 7(4) | 6(12) | 3(16) | 3(5) | 7(8) | 3 > 1 |
| Panic Disorder | 4(2) | 0(0) | 0(0) | 3(5) | 2(3) | NS |
| Obsessive Compulsive Disorder | 1(1) | 1(2) | 0(0) | 1(2) | 1(1) | NS |

[+] P values are based on chi-square tests. NS indicates not significant based on 5% significance level.

**Table 4**

Number (%) of Lifetime Diagnoses at Baseline in HIV Positive and HIV Negative Men (N = 387)

| Number of Diagnoses | GROUP | | | |
|---|---|---|---|---|
| | A (N=213) | B (N=66) | C (N=18) | HIV− (N=90) |
| 0 | 102 (47.8) | 24 (36.4) | 11 (57.9) | 44 (48.9) |
| 1 | 65 (30.5) | 20 (30.3) | 3 (15.8) | 24 (26.7) |
| 2 | 25 (12.7) | 14 (21.2) | 1 (5.3) | 12 (13.3) |
| ≥3 | 10 (4.7) | 5 (7.6) | 3 (15.8) | 9 (10.0) |