Meta-Analysis of the Relationship Between HIV Infection and Risk for Depressive Disorders

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Objective: Each of 10 published studies investigating the relationship between HIV infection and risk for depressive disorders concluded that HIV-positive individuals are at no greater risk for depression than comparable HIV-negative individuals. This study used meta-analytic techniques to further examine the relationship between depressive disorders and HIV infection.

Method: Meta-analytic techniques were used to aggregate and reanalyze the data from 10 studies that compared HIV-positive and HIV-negative individuals for rates of major depressive disorder (N=2,596) or dysthymic disorder (N=1,822).

Results: The frequency of major depressive disorder was nearly two times higher in HIV-positive subjects than in HIV-negative comparison subjects. On the other hand, findings were inconclusive with regard to dysthymic disorder. Rates of depression do not appear to be related to the sexual orientation or disease stage of infected individuals.

Conclusions: Although the majority of HIV-positive individuals appear to be psychologically resilient, this meta-analysis provides strong evidence that HIV infection is associated with a greater risk for major depressive disorder. Future research should focus on identifying pathways of risk and resilience for depression within this population.

(Rceived estimates suggest that more than 30 million people are living with HIV infection worldwide (1). With the help of new medical treatments, a large percentage of these individuals have been able to lead otherwise healthy lives for many years. Nonetheless, infected individuals face the prospect of social stigma, long-term physical discomfort and illness, and eventual death. Given this state of chronic stress for infected individuals, researchers have been naturally concerned about their psychological adjustment to living with this disease. Because depressive disorders have been shown to be closely associated with a number of other serious medical illnesses (2, 3), rates of depression have been of considerable interest.

Over the past 15 years, several studies have estimated the frequency of depressive disorders, particularly major depressive disorder, in HIV-positive populations. These rates have differed dramatically, from 0% (4) to 47.8% (5). Yet, rates of depression in HIV-negative comparison groups matched on relevant characteristics (e.g., gender, sexual orientation, and drug use) also have differed widely. It is surprising that each of 10 studies published between 1988 and 1998 that compared rates of current depressive disorders between HIV-positive and HIV-negative groups concluded that HIV infection is not associated with a higher rate of the disorder (4, 6–14). These consistent null findings have led investigators to conclude that risk for clinically significant depression is not affected by HIV infection. As Rabkin (15) stated, “In none of the reviewed studies is the difference in one-month prevalence rates between HIV-positive and HIV-negative samples statistically significant.... HIV status is not by itself a strong predictor of mood or anxiety disorders” (pp. 163–165). Likewise, Lyketsos et al. (16) noted, “Rates of depressive disorder are not clearly increased compared to the general population in the early and middle stages of infection” (p. 218).

Unfortunately, each of these 10 studies had low statistical power, failing to include enough participants to detect anything but a very large effect of HIV status. Statistical tests involving the prediction of one dichotomous variable (presence or absence of depressive disorder) from another dichotomous variable (presence or absence of HIV) require very large numbers of participants to provide adequate power. For example, assuming a 5% base rate of major depressive disorder in the relevant comparison community, a sample size of approximately 140 participants is needed to detect reliably (alpha=0.05; beta=0.80) a threefold increase in the risk for depression. To detect a twofold increase, a sample size of approximately 400 individuals would be required. Unequal numbers of participants in the HIV-positive and HIV-negative groups would necessitate even larger samples (17).

Only one of the reviewed studies (11) would have been able to detect a twofold increase in risk for depression among HIV-positive individuals. However, this study did not capitalize on the relatively large size of its study group. Instead, data from its five different study locations were
analyzed separately, without aggregation. Thus far, the available studies are able to rule out only very large differences in rates of depression. It therefore remains possible that HIV infection is associated with higher rates of depression, although this difference may be modest and undetectable in these studies because of poor statistical power.

It also is possible that the effects of HIV infection are moderated by other characteristics of infected individuals. In other words, high risk for depression might be present only among certain HIV-positive individuals. For example, risk for depressive disorders might vary over the course of HIV infection. Some evidence from questionnaire studies has suggested that rates of depressive symptoms increase as HIV disease progresses (9, 18). Likewise, sexual orientation, disease stage, gender, or intravenous drug use may influence the degree to which HIV status is associated with risk for depressive disorders. In this regard, it is important for investigations that contrast an HIV-positive group and an HIV-negative comparison group to match participants on these potentially important characteristics. Populations at particular risk for contracting HIV (e.g., gay men, intravenous drug users) may concurrently be at risk for depression, independent of HIV status. Failure to select appropriate comparison groups could lead to biased results. It is fortunate that all of the studies in this meta-analysis attempted to match their comparison and HIV-positive study groups on at least one of these demographic factors.

The present study is a quantitative review of risk for depressive disorders in the context of HIV infection. Metaanalytic techniques were used to aggregate and reanalyze the data provided in 10 previous studies that compared the relative risk for depressive disorders among HIV-negative and HIV-positive subjects. Three main questions were addressed. First, we tested whether HIV status was associated with either major depressive disorder or dysthymic disorder. Second, we tested whether risk for depressive disorders was moderated by the sexual orientation of the HIV-positive subjects. Finally, we investigated the degree to which HIV-related symptoms affected rates of depression in groups of HIV-positive subjects.

### Method

#### Selection of Studies

To identify studies for inclusion in this review, we conducted a thorough literature search using the standard electronic databases PsychInfo, MEDLINE, and AIDSLine. In addition, we reviewed the introduction and reference sections of relevant studies. Studies were eligible for inclusion if 1) both an HIV-positive group and an HIV-negative comparison group were evaluated, 2) diagnostic interviews were conducted, 3) current (1- to 6-month) rates of major depressive disorder and/or dysthymic disorder were reported, 4) data were provided from the earliest assessment if the study was longitudinal, and 5) the study subjects were not recruited specifically through the mental health system.

Criterion 1 was adopted to limit the influence of factors that vary across studies such as recruitment strategy, diagnostic system or interview, and demographic characteristics. This type of control is particularly important because of the large differences in mood disorder rates observed between studies (and even within studies [10]). If a study adopted strategies leading to conservative or liberal estimates of psychopathology, presumably these same strategies were applied to both the HIV-positive and HIV-negative study groups. Criterion 2 was adopted to avoid the difficulties associated with diagnosis of depression on the basis of self-report inventories (19). Self-report inventories are particularly problematic for use with this population. Many of the physical symptoms of HIV disease overlap with symptoms of depression (20–23). In an interview, the clinician can investigate such overlapping symptoms and decide whether the symptom in

### Table 1. Studies Comparing Rates of Depressive Disorders in Groups of HIV-Positive and HIV-Negative Subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Subjects in HIV-Positive Study Group and HIV-Negative Comparison Group</th>
<th>Major Depressive Disorder</th>
<th>Dysthymic Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkinson et al. (7)ab</td>
<td>1988</td>
<td>45 HIV-positive gay men</td>
<td>11.11 (23.55)</td>
<td>—</td>
</tr>
<tr>
<td>Williams et al. (14)b</td>
<td>1991</td>
<td>124 HIV-positive gay men</td>
<td>3.03 (10.70)</td>
<td>—</td>
</tr>
<tr>
<td>Chuang et al. (8)</td>
<td>1992</td>
<td>144 HIV-positive men and women</td>
<td>4.03 (10.70)</td>
<td>2.42 (4.87)</td>
</tr>
<tr>
<td>Rosenberger et al. (13)b</td>
<td>1993</td>
<td>166 HIV-positive gay men</td>
<td>10.24 (1.65)</td>
<td>—</td>
</tr>
<tr>
<td>Chuang et al. (8)</td>
<td>1994</td>
<td>124 HIV-positive men and women</td>
<td>22.58 (127)</td>
<td>11.29 (2.25)</td>
</tr>
<tr>
<td>Maj et al. (11)</td>
<td>1994</td>
<td>602 HIV-positive men and women</td>
<td>7.14 (3.59)</td>
<td>0.66 (1.09)</td>
</tr>
<tr>
<td>Perkins et al. (12)b</td>
<td>1994</td>
<td>98 HIV-positive gay men</td>
<td>8.16 (2.60)</td>
<td>0.00 (0.14)</td>
</tr>
<tr>
<td>Fukunishi et al. (4)</td>
<td>1997</td>
<td>335 HIV-negative men and women</td>
<td>2.82 (2.28)</td>
<td>—</td>
</tr>
<tr>
<td>Rabkin et al. (6)b</td>
<td>1997</td>
<td>183 HIV-positive gay men</td>
<td>7.65 (0.88)</td>
<td>11.29 (2.25)</td>
</tr>
<tr>
<td>Kelly et al. (9)b</td>
<td>1998</td>
<td>164 HIV-positive gay men</td>
<td>18.29 (2.08)</td>
<td>—</td>
</tr>
</tbody>
</table>

\*a DSM-III-R criteria used for diagnoses in all studies except Atkinson et al. (7), which used DSM-III criteria, and Rabkin et al. (6), which used DSM-IV criteria.

\*b All HIV-positive subjects were gay or bisexual.
question is likely to be a manifestation of clinical depression or of HIV disease progression. Criterion 3 was adopted to ensure that the data being aggregated were estimates of current mood disorders and were not overly influenced by past depression. Inclusion of rates for periods of 12 months or longer would lead to an overestimation of current mood disorder for both groups. Criterion 4 was adopted to protect against counting individuals more than once and against possible influences of attrition. Criterion 5 was adopted to avoid the obvious overestimation of pathology that would occur if participants had been recruited through consultations for psychiatric evaluation.

Using these criteria, we identified 10 studies for review; the 10 studies provided information on a total of 2,596 participants (Table 1). As Table 1 shows, every study provided information on major depressive disorder. However, only half of the studies provided rates of dysthymic disorder. Eight studies used DSM-III-R criteria (4, 8–14), one used DSM-III (7), and one used DSM-IV (6). In addition, six studies exclusively recruited gay men, allowing us to examine this subpopulation separately. Unfortunately, no other subpopulation was specifically represented in multiple studies. As for the remaining studies, three involved mixed groups and only one involved intravenous drug users.

Statistical Analyses

Three separate meta-analytic techniques were used to reexamine the 10 studies. The first technique was selected because of its ease of interpretation, straightforward methods, and statistical simplicity. Frequently called the vote-counting technique, it involves the simple aggregation of caseness at the participant level. All of the identified studies provided enough information to determine the data of interest. The question at hand involved a two-by-two contingency: the presence or absence of depressive disorder and the presence or absence of HIV infection. Using the vote-counting technique, we added the numbers of participants in each of the four contingency cells. These data were then reanalyzed as if we had one very large investigation. Although this type of analysis has great intuitive appeal and is quite easily carried out, the resulting analysis becomes cumbersome and the straightforward nature of this method is lost.

The second and third meta-analytic methods we used involve the aggregation of study effect sizes and probability levels. First, we will describe the method of calculating the effect size. Effect sizes for each of the identified studies were determined with the approach described by Schaffer (26). This effect size is computed by taking the natural log of the ratio of two variables observed in each study. Before computing these values, 0.5 was added to each cell so that undefined values were not possible. A zero value indicates complete independence of the two variables. Negative or positive values indicate the direction of association. These effect sizes are weighted by the number of subjects in the respective studies, and the average effect size and standard error are computed. Finally, a confidence interval is used to statistically test the average effect size.

We used another technique as a check of the effect-size method and to estimate the probability that a relationship was observed merely by chance. Many methods have been developed to combine the probability levels from multiple studies (see reference 24). Of these, the inverse normal method (25, pp. 39–40) is routinely applicable and has the advantage of being able to incorporate weights based on the number of subjects. This method converts the probability levels from each investigation into z scores. These scores are weighted, summed, and divided by the square root of the number of studies. The probability associated in a normal distribution with the obtained value of z becomes the overall probability level of the observed relationship. In contrast to the technique that uses effect sizes, the inverse normal method provides a precise index of probability, although it does not provide an index of the strength of the observed relationship.

Results

HIV and Presence of Depressive Disorders

Our first question was whether there was a relationship between HIV status and the presence of major depressive disorder. Stated another way, are HIV-positive individuals at a higher relative risk for developing major depressive disorder than HIV-negative individuals? Using the vote-counting method, we found a highly significant relationship ($\chi^2=14.04$, df=1, $N=2,596$, $p<0.001$). Whereas 9.4% of HIV-positive participants ($N=160$ of 1,700) met criteria for current major depressive disorder, only 5.2% of the comparison participants ($N=47$ of 896) did. The effect-size method showed that the average weighted effect size was approximately 0.69 (a moderate to large effect size [17]), with a standard error of 0.21. By transforming this statistic into an odds ratio, we found that that HIV-positive individuals were 1.99 times more likely to be diagnosed with major depressive disorder than HIV-negative individuals. Thus, the associated 95% confidence interval was 0.28–1.1 (significant at $p<0.05$). This translates into a confidence interval of 1.32–3.00 for the odds ratio. The associated 99% confidence interval was 0.15–1.23. Average weighted rates of major depressive disorder were 8.1% for the HIV-positive group and 5.2% for the HIV-negative group. Finally, to estimate the probability of this finding given a true null relationship, we employed the inverse normal method. The result was a highly significant relationship ($p[\geq 3.79] < 0.0001$, $N=10$). All three meta-analytic methods converged on the conclusion that there is a statistically significant relationship between the risk for major depressive disorder and HIV status.

An important limitation of any literature review is what has become known as the file-drawer problem (27), in which studies with significant results may be more likely to find their way into academic journals, whereas studies with null results may be more likely to remain in the file drawers of the investigators. A procedure has been proposed by Orwin (28) to calculate the number of null results that are necessary to reduce the average effect size to a negligible level. Using this method, we found that the failsafe N for the relationship between major depressive disorder and HIV status was 17. Thus, 17 studies with null results would be needed to overturn the previously significant effect (to raise the probability level above 0.05). Although this number is not impressively large, a few things must be remembered. First, these 17 studies would need to have an average weight equal to the existing average weight for the 10 studies included in the analysis. Put
Table 2. Studies Comparing Rates of Major Depressive Disorder in Asymptomatic and Symptomatic HIV-Positive Subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Group</th>
<th>Asymptomatic Comparison Group</th>
<th>Rate (%)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkinson et al. (7)</td>
<td>1988</td>
<td>28 symptomatic</td>
<td>17 asymptomatic</td>
<td>7.14</td>
<td>0.39</td>
</tr>
<tr>
<td>Chuang et al. (8)</td>
<td>1992</td>
<td>97 symptomatic</td>
<td>47 asymptomatic</td>
<td>7.22</td>
<td>1.05</td>
</tr>
<tr>
<td>Rosenberger et al. (13)</td>
<td>1993</td>
<td>64 symptomatic</td>
<td>10 asymptomatic</td>
<td>10.94</td>
<td>1.15</td>
</tr>
<tr>
<td>Maj et al. (11)</td>
<td>1994</td>
<td>294 symptomatic</td>
<td>304 asymptomatic</td>
<td>8.50</td>
<td>1.47</td>
</tr>
<tr>
<td>Kelly et al. (9)</td>
<td>1998</td>
<td>85 symptomatic</td>
<td>79 asymptomatic</td>
<td>21.18</td>
<td>1.48</td>
</tr>
</tbody>
</table>

Major Depressive Disorder

Another way, these 17 studies would need to have an average number of participants equal to or exceeding 259, the average number in the 10 published studies. Thus, at minimum, there would need to exist some number of unpublished studies with 4,403 HIV-positive and HIV-negative participants and an average effect size of zero. Given the labor-intensive nature of this research, it seems unlikely that such a large number of unpublished data exist. Furthermore, there is an intense demand for research involving HIV-positive individuals, given the numerous academic journals specifically devoted to this population. In our view, it is unlikely that there exists such a large amount of data that has remained unpublished because of null findings.

The next question was whether there was a relationship between HIV status and the presence of dysthymic disorder. The vote-counting method found that 4.2% of the HIV-positive participants (N=48 of 1,131) had dysthymic disorder, compared to 2.0% of the HIV-negative participants (N=14 of 691), a significant difference (χ²=6.01, df=1, N=1,148, p<0.05). By using the second meta-analytic method, the weighted effect size was 0.28 with a standard error of 0.28. The resulting 95% confidence interval was −0.27 to 0.83, a nonsignificant finding. Weighted rates were 2.8% among HIV-positive and 1.6% among HIV-negative participants. The inverse normal method of combining significance levels also fell short of rejecting the null hypothesis (p>|z|=1.10|>0.05, N=5). Although the observed rate of dysthymic disorder among the HIV-positive subjects was roughly double that of the HIV-negative subjects, statistical analyses of this difference provided mixed results. It is unclear whether there is a meaningful difference in rates of dysthymic disorder between these populations.

Sexual Orientation and Risk for Depressive Disorders

The next question was whether sexual orientation moderated the relationship between HIV status and the presence of major depressive disorder. To address this question, we created a dummy variable reflecting whether a study group consisted of exclusively homosexual and/or bisexual men. This variable was not significantly associated with either effect size (z=0.40, df=9, p>0.05) or probability levels (z=0.47, df=9, p>0.05). Thus, across studies, the sexual orientation of participants was not associated with observed effect sizes. When the vote-counting method was applied specifically to studies that recruited only gay and bisexual men for the HIV-positive group, an association between HIV status and major depressive disorder status was found (χ²=6.76, df=1, N=1,148, p<0.01). Comparable to the findings for entire aggregated group, 10.4% of HIV-positive gay and bisexual participants (N=81 of 780) and 5.7% of HIV-negative participants (N=21 of 368) currently met criteria for major depressive disorder. The degree to which HIV is associated with a greater risk for major depressive disorder appears to be the same for gay and bisexual men as it is for the general HIV-positive population.

Course of HIV and Depressive Disorders

We examined the possibility that the stage of HIV infection influenced risk for depression. Because of a scarcity of studies providing separate rates of depression for asymptomatic and symptomatic HIV-positive subjects and for subjects with AIDS, data for symptomatic HIV-positive subjects and subjects with AIDS were combined. As Table 2 shows, five studies indicated rates of major depressive disorder in both asymptomatic HIV-positive and symptomatic HIV-positive patients. We predicted that HIV-positive individuals with physical manifestations of the disease would have higher rates of major depressive disorder than HIV-positive asymptomatic individuals. Unfortunately, we were unable to test whether stage of HIV infection influences rates of dysthymic disorder because only one study provided the necessary information for this analysis.

Contrary to our hypothesis, individuals with advanced HIV disease did not differ in rates of major depressive disorder from asymptomatic HIV-positive individuals. This conclusion was backed by the vote-counting method (χ²=1.76, df=1, N=1,117, p>0.05), the effect-size method (95% confidence interval=0–0.56), and the inverse normal method (p|z|=1.54|>0.05, N=5). Overall, major depressive disorder was present in 8.6% of asymptomatic HIV-positive subjects (N=47 of 549) and in 10.9% of symptomatic HIV-positive subjects and subjects with AIDS (N=62 of 568). These results suggest that physically symptomatic HIV-positive individuals, as a group, appear no more likely to experience major depressive disorder than asymptomatic HIV-positive individuals.

Discussion

The present study used meta-analytic techniques to reanalyze existing research findings about the association between HIV infection and the risk for depressive disor-
der. We tested the hypothesis that HIV-positive individuals would have higher rates of depressive disorders than demographically similar HIV-negative individuals, and we examined whether sexual orientation and stage of HIV infection moderate the association between HIV status and depression.

Whereas all 10 previous investigations directly comparing HIV-positive to HIV-negative subjects on the frequency of depressive disorder failed to find a statistically significant relationship, our meta-analysis indicated that HIV-positive individuals are nearly two times more likely to have had a recent episode of major depressive disorder than HIV-negative individuals. This finding is consistent with the large body of research demonstrating a strong association between other serious medical illnesses and depression (2, 3). On the other hand, only one of three analyses provided evidence that HIV status is associated with a greater risk for dysthymic disorder. There was no evidence that risk for major depressive disorder is associated with the sexual orientation of HIV-positive individuals. Finally, no support was found for the hypothesis that physically symptomatic patients are more likely to be depressed than asymptomatic individuals.

The results of this analysis suggest that the rate of major depressive disorder in the general HIV-positive population is at the very upper end of the 4%-9% range suggested in previous reviews of this literature (15, 29, 30). Yet, the pursuit of a single estimate of the percentage of HIV-positive individuals affected by depression ignores the variance in observed rates, which itself may be of particular interest. There are likely differences between these study groups in a number of potentially important factors, such as gender, mode of transmission, access to quality health care, and socioeconomic status. Furthermore, the significant advances in the treatment of HIV infection may affect rates of depression. Whereas new treatments may increase life expectancy, they are also frequently burdensome. More fine-grained examination of these factors in future research could further our understanding of the association between HIV status and depression.

It is important to note that although HIV-positive individuals had higher rates of major depressive disorder than HIV-negative subjects, depressive disorders seem to be the exception rather than the rule for this population. Only one in 10 HIV-positive individuals had a current episode of major depressive disorder. The observed rates of depression were higher than those typically seen in general primary care patients, but lower than those often seen in general medical inpatients (3). Such findings suggest that HIV infection is not directly associated with depressive disorders and that other correlates of HIV infection play a more direct role. These factors might involve social stigma and other environmental stressors (31). These findings may also encourage investigators to consider the psychological strengths and assets that are involved in protecting the majority of HIV-positive individuals from developing depressive disorders. Future research should explore factors that contribute to resiliency to depression, such as adaptive coping styles, hardness, and positive social support.

On the basis of a dichotomy between asymptomatic and symptomatic HIV-positive individuals, our analyses suggested that rates of major depressive disorder are stable across the course of HIV disease. Yet, this symptomatic/asymptomatic dichotomy is not entirely adequate for representing the physical progression and psychological experience of HIV infection. Perhaps the period immediately after receipt of a positive test result is most critical. We might anticipate that the greatest amount of psychological adjustment would need to take place during this period and consequently that the greatest vulnerability to major depressive disorder also might reside here. Although it has been shown that dysphoria is a common response to receiving a positive test result (32, 33), other work has suggested that individuals typically adjust rather quickly and are unlikely to develop clinically significant depression at this time (34, 35). Unfortunately, too few studies were available for us to examine this issue more systematically in our meta-analysis.

The present meta-analytic study provides the strongest evidence we are aware of that HIV-positive individuals are at an elevated risk for developing major depressive disorder. On the other hand, we did not find compelling evidence that these individuals are at heightened risk for dysthymic disorder. The lack of consistent, significant findings for dysthymic disorder could have been the result of issues of statistical power, diagnostic reliability, or true differences between major depressive disorder and dysthymic disorder. First, the analyses of dysthymic disorder had lower statistical power than those of major depressive disorder because fewer studies assessed dysthymia and because this condition has a lower prevalence than major depressive disorder. Second, relative to major depressive disorder, dysthymia is a less severe condition whose symptoms may be more difficult to reliably tease apart from symptoms of HIV. Finally, it may be the case that HIV is more strongly associated with acute forms of depression, such as the majority of cases of major depressive disorder, than with chronic conditions, such as dysthymic disorder.

Risk for episodes of major depression was apparent for both symptomatic and asymptomatic HIV-positive individuals, suggesting that these episodes had not been misdiagnosed as a result of overlapping symptoms between HIV infection and depression (e.g., appetite disturbance, fatigue, and concentration difficulties). Clearly, such symptoms should not automatically be dismissed as mere reflections of HIV disease progression, particularly if they are present during the early stages of illness. Nonetheless, in practice, determining whether such symptoms are better attributable to depression or to HIV disease requires considerable skill. Although our findings suggest the need for routine screening for mood disorders among HIV-positive patients, it is also clear that such evaluations need to
be conducted by trained mental health professionals who have extensive experience with both mood disorders and HIV infection.

References


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