Effects of Depression and Selective Serotonin Reuptake Inhibitor Use on Adherence to Highly Active Antiretroviral Therapy and on Clinical Outcomes in HIV-Infected Patients

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Objectives: To determine the impact of depression on highly active antiretroviral therapy (HAART) adherence and clinical measures and investigate if selective serotonin reuptake inhibitors (SSRIs) improve these measures.

Design: Retrospective cohort study.

Methods: In 2 large health maintenance organizations, we measured the effects of depression (with and without SSRI use) on adherence and changes in viral and immunologic control among HIV-infected patients starting a new HAART regimen. HAART adherence, HIV RNA levels, and changes in CD4 T-cell counts through 12 months were measured.

Results: A total of 3359 patients were evaluated; 42% had a depression diagnosis, and 15% used SSRIs during HAART. Depression without SSRI use was associated with significantly decreased odds of achieving ≥90% adherence to HAART (odds ratio [OR] = 0.81, 95% confidence interval [CI] = 0.70 to 0.98; P = 0.03). Depression was associated with significantly lower odds of an HIV RNA level <500 copies/mL (OR = 0.77, 95% CI: 0.62 to 0.95; P = 0.02).

Less than optimal adherence was found to be the most common cause for virologic failure in the early treatment phases of HIV infection1–3 and in analysis of causes of virologic failure.6 Diseases affecting cognitive function can have a negative impact on adherence.7–9 As such, depression has been considered a risk factor for nonadherence to highly active antiretroviral therapy (HAART).7,10–17 Previous studies, however, were based on smaller study populations or self-reported adherence and did not quantify the relative impact of depression on adherence or clinical outcome measures. Further, treating depression as a means of improving adherence has not been well studied. The presence of comorbidities (including depression) can also play a role in adherence to the extent that they require other medications that may interact pharmacologically with the HAART medicines.2,18–21 Of further concern, depression in HIV infection has been shown to be associated with earlier mortality, but the effect of depression on CD4 T-cell counts or progression to clinical AIDS is debated.15

In clinical practice, selective serotonin reuptake inhibitors (SSRIs) have become widely used in HIV-infected depressed patients because of their efficacy and tolerability.22 Although several studies demonstrated that SSRI therapy was...
beneficial in reducing depressive symptoms in patients with HIV disease,\textsuperscript{30–33} the role of SSRIs in improving adherence to HAART regimens among HIV-infected patients remains unclear. To our knowledge, only 1 prior study investigated the association of SSRI use and HAART adherence. Yun et al\textsuperscript{27} showed a benefit of antidepressive therapy on HAART adherence, but it was not exclusive to SSRI medications and it was early in the HAART treatment era. Only 1 other study investigated clinical outcomes with SSRI use (fluoxetine), but it failed to find improvement in CD4 T-cell counts with this medication.\textsuperscript{24}

Depression is a significant comorbidity with a prevalence >30% in some studies in HIV-infected patients.\textsuperscript{28,29} It is conceivable that SSRI use, which is commonly prescribed in this population, might improve HAART adherence by improving mood and treating any underlying depression and/or anxiety. Thus, we studied the association of depression and SSRI use with adherence to HAART and with HIV-related clinical outcomes, specifically HIV viral control and CD4 T-cell count, among HIV-infected patients in 2 integrated health maintenance organizations (HMOs) in the United States.

METHODS

Study Design
We performed a retrospective cohort analysis of HIV-infected patients in 8 states (California, Colorado, Georgia, Maryland, Ohio, Oregon, Virginia, and Washington) and the District of Columbia. All patients were enrolled in the Kaiser Permanente and Group Health Cooperative HMOs and were treated with a new HAART regimen in the period January 2000 through December 2003. We defined a HAART regimen as ≥3 antiretroviral drugs used in combination (excluding ritonavir at doses ≤400 mg/d). We examined the impact of an outpatient diagnosis of depression on adherence to HAART using previously validated pharmacy refill adherence measures.\textsuperscript{30–33} We also evaluated the effect of depression on HIV RNA levels and CD4 T-cell counts over the 12 months after initiation of the new HAART regimen. Finally, we studied whether SSRI use in HIV-infected patients diagnosed with depression altered the association of depression with HAART adherence and with the 2 clinical outcome measures.

Subjects
Kaiser Permanente and Group Health Cooperative are integrated HMOs serving various geographic populations in the United States. Patients in these systems receive multidisciplinary health care, including HIV specialty care. The Kaiser Permanente and Group Health Cooperative HIV-infected populations are representative of the states they serve. Recent data from Kaiser Permanente indicated that, overall, members were similar to the general population with regard to age, gender, and race/ethnicity, with only slight underrepresentation of those in lower and higher income and education categories.\textsuperscript{34} However, HIV-infected patients more accurately reflect the general populations, because patients with low incomes are eligible for state Medical Health Maintenance Organization programs, and many such individuals obtain Kaiser Permanente and Group Health Cooperative membership. Current Kaiser Permanente Northern California HIV-infected patients, for example, are largely male (89.3%), men who have sex with men (MSM; 77.9%), and white (62.7%); these statistics are remarkably similar to demographics of reported AIDS-infected patients in California, who were also largely male (91.1%), MSM (76.9%), and white (56.8%).\textsuperscript{35}

Electronic databases in all Kaiser Permanente and Group Health Cooperative regions capture a variety of data, including patient demographics, hospitalization and outpatient visit diagnoses, laboratory results, and pharmacy dispenses. Appropriate databases and disease registries were queried to identify eligible patients. Subjects were HIV-infected patients older than 17 years of age who initiated a new HAART regimen (initial HAART or switch to a new HAART regimen) in the period January 1, 2000 through December 31, 2003. For inclusion in the analysis, patients also were required to have at least 12 months of membership before initiation of the new HAART regimen, to receive their laboratory testing and medications through the health plan’s laboratories or pharmacies, and to have an initial HIV RNA load >500 copies/mL. Patients were considered depressed if the patient also had a coded outpatient or inpatient depression diagnosis based on clinical evaluation of the patient. In the 2 HMOs, the diagnosis of depression was determined by board-certified internal medicine or family practice specialists, infectious disease specialists, or psychiatry consultations. For this analysis, a depression diagnosis was defined as having at least 1 outpatient visit with a coded clinical diagnosis of depression, major depression, or dysthymia. We could not ascertain severity of depression from electronic records.

Measurements
We identified SSRI use from administrative pharmacy databases and defined SSRI use as the filling of at least a 2 months’ supply of any of the following agents: citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. We assumed that SSRI medications were prescribed for the depression diagnosis, which was concurrently or previously recorded. We obtained date of birth (to calculate age at time of the new HAART regimen) and gender and recorded geographic region. We retrieved baseline HIV RNA levels (measured as copies/mL and log\textsubscript{10} copies/mL) and CD4 T-cell counts (measured as cells/µL) taken at the closest time before the initiation of the new HAART regimen and all CD4 T-cell counts and HIV RNA levels measured in the 12 months after initiation of the new HAART regimen. We assigned plasma HIV RNA level measures during follow-up that were below the limit of quantification of the assay used as 1 unit less than the lowest measurable quantity.

We obtained pharmacy dispensing and refill data for assigning SSRI therapy status and adherence to SSRI medication. Pharmacy records also provided details of the specific antiretrovirals used, including regimen composition and other medications prescribed, date of first antiretroviral prescription fill, and all refill data for these patients during study follow-up. Adherence to the HAART regimen over the 12-month observation period was calculated using established methods developed for administrative pharmacy databases. These methods
account for all the component medicines of an individual patient’s HAART regimen.\textsuperscript{30–33} This measure of adherence is computed across all antiretroviral medications as the number of doses in an interval bounded by the first and last fill dates of a drug (at least 2 fills required per drug) for which the patient has the drug in possession (based on quantity supplied and dosing in the interval between fills) as a percentage of total intended doses in the span between the first and last fills. Use of pharmacy records to ascertain HAART adherence has been validated in previous studies at other institutions and at Kaiser Permanente.\textsuperscript{30–33}

**Statistical Methods**

We defined different groups of patients starting a new HAART regimen for purposes of analysis. A first group included patients with a diagnosis of depression; these patients constituted the depression group. We split these patients for further analysis between patients having depression but no evidence of SSRI use, patients having depression and evidence of greater than 2 months of SSRI medication use irrespective of SSRI adherence, and a third group having depression with evidence of greater than 2 months of SSRI medication use with >80% adherence to the SSRI medication. We used 80% as the cutoff for adherence to SSRI medications based on previous studies and National Committee on Quality Assurance recommendations.\textsuperscript{9,40} A final group had no depression and no evidence of SSRI use; these patients served as the control group for all analyses.

We also identified a group of patients with depression who had 12 months of HAART and no SSRI use and then a subsequent 12 months of HAART but with concomitant SSRI use. This group provided an opportunity for before and after comparison of SSRI use on outcomes of interest.

Our primary research questions were to determine to what extent depression affects HAART adherence and HIV outcome measures and to determine if SSRI use can modify that effect. The primary predictor of interest was the presence of depression. The other major predictor of interest was the use of SSRI medications and, specifically, if patients were >80% adherent to SSRI medications (dichotomous). The main outcome measures were adherence to a HAART regimen over a 12-month observation period (measured as a continuous measure and as a dichotomous outcome of achieving/not achieving at least 90% adherence to HAART), change in HIV RNA levels over the 12-month observation period (measured as a continuous measure and as a dichotomous outcome of achieving <500 copies/mL [indication of maximal HIV RNA control]), and change in CD4 T-cell count over the 12-month observation period. We chose 500 copies/mL as the plasma HIV RNA odds cutoff because assays before 2001 used this as the lower limit of quantification.

We analyzed adherence as a continuous measure using longitudinal linear regression with clustering by geographic region (to account for variability between health care regions and HMOs) with random effects modeling with maximal likelihood estimation. We analyzed odds of achieving at least 90% adherence to HAART using conditional logistic regression with clustering by geographic region.

We used linear mixed models longitudinally to examine changes over time in CD4 T-cell counts and HIV RNA levels with random intercepts and slopes. A 2-piece segmented linear model was used to allow for changing CD4 cell or HIV RNA slopes over time, as done in previous studies,\textsuperscript{31,33} with time segments from 0 to 6 months and from 6 to 24 months. For these analyses, we clustered by patient and time. We used conditional logistic regression for the outcome of achieving <500 copies/mL with clustering by geographic region.

Other predictive variables included in the adjusted models were gender, age at start of the regimen, antiretroviral-naïve status (defined as no documented prior history of antiretroviral use), regimen type (nonnucleoside reverse transcriptase inhibitor [NNRTI] or protease inhibitor [PI] based, nucleoside reverse transcriptase inhibitor [NRTI] only, or PI plus NNRTI mixed), baseline CD4 T-cell count (for HIV RNA analyses), and year that the regimen began (to account for temporal trends). All predictor variables were included in the final models. Results were stratified by use or nonuse of SSRI medications and if there was >80% adherence to SSRI medication. No potential interactions achieved a statistical significance of $P < 0.20$ and are not reported. We also performed all the aforementioned analyses on the patients eligible for the before and after comparison of SSRIs but, here, with clustering by the patient as a fixed effect with robust standard errors. STATA v.9.2SE (Stata Corporation, College Station, TX) was used for all analyses, employing the commands xtregr, xtmixed, and xtofit.

We obtained approval from all Kaiser Permanente regional and Group Health Cooperative Institutional Review Boards. Consistent with other HIV-related retrospective cohort studies,\textsuperscript{31,33} the Institutional Review Boards waived the requirement for informed consent before the start of the study for all patients.

**RESULTS**

We identified 13,874 HIV-infected patients with active membership during the study period. A total of 7596 patients never had a diagnosis of depression or evidence of SSRI use. Of these, 1961 had a new HAART regimen in the study period and constituted the control group. We identified 1398 patients with depression, of whom 508 patients had depression and had evidence of greater than 2 months of SSRI medication use.

Forty-two percent of the study population (3359 subjects) had depression, and 15% of the entire cohort was prescribed SSRIs. Thirty-six percent of the patients with depression were prescribed an SSRI medication. Patient characteristics at the start of the new HAART regimen are shown in Table 1. The groups were heterogeneous with respect to age and CD4 T-cell counts at the start of this HAART regimen but were similar for gender, HIV RNA levels, and HAART regimen type. Absolute differences in HIV RNA levels and CD4 T-cell counts were small and not likely clinically significant.

The mean rate of adherence to HAART over the 12-month observation period for all patients analyzed was 80.9% (95% confidence interval [CI]: 76.5 to 85.3). The nondepressed patients had an unadjusted mean adherence rate of
82.6% (95% CI: 77.6 to 87.6). Among the patients prescribed SSRI medications, mean adherence to an SSRI over 12 months was 76.9% (95% CI: 24.1 to 100) and 57.9% had ≥90.0% adherence to SSRIs. Depressed patients not using an SSRI medication had a significantly lower HAART adherence rate than the control group (Table 2). Rates of HAART adherence, measured as a continuous variable, among depressed patients treated with SSRIs did not differ significantly from HAART adherence rates in depressed patients not treated with SSRIs. Depressed patients taking SSRI medications who were adherent to their SSRI medication had HAART adherence rates statistically superior to those of nondepressed patients (P < 0.001) and statistically better HAART adherence than depressed patients not taking SSRI medications (P = 0.001).

Depressed patients without SSRI exposure had significantly lower odds of achieving at least 90% HAART adherence (P = 0.03, adjusted). Depressed patients prescribed SSRIs were statistically as likely to achieve at least 90% adherence (adjusted analysis) as were nondepressed comparison group patients. These results improved further if patients were adherent to their SSRI medication and became statistically superior to those of depressed patients not taking SSRIs (P = 0.01).

Overall, the mean decline in HIV RNA level over 12 months was 1.82 log_{10} copies/mL (95% CI: −1.94 to −1.17; Table 3). The control group had a mean HIV RNA level decrease of 1.97 log_{10} copies/mL. Seventy percent of the entire cohort and 85% of the nondepressed patients achieved an HIV RNA level <500 copies/mL by 12 months. The depressed groups of patients (with or without SSRI use) had fewer patients achieving an HIV RNA level <500 copies/mL by 12 months than the control group (P < 0.001). Odds of achieving an HIV RNA level <500 copies/mL by 12 months were significantly less among depressed patients without SSRI use compared with controls (P = 0.02). This negative association persisted even if HAART adherence was considered (adjusted OR = 0.88, 95% CI: 0.69 to 0.99; P = 0.05). The depressed patients with SSRI use had statistically similar odds of achieving an HIV RNA level <500 copies/mL compared with control patients, however, especially if they were adherent to their SSRI medication. We found similar differences when

### Table 1. Baseline Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Control</th>
<th>Coded Depression Diagnosis</th>
<th>Coded Depression Diagnosis With SSRI Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>3359</td>
<td>1961 (58.4%)</td>
<td>1398 (41.6%)</td>
<td>508 (15.1%)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>2848 (83.0%)</td>
<td>1618</td>
<td>1171</td>
<td>436</td>
</tr>
<tr>
<td>Regimen type, NNRTI based</td>
<td>1331 (38.8%)</td>
<td>832</td>
<td>469</td>
<td>175</td>
</tr>
<tr>
<td>PI based</td>
<td>1454 (42.4%)</td>
<td>810</td>
<td>617</td>
<td>203</td>
</tr>
<tr>
<td>NRTI only</td>
<td>204 (5.9%)</td>
<td>122</td>
<td>81</td>
<td>22</td>
</tr>
<tr>
<td>PI+NNRTI mixed</td>
<td>359 (10.5%)</td>
<td>196</td>
<td>149</td>
<td>65</td>
</tr>
<tr>
<td>Antiretroviral naive at HAART regimen initiation</td>
<td>1183 (35.2%)</td>
<td>294</td>
<td>889</td>
<td>271</td>
</tr>
<tr>
<td>Age at start of study period, y (median, IQR)</td>
<td>40, 35 to 47</td>
<td>40.9, 34 to 47</td>
<td>40.5, 25 to 47</td>
<td>42.0, 36 to 48</td>
</tr>
<tr>
<td>Viral load log_{10} copies/mL at start of regimen (median, IQR)</td>
<td>4.63, 3.90 to 5.16</td>
<td>4.60, 4.07 to 5.21</td>
<td>3.90, 3.90 to 4.78</td>
<td>3.90, 3.39 to 4.70</td>
</tr>
<tr>
<td>CD4 T-cell count (cells/µL) at start of regimen (median, IQR)</td>
<td>245, 100 to 401</td>
<td>226, 79 to 384</td>
<td>261, 125 to 420</td>
<td>264, 112 to 452</td>
</tr>
</tbody>
</table>

### Table 2. Differences in Mean HAART Adherence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Depression Diagnosis Without SSRI Use</th>
<th>Depression Diagnosis With SSRI Use*</th>
<th>Depression Diagnosis With SSRI Use and SSRI Adherence ≥80%†</th>
<th>P Comparing Patients With Depression Without SSRI With Patients Adherent to SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous outcome‡</td>
<td>79.2% (74.5 to 84.1; &lt;0.001)</td>
<td>81.4% (76.4 to 86.5; &lt;0.001)</td>
<td>84.7% (79.4 to 90.0; &lt;0.001)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted‡</td>
<td>−2.6% (−4.6 to −0.6; 0.01)</td>
<td>−2.1% (−4.6 to −0.4; 0.10)</td>
<td>+1.6% (−1.4 to +4.6; 0.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Odds ≥90% adherence</td>
<td>0.72 (0.61 to 0.85; &lt;0.001)</td>
<td>0.88 (0.71 to 1.09; 0.25)</td>
<td>1.07 (0.82 to 1.39; 0.60)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted‡</td>
<td>0.81 (0.70 to 0.98; 0.03)</td>
<td>0.91 (0.72 to 1.15; 0.41)</td>
<td>1.13 (0.86 to 1.49; 0.39)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

All patients, unadjusted: 80.9% (76.5 to 85.3).
Control group adherence at 12 months, unadjusted: 82.6% (78.1 to 87.1).
*Adherence to SSRI medication among patients prescribed SSRIs: 76.9% (24.1 to 100).
†57.9% of patients prescribed SSRI medication had ≥90.0% adherence to SSRI medication over time period.
‡Continuous outcomes analyzed by longitudinal linear regression with random effects, dichotomous outcomes analyzed by conditional logistic regression, with clustering by where patient received care.
§Adjusted for age, gender, antiretroviral-naive status, HAART regimen type, and temporal trend.
### TABLE 3. Differences in Viral and Immunologic Control

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Depression Diagnosis Without SSRI Use</th>
<th>Depression Diagnosis With SSRI Use</th>
<th>Depression Diagnosis With SSRI Use and SSRI Adherence ≥80%</th>
<th>P Comparing Patients With Depression Without SSRI Use and Patients Adherent to SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HIV RNA log_{10} copies/mL at 12 mo: continuous outcome†</td>
<td>+0.24 (+0.11 to +0.36; &lt;0.001)</td>
<td>+0.11 (-0.17 to +0.38; 0.75)</td>
<td>0.00 (-0.14 to +0.14; 0.98)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adj usted‡</td>
<td>+0.08 (-0.02 to +0.17; 0.10)</td>
<td>-0.06 (-0.21 to +0.09; 0.43)</td>
<td>-0.05 (-0.20 to +0.11; 0.54)</td>
<td>0.16</td>
</tr>
<tr>
<td>Percent achieving HIV RNA level &lt;500 copies/mL by 12 mo</td>
<td>69.9%</td>
<td>65.0%</td>
<td>65.0%</td>
<td>-</td>
</tr>
<tr>
<td>Odds of HIV RNA level at 12 mo &lt;500 copies/mL</td>
<td>0.51 (0.42 to 0.61; &lt;0.001)</td>
<td>0.60 (0.48 to 0.75; &lt;0.001)</td>
<td>0.69 (0.53 to 0.89; 0.005)</td>
<td>0.05</td>
</tr>
<tr>
<td>Change in CD4 T-cell count (cells/μL) at 12 mo: continuous outcome</td>
<td>-9 (-34 to +16; 0.47)</td>
<td>-27 (-47 to -7; 0.009)</td>
<td>-24 (-46 to -3; 0.03)</td>
<td>0.27</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>-19 (-45 to +8; 0.17)</td>
<td>+9 (-13 to +32; 0.41)</td>
<td>+19 (-4 to +43; 0.10)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted‡</td>
<td>-14 (-39 to +1; 0.85)</td>
<td>-22 (-42 to +1; 0.76)</td>
<td>-20 (-43 to -1; 0.89)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Continuous outcome analyzed by mixed models linear regression; dichotomous outcome analyzed by conditional logistic regression.
†Adjusted for age, gender, antiretroviral status, HAART regimen type, baseline CD4 T-cell count, and temporal trend, with clustering by wher.
‡Adjusted for age, gender, antiretroviral-naive status, HAART regimen type, baseline CD4 T-cell count, and temporal trend, with clustering by where patient received care.
§Control group change in HIV RNA level (log_{10} copies/mL) at 12 months, unadjusted: +140 (±13 to +151); 84.8% achieved HIV RNA level <500 copies/mL by 12 months.

Comparing relative changes in HIV RNA levels over the 12-month period.

CD4 T-cell count changes over 12 months (see Table 3) were robust overall, with a mean increase of 140 cells/μL (95% CI: 129 to 151) in all patients; the nondepressed group had a mean increase of 152 cells/μL over 12 months. The depressed patients not on SSRIs had no statistically or clinically significant change in CD4 T-cell responses compared with control patients, but the patients who were adherent to their SSRI medication did have a greater CD4 T-cell count rise over 12 months (+19 cells/μL adjusted; P = 0.10) as compared with controls and a statistically significantly greater rise in CD4 T cells compared with depressed patients without SSRI use (P = 0.01).

In a separate analysis, we identified 428 patients who had been treated with a particular HAART regimen and then started a new HAART regimen and were given SSRI medication for the first time with this subsequent HAART regimen. In an adjusted analysis comparing the 12 months with SSRI use with the 12 months of HAART without SSRI use, we found no significant difference in adherence (+0.5%, 95% CI: -2.4 to +3.4; P = 0.75), odds of ≥90% adherence (OR = 0.72, 95% CI: 0.43 to 1.20; P = 0.21), odds of achieving an HIV RNA level <500 copies/mL (OR = 1.11, 95% CI: 0.65 to 1.88; P = 0.70), change in HIV RNA log_{10} copies/mL (+0.11 log_{10} copies/mL; 95% CI: -0.24 to +0.46; P = 0.54), or change in CD4 T-cell count (+16 cells/μL; 95% CI: -28 to +60; P = 0.48).

### DISCUSSION

This study’s significance is related to its large sample size, ability to quantify the impact of depression on HAART adherence and HIV-related laboratory parameters, and ability to study the association of SSRI use and adherence to SSRI medications on these same outcome measures. Few previous studies have addressed the significant issue of the association of depression on HAART adherence in patients with this comorbidity. We demonstrate that a diagnosis of depression is associated with significantly reduced adherence to HAART regimens. Further, a diagnosis of depression was associated with significantly decreased odds of achieving HIV RNA levels <500 copies/mL by 12 months. Depressed patients who took SSRI medications and were adherent to their SSRI medications, however, had results similar to nondepressed patients. Although a diagnosis of depression did not have a significant impact on CD4 T-cell count changes over 12 months, depressed patients adherent to their SSRI medication were observed to have significantly greater increases in CD4 T-cell counts than depressed patients not taking SSRI medications and nearly statistically significant greater CD4 T-cell increases than nondepressed patients.

Adherence to HAART is critical for positive clinical outcomes in HIV disease. Previous studies have suggested that depression has a negative impact on adherence in HIV disease, but no study has clearly demonstrated this negative association with HAART in the modern HIV treatment era. We...
show that depression does decrease HAART adherence in the clinical setting. Improved adherence as a result of SSRI use did lead to significant improvement in HIV RNA levels or CD4 T-cell counts, abating much of the negative impact of depression in these patients. Of note, however, depressed patients who were on a particular HAART regimen and then started another HAART regimen along with SSRI medication had no improvement in adherence outcomes. It is possible, however, that the patients more likely to be adherent to medications in general were the more compliant patients to their SSRI medication and also to their HAART regimen, explaining the apparent positive association of SSRI and HAART adherence.

The probability of maximal HIV viral control in HAART-treated HIV-infected patients was lower among patients with depression. Inadequate adherence to HAART alone could account for this, but depression has been associated with poorer clinical progression independent of other factors. If depression and poorer viral control were attributable solely to poor HAART adherence, this effect should be fully ameliorated with greater HAART adherence. This was not the case, however, implying that depression itself may affect viral control. Viral control was improved among patients prescribed SSRI medications, even more so if SSRI adherence is considered. This negative association between depression and HIV RNA levels has been described previously.

Depression did not significantly affect CD4 T-cell counts in our study; this has been previously described but mainly in the pre-HAART era. SSRI use was associated with greater increases in CD4 T-cell counts among depressed patients compared with depressed patients not taking SSRI medications. These results are particularly important, because depression has been associated with earlier mortality in HIV-infected patients. Although in the pre-HAART era, Rakbin et al14 found that fluoxetine use in HIV-infected depressed patients did not improve CD4 T-cell counts; our results indicated that SSRI use may help to improve CD4 T-cell counts.

Our results have clinical implications. Because depression is negatively associated with HAART adherence and with clinical outcome measures for these patients, screening for depression is essential. Patients who are found to be depressed should be offered therapy, because compliant SSRI medication use was associated with improved HAART adherence and HIV laboratory parameters. Clinical trials investigating which SSRI medications would be most effective for this purpose are needed, because our study was not powered to analyze the effect of individual SSRIs on HIV clinical outcomes. We could not find previous trials that have studied specific agents for improving HAART adherence in depressed patients in settings similar to those of our patients.

There are some limitations with our study. Because we used electronic databases only, we cannot guarantee that none of the control patients had clinical depression. This potential misclassification is likely nondifferential, however, and thus resulted in conservative estimates for the association of depression and the outcome measures. Also, it is possible that the degree of depression among patients was not uniform across our various groups of depressed patients, resulting in residual confounding. Standardized depression scales for assessment of severity of depression have been infrequently used in the primary care setting; however, a previous study indicated that prescription of antidepressants in the primary care setting is an indicator of more severe depression. Thus, it is conceivable the depressed patients on SSRI medications in our study were the more severely depressed patients. We did not measure different potency and dosing of individual antidepressants, which certainly could have an impact on their effect on an individual patient. Also, our pharmacy databases do not record over-the-counter medications or supplements, which also could affect depression in our patients. Finally, we do not uniformly record illicit substance use, which could affect our results.

In conclusion, depression negatively affects adherence and clinical parameters among HIV-infected patients taking HAART, including the odds of achieving at least 90% adherence over 12 months and achieving an HIV RNA level <500 copies/mL by 12 months. We found that improved SSRI adherence is associated with improved HAART adherence, leading to improved HIV RNA levels and CD4 T-cell counts approaching or even exceeding results seen with nondepressed HIV-infected patients. SSRI use is likely beneficial in depressed HIV-infected patients if they can be compliant with their SSRI medication.

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REFERENCES


