

# Management of depression associated with HIV/AIDS and antiretroviral therapy

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Depressed mood is a common psychiatric complaint in persons with HIV/AIDS, with a meta-analysis indicating that the rates of depression within this group may be as high as double that of the general population. Depression may result from a biological diathesis to mood disorders, a physiological reaction to a medical illness or its treatment, and/or a psychological reaction to challenging life circumstances. Associated symptoms include sleep, energy and appetite disturbances; social withdrawal; diminished capacity to experience pleasure; diminished concentration; feelings of worthlessness, shame and guilt; and recurrent thoughts of death, including suicidal ideation. The emotionally and physically painful state of major depression is associated with decreased antiretroviral adherence and poorer HIV/AIDS disease outcomes.

Neuropsychiatric symptoms have been reported with several of the medications taken by patients with HIV/AIDS, including lamivudine, zidovudine, interferon and, most notably, efavirenz. However, data from several sources demonstrate that neuropsychiatric symptoms associated with efavirenz use are generally transient, with onset early after treatment initiation, peaking after one week and decreasing over the first one to four months of treatment. Recent comparative studies have not found elevated incident rates of major depression in patients treated with efavirenz, but they have confirmed the typical neuropsychiatric symptoms reported in earlier open-label studies and case reports. Becoming skilled in the management of depression and psychiatric symptoms is integral to the provision of comprehensive care for patients with HIV/AIDS.

**Key Words:** *Antiretrovirals; Depression; Efavirenz; HIV/AIDS*

Depressed mood is a common psychiatric complaint in persons with HIV/AIDS (1). Depression may result from a biological diathesis to mood disorders, a physiological reaction to a medical illness or its treatment, and/or a psychological reaction to challenging life circumstances. The diagnosis of a major depressive episode is made by identifying its classic symptoms as outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (2). It is characterized by persistently depressed mood and associated symptoms of sleep, energy and appetite disturbances; social withdrawal; diminished capacity to experience pleasure; diminished concentration; feelings of worthlessness, shame and guilt; and recurrent thoughts of death, including suicidal ideation (2). Several studies (3-7) have found high rates of major depression in persons with HIV/AIDS, and a meta-analysis (8) confirmed that rates of major depression in persons with HIV/AIDS are at least double that of the general population. Major depression is an emotionally and physically painful state, associated

## La prise en charge de la dépression associée au VIH-sida et aux antirétroviraux

Les personnes atteintes de VIH-sida se plaignent souvent du problème psychiatrique qu'est le sentiment de dépression. D'après une méta-analyse, le taux de dépression au sein de ce groupe pourrait atteindre le double de celui de la population générale. La dépression peut être imputable à une diathèse biologique à des troubles de l'humeur, à une réaction physiologique à une maladie ou à son traitement ou à une réaction psychologique à une situation de vie difficile. Les symptômes connexes sont les troubles du sommeil, de l'énergie et de l'appétit, un retrait social, une diminution de la capacité de ressentir le plaisir, une baisse de la concentration, un sentiment d'inutilité, de honte et de culpabilité et des pensées récurrentes de mort, y compris l'idéation suicidaire. L'état émotif et physiquement douloureux de dépression majeure est relié à une diminution de l'observance du traitement et à de moins bonnes issues du VIH-sida.

Plusieurs des médicaments que prennent les personnes atteintes du VIH-sida, y compris la lamivudine, la zidovudine, l'interféron et, surtout, l'efavirenz, sont reliés à des symptômes neuropsychiatriques. Cependant, selon les données provenant de plusieurs sources, les symptômes neuropsychiatriques associés à l'efavirenz sont généralement transitoires, se manifestant peu après le début du traitement, atteignant un sommet au bout d'une semaine et diminuant entre le premier et les quatre premiers mois du traitement. Des études comparatives récentes ne font pas état de taux accessoires élevés de dépression majeure chez les patients traités à l'efavirenz, mais elles ont confirmé les symptômes neuropsychiatriques classiques déclarés dans le cadre d'études ouvertes et de rapports de cas précédents. L'acquisition de compétences dans la prise en charge de la dépression et des symptômes psychiatriques fait partie intégrante de la prestation de soins complets aux patients atteints du VIH-sida.

with decreased antiretroviral adherence (9,10) and poorer HIV/AIDS disease outcomes.

## ANTIRETROVIRAL TREATMENT-EMERGENT NEUROPSYCHIATRIC SYMPTOMS

Neuropsychiatric symptoms, including depressed mood, agitation and insomnia, have been reported with several of the medications taken by patients with HIV/AIDS (11), including lamivudine (12,13), zidovudine (14,15), interferon (16) and, most notably, efavirenz (17,18). In early controlled trials evaluating the safety and efficacy of efavirenz, a mean 53% of patients experienced central nervous system (CNS) symptoms and, less frequently, psychiatric symptoms (17-19). The most commonly reported symptoms included the feeling of being 'stoned', having vivid dreams and being anxious. Other reported symptoms included abnormal thinking, impaired concentration, amnesia, confusion, depersonalization, depression, agitation,

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**TABLE 1**  
**Summary of studies: Neuropsychiatric symptoms in patients on efavirenz-containing regimens versus patients on other regimens with depression as the outcome variable**

Author (reference), year	Study design	Treatment group	Number treated	Rate of depression
Fumaz et al (34), 2005	Uncontrolled, cross-sectional	Efavirenz	22	Prevalence reporting sadness = 37%
		Protease inhibitor	9	Prevalence reporting sadness = 15%
van Leth et al (35), 2004	Randomized, controlled	Efavirenz	400	Depression, grade 3 and 4 = 1.5%
		Nevirapine	387	Depression, grade 3 and 4 = 1.5%
von Giesen et al (36), 2003	Uncontrolled, retrospective	Efavirenz	414	Incidence of depression = 31%
		Nevirapine	320	Incidence of depression = 25%
Parianti et al (37), 2004	Uncontrolled, retrospective	Efavirenz	40	Prevalence of depression = 30%
		Nevirapine	31	Prevalence of depression = 23%
Clifford et al (38), 2005	Randomized, controlled	Efavirenz-containing regimen	338	No significant difference in depression change scores
		Non-efavirenz-containing regimen	169	
Journot et al (39), 2006	Randomized, controlled	Efavirenz	178	Incidence of depression = 8%
		Protease inhibitor	177	Incidence of depression = 7%

euphoria, insomnia, somnolence and, rarely, hallucinations (18). Treatment-emergent neuropsychiatric side effects were usually reported soon after the first dose, with a median onset of one day, and then generally subsided over the first one to four months of treatment. Compared with a non-efavirenz-containing regimen (zidovudine, lamivudine and indinavir) (17,19), there were more neuropsychiatric side effects in the efavirenz-containing protocol group (53% versus 26%) (17). Antiretroviral regimen discontinuation due to CNS symptoms was higher, with 2.1% of patients discontinuing efavirenz therapy compared with 1.1% of patients in the non-efavirenz-containing treatment arms (18).

With widespread use, data on psychiatric symptoms in efavirenz-treated patients continues to be reported from several sources, including case reports, observational cohorts and comparative trials. Severe depression with suicide attempt (20-22), mania (23), recurrence of post-traumatic stress disorder (24) and acute psychotic episodes (25,26) with onset temporally related to initiation of efavirenz have all been described in case reports. Some of these reports suggest an association between the emergence of psychotic symptoms or severe depression and elevated plasma efavirenz levels (20,27-29).

Observational studies in community settings that reflect experience with efavirenz use in a broad range of patients, including those with mental health and substance abuse disorders, have also reported a characteristic neuropsychiatric syndrome associated with the use of efavirenz. In a study using retrospective recall of experiences, Lochet et al (30) reported high rates of neuropsychiatric symptoms before treatment, which increased in prevalence in the first month following treatment initiation and then steadily fell with continued treatment, with an overall 6% discontinuation rate due to neuropsychiatric side effects. Patients who recalled no symptoms before the initiation of therapy did report symptoms of sadness (20%), anxiety (15%) and suicidal ideation (9%) that materialized in the first month of treatment, suggesting that psychiatric symptoms may emerge even in patients who are feeling mentally healthy at the time of regimen initiation. In an open-label, prospective study, Blanch et al (31) stated that 71% of patients reported at least one neuropsychiatric side effect associated with efavirenz use, with a discontinuation rate of 13%. Patients maintained on efavirenz treatment showed an overall

reduction in levels of distress on longer term follow-up, reflecting the benefits that come with successful treatment. In a small, open-label study of 17 patients on longer term (median 18 months) efavirenz treatment, Gutierrez et al (32) reported persistent, generally mild-to-moderate neuropsychiatric symptoms in 10 (58.8%) of those patients. Four patients, including two with significant depression, required efavirenz discontinuation. Their results also suggest that patients with higher plasma efavirenz levels may be at greater risk of experiencing neuropsychiatric symptoms.

Data from studies that compared neuropsychiatric symptoms in patients on efavirenz-containing regimens with patients on other regimens also suggest that transient neuropsychiatric symptoms occur more frequently in efavirenz-treated patients (33-39) (Table 1). One prospective study (33) compared neuropsychiatric side effects in patients who had failed a regimen containing a protease inhibitor (PI) who were then randomly assigned to start either a new PI or efavirenz. In that study, Fumaz et al (33) reported high rates of neuropsychiatric symptoms on initiation of the efavirenz regimen, with symptoms decreasing over time but exceeding rates reported by patients on PIs at all time points. In a subsequent cross-sectional study comparing patients who had been on either efavirenz-containing regimens or PI-containing regimens for at least one year, Fumaz et al (34) reported that patients on the efavirenz regimens continued to experience psychiatric symptoms of sadness, mood changes and irritability, also at rates that exceeded those on PI regimens. Both groups reported similarly good levels of quality of life and judged the persistent neuropsychiatric symptoms to be mild and generally tolerable; however, the study did suggest that subjective neuropsychiatric symptoms associated with efavirenz use may persist in some patients for a longer duration than had been previously reported (34). In the 2NN study comparing efavirenz and nevirapine, van Leth et al (35) found relatively low rates of composite CNS/psychiatric side effects in all treatment groups, although more severe grade 3 and 4 neuropsychiatric adverse events were reported only in patients taking efavirenz. In a large retrospective study of patients referred for neuropsychological assessment, von Giesen et al (36) found high rates of incident depression in patients treated with either efavirenz (31%) or nevirapine (25%). Cases of incident psychosis in this study were rare, and attention and memory issues

were equal in both groups (9%) (36). Parienti et al (37) also found comparable rates of depression reported in patients taking efavirenz- (30%) and nevirapine- (23%) based regimens in a small retrospective analysis.

A recent substudy by Clifford et al (38) of a randomized controlled trial that compared efavirenz-containing regimens and non-efavirenz-containing regimens reported on neuropsychological assessments collected prospectively on patients through 24 weeks of antiretroviral treatment. In the study, no statistically significant differences in neuropsychological performance were found at any time points between the groups. The study did confirm the presence of the typical subjective neuropsychiatric experiences described in earlier open studies, with the usual time course of onset occurring early after initiation of efavirenz, peaking at week 1, and usually decreasing over the first month of treatment. The study found high levels of anxiety in patients initiated on both regimens and no statistically significant difference in changes in depression or anxiety scores between the groups. Significantly more patients required treatment regimen modification due to neuropsychiatric symptoms in the efavirenz group (6%) than in the non-efavirenz-containing regimen group (0%) (38). Another comparative study (39) looked at patients who were randomly assigned to either remain on their PI-based regimen or switch to an efavirenz-containing regimen. The study also demonstrated no increased incidence of depressive disorders associated with efavirenz use. The investigators did find high rates of depressive disorders in both treatment groups and concluded that there was an increased likelihood of incident cases of depression among patients with a history of depression, regardless of treatment arm (39). No studies have reported on the optimum management of neuropsychiatric symptoms associated with efavirenz treatment, and there is no evidence to suggest whether it is better to modify the efavirenz-containing regimen or to use standard psychiatric interventions to manage the emergent symptoms.

### TREATMENT AND MANAGEMENT OF MAJOR DEPRESSION IN HIV-POSITIVE PATIENTS

Identification and management of depressive symptoms is an integral component of comprehensive HIV patient care. A number of studies (40,41) have demonstrated the important relationship between depression and HIV disease progression, a relationship that persists even in the era of highly active antiretroviral therapy (HAART) (42). The effects of depression may influence HIV disease progression on several levels, including through biological mechanisms that link the two processes (43), delayed health care access and delayed initiation of HAART (44,45), and impact on HAART medication adherence (46,47).

Optimal primary care treatment of major depression includes psychopharmacological management combined with psychotherapy (48). Antidepressant medication, cognitive behavioural therapy and interpersonal therapy have all proven to be effective treatments for depression in the general population, although psychotherapy alone may be less effective than medication management in patients with severe depressive symptoms (49). Some trials (50-52) have demonstrated the effectiveness of psychotherapy for symptom reduction in depressed HIV-positive patients, and a recent cohort study (44) demonstrated that mental health therapy with or without the use of antidepressants was associated with increased probability of HAART use in depressed HIV-positive women. Several

**TABLE 2**  
Antidepressant drugs that are recommended as therapeutic options in HIV-positive patients, together with the usual doses

Class/individual agent	Usual starting dose (mg)	Usual treatment dose (mg)	Maximum recommended dose (mg)
<b>SSRIs</b>			
Citalopram*	10	20	60
Sertraline*	50	50–200	200
Paroxetine†	10	20	60
Fluoxetine*†	10	20	80
Escitalopram	10	10–20	30
<b>SNRIs</b>			
Venlafaxine XR	37.5	150–225	375
<b>NaSSAs</b>			
Mirtazapine*	30	30	60
<b>TCA</b> s			
Nortriptyline	10	50–150	200
Imipramine†	25	75–200	300
Desipramine	25	100–200	300
Amitriptyline	25	75–200	300
<b>NDRIs</b>			
Bupropion SR*	100	150–300	300–450

\*Open-label trial; †Randomized controlled trial. NaSSA Noradrenergic and specific serotonergic antidepressant; NDRI Noradrenergic and dopamine reuptake inhibitor; SNRI Serotonin-norepinephrine reuptake inhibitor; SSRI Selective serotonin reuptake inhibitor; TCA Tricyclic antidepressant. Notes: 1. The more debilitated the patient or the more evidence of organic brain disease, the lower the starting dose should be. Also, dosing titration should be done more slowly. 2. All antidepressants carry side effects and risks, including agitation. In rare cases, patients starting on antidepressants have experienced an intensification or precipitation of suicidal ideation. All patients started on antidepressants need to be monitored for emergent agitation. 3. All antidepressants may precipitate manic episodes, particularly in patients with a personal or family history of bipolar disorder. Patients with a history of bipolar disorder should be started on mood stabilizer therapy rather than an antidepressant alone. 4. The metabolism of fluoxetine, sertraline, amitriptyline, imipramine, desipramine, nortriptyline and bupropion SR may all be affected by P450 enzyme inhibition by some antiretroviral medications, such as ritonavir, and may require dose modification of the antidepressant. Fluoxetine may also inhibit the metabolism of some antiretroviral agents. For more information on drug interactions go to <[www.thhivclinic.com/pdf/psych-int.pdf](http://www.thhivclinic.com/pdf/psych-int.pdf)>

antidepressant medications, found to be effective in the treatment of major depression in the general population, have also proven effective in decreasing depressive symptoms in HIV-positive patients (Table 2). Open-label trials in depressed HIV-positive patients have shown the treatment benefits of several selective serotonin reuptake inhibitors (SSRIs), including citalopram (53), sertraline (54), fluoxetine (55) and mirtazapine (56), as well as the agent bupropion (57). Randomized, placebo-controlled trials have demonstrated reductions in depressive symptoms using the SSRIs paroxetine (58) and fluoxetine (59) and the tricyclic antidepressant imipramine (58,60). A recent meta-analysis (61) of those trials confirmed that treatment with antidepressant medication is efficacious in HIV-positive patients, but cautions that the results may not be generalizable due to underrepresentation of women and minorities in the treatment studies.

Major depression in patients with HIV/AIDS is managed using standard psychiatric interventions, and these are useful regardless of the presumed underlying cause of the major depression. To date, there are no studies that provide evidence for the

optimal management of depression in the context of efavirenz treatment. Clinical options include the use of standard psychiatric interventions and/or discontinuation of efavirenz, and must take into account patient preference and antiretroviral options.

### Dosage

For all HIV-positive patients with major depression, antidepressant treatment is generally initiated with the SSRI agents because they are the best tolerated and least likely to result in problematic drug interactions with antiretroviral agents (62). Antidepressant dosing in HIV-positive patients is essentially the same as in the depressed HIV-negative population; however, some caution must be used, particularly in patients with advanced systemic HIV disease and those on multiple medications. While drug interactions between antiretroviral medications and antidepressants must be considered, they are not a reason to withhold antidepressant treatment. Clinically significant interactions have been reported when antiretroviral agents that are powerful inhibitors of the cytochrome P450 system, such as ritonavir, are combined with antidepressants that rely on this enzyme system for drug metabolism (63). Dosage adjustment may be necessary when adding PIs, particularly ritonavir, to a tricyclic antidepressant, bupropion or fluoxetine (64).

Antidepressant medications should be initiated at one-half of the recommended starting dose and titrated to the starting dose after seven days if the drug is well tolerated. Target treatment doses are the same as in the general population. The patient's clinical response and drug tolerability should be evaluated regularly, with special attention paid to patient safety, specifically assessment of suicide risk. Treatment response is anticipated at weeks 4 to 6 of optimal drug dosage. Antidepressant treatment dose should be optimized as tolerated. In cases of nonresponse to antidepressant therapy, it is essential to ensure correct diagnosis, including examining for systemic disorders (eg, hypothyroidism) or concurrent substance-related disorders that may be limiting treatment response. It is also important to ensure adequate adherence to antidepressant therapy, assess psychosocial supports, and direct patients to appropriate psychotherapy and counselling support services, as available. Continued nonresponse may be managed by switching antidepressants within a class (eg, from paroxetine to citalopram) or between classes (eg, from citalopram to venlafaxine, bupropion or nortriptyline) (49,65,66), or with standard augmentation strategies (eg, adding lithium, triiodothyronine, buspirone or a second antidepressant, such as bupropion) (49,67). In depressed HIV-positive patients taking efavirenz, continued nonresponse to standard psychiatric interventions may necessitate drug discontinuation and substitution with another antiretroviral combination, or therapeutic drug monitoring of efavirenz levels, if available. Antidepressant medications should be maintained at full treatment doses for a minimum of six to nine months or longer if the patient has experienced frequent or recurrent depressive episodes, or episodes that are severe and/or difficult to treat (68,69). Psychiatric consultation should be initiated for patients with nonresponse to standard antidepressant therapy, patients with significant suicidal ideation, patients with a history of bipolar mood disorder and patients with psychotic symptoms. Patients with concurrent substance-related disorders should be referred for integrated psychiatric and substance abuse treatment.

## CONCLUSIONS

In summary, data from several sources confirm the presence of subjective neuropsychiatric symptoms associated with efavirenz use, with onset early after treatment initiation, peaking after one week and decreasing over the first one to four months of treatment. Some studies suggest the symptoms may persist in some patients for a longer duration and some, but not all, studies suggest that symptoms may be associated with elevated plasma efavirenz levels. No studies have systematically evaluated the management of these symptoms, but in some patients antiretroviral regimen modification is necessary. Several studies report high rates of psychiatric symptoms, including depression, in HIV-positive patients in general. As such, becoming skilled in the management of depression is integral to the provision of comprehensive care for patients with HIV/AIDS.

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