REVIEW ARTICLE

Drug Safety 2006; 29 (10): 865-874
0114-5916/06/0010-0865/$39.95/0

Neuropsychiatric Complications of Antiretroviral Therapy

Michelle S. Cespedes and *Judith A. Aberg*

Division of Infectious Disease, Department of Medicine, New York University School of Medicine, New York, New York, USA

Contents

Abstract

Neuropsychiatric adverse effects related to potent antiretroviral therapy are among the complications that can lead to poor adherence, treatment interruptions, or change of antiretroviral therapy regimens. For a historical perspective, we review early literature and case reports with CNS adverse effects attributed to antiretrovirals. The variability of the cerebrospinal fluid penetration of individual antiretrovirals may contribute to their potential for behavioural and psychiatric manifestations.

The majority of neuropsychiatric complications related to potent antiretroviral therapy have been associated with the use of the efavirenz. Updates on the risk of neuropsychiatric manifestations with efavirenz use in patients with a history of psychiatric disorders or substance abuse are reviewed. We include a critical review of recently published data on the long-term CNS adverse effects with efavirenz. Special attention is given to the results of recent investigations on the relationship between the pharmacogenomics of genes responsible for efavirenz metabolism and the plasma concentration of efavirenz. It is important to note that there is no established direct correlation of efavirenz concentrations and symptoms. It is not recommended for practitioners to adjust efavirenz doses in order to prevent or alleviate CNS adverse effects. Patients may be placed at risk for virological failure and resistance if they receive suboptimal doses of efavirenz.

The aim of this article is to give a concise review and an update on recent literature concerning neuropsychiatric effects of antiretroviral use in HIV-infected patients. Our intent is to present practitioners with data that can be used in a practical way to both educate and improve outcomes in the HIV-infected patient population.

The availability of potent antiretroviral therapy (ART) has dramatically decreased the mortality and morbidity of HIV-infected patients.[1] The presence of opportunistic infections and late sequelae of chronic infection such as encephalitis are rare among patients who have access to care and are identified before the onset of severe immunocompromise.

A number of strides have been made to improve patient compliance to regimens that may require lifelong adherence. Reduced pill burden increases compliance, but medication-related adverse effects continue to be a major barrier. Neuropsychiatric effects related to ART are among the complications that can lead to poor adherence, treatment interruptions or change of ART regimens.

Prior to the introduction of ART, psychiatric manifestations were recognised as a complication of HIV infection. Questions arose as to the aetiology of the observed disorders. Investigators theorised that the manifestations were related to the unmasking of underlying psychiatric disorders.[2] Others suggested that they were secondary to the effect of the virus itself, an opportunistic infection, or exacerbated by numerous stressors.[3,4] Later literature documented several incidents of psychiatric manifestations including mania and psychosis that were associated with the introduction of ART.[5] Neuropsychiatric disturbances attributed to the use of ART can run the continuum from sleep disorders to cognitive impairment to frank psychosis.[6]

A more extensive body of literature exists detailing experience with the neuropsychiatric effects of efavirenz and the proposed mechanism of action. Sleep disturbance, vivid dreams and impaired concentration are the most frequently reported CNS adverse effects associated with the use of efavirenz.[7] Reports indicate that some form of CNS symptoms are present in as many as 73% of patients who initiate treatment with an efavirenz-containing regimen.[6] Symptoms usually occur within the first few weeks of initiation then resolve, or are mild enough for patients to continue the regimen.

The aim of this article is to give a concise review and an update on recent literature concerning neuropsychiatric effects of antiretroviral use in HIV-infected patients.

1. CNS Exposure to Antiretroviral Therapy (ART)

While it is generally accepted that ART-associated neuropsychiatric manifestations are related to drug toxicity, there is increasing interest into whether symptoms may be due to CNS cellular damage by the HIV virus.

Psychiatric and neurocognitive changes associated with HIV infection have been attributed to the effect of the virus on brain tissue.[8-11] Early in infection, cells infected with HIV cross the blood-brain barrier and enter the CNS, which can lead to a chronic state of inflammation. Cognitive impairments are thought to be secondary to neurodegeneration and decreased neuronal cell-to-cell communication. Neuronal loss is the hallmark of HIV-associated dementia.

The CNS should be considered a distinct virological and pharmacological entity in relation to antiretroviral penetration and efficacy. The majority of antiretrovirals do not effectively cross the blood-brain barrier. Factors that influence antiretroviral penetration into the cerebrospinal fluid (CSF) include percentage of protein binding, molecular weight and the oil/water partition coefficients.[12] Protease inhibitors once bound to plasma glycoproteins can be restricted from crossing the blood-brain barrier via efflux pumps.[13] Although protease inhibitor penetration into the CSF is low as measured by CSF to plasma concentration, the use of protease inhibitor-containing regimens have proven to be effective in the treatment of neurological manifestations of HIV including cognitive impairment and progressive multifocal leukoencephalopathy.

Virus that has infected brain tissue may theoretically continue to damage neurons even in the presence of viral suppression in the peripheral compartment. Researchers have documented HIV with differing genotypic and phenotypic resistance patterns between those recovered from the CSF and peripheral blood.[14] While reduction in viral replication in brain tissue in the presence of antiretrovirals has been demonstrated *in vitro*, the ability of ART to reach neuronal tissue *in vivo* has not been formally documented.[15] Drugs that cross the blood-brain barrier more effectively may be more likely to produce CNS adverse effects. Effective ART treatment

has been shown to positively influence HIV-associated neuropsychiatric disorders once it reduced the HIV burden in the CSF and brain tissue.[16]

Recently presented data from the AACTG (Adult AIDS Clinical Trial Group) study 736 showed that improvement in neuropsychiatric testing correlated with sustained suppression of HIV viral load in the CSF.[17] The use of an antiretroviral regimen that had higher CSF penetration correlated with decreased CSF viral load. Neuropsychiatric and progressive cognitive dysfunction associated with prolonged ART use may require effective HIV therapy with high CSF penetration directed against possible resistant HIV isolates.

2. ART-Associated Neuropsychiatric Manifestations

The majority of reports of antiretroviral-induced psychiatric manifestations involve case reports of symptoms that occur within the first weeks of initiation of therapy (table I). Early reports of mania and psychosis arose in the era preceding the availability of potent ART.

The advent of combination therapy as the standard of care for the treatment of HIV makes attributing unexpected CNS manifestations of therapy to one drug in particular more complex. The possibility exists that drug-drug interactions that alter antiretroviral metabolism contribute to these adverse effects by increasing drug concentrations beyond their therapeutic range.

2.1 Zidovudine

One of the first observations reported new onset delusions and hallucinations in a patient who received zidovudine monotherapy following treatment of *Pneumocystis jiroveci* pneumonia (formerly known as PCP).[18] Symptoms started 3 days after initiating zidovudine and resolved within 24 hours of its withdrawal. Pressured speech and delusions recurred when the patient was rechallenged with zidovudine. Another case of psychosis relating to zidovudine monotherapy occurred in a patient taking concomitant acyclovir.[19] Fourteen months after the start of therapy the patient presented with bizarre behaviour, agitation and psychosis. Again, symptoms resolved with discontinuation of both medications and only returned after the reintroduction of zidovudine. Since zidovudine and acyclovir are metabolised and excreted through different pathways (hepatic and renal, respectively), significant pharmacokinetic interactions between the medications are not thought be the aetiology of the psyche manifestations.

Zidovudine monotherapy-associated mania was originally reported in a patient 7 months after the regimen was initiated.[20] Symptoms resolved after zidovudine administration was interrupted, but in contrast to the aforementioned cases, manic symptoms did not return once the antiretroviral treatment was restarted. No return of symptoms was noted at 3 months' follow-up.

These reports suggest that the resolution of symptoms once zidovudine was discontinued serves as proof of causality. The reader should take into account that in earlier reports, patients received monotherapy, which is no longer considered standard of care. They also received higher doses than are now recommended. It is possible that higher drug concentrations predisposed these patients to the CNS effects observed. Support for this theory includes case reports of the appearance of zidovudine monotherapy-induced psychosis following increased dose adjustments of zidovudine.[20] The patients involved in these case reports all had a personal or family history of an affective disorder, suggesting the possibility of genetic vulnerability to CNS toxicity. Unfortunately, these early reports did not include more information on the level of immunosuppression of the patients or information on comorbidities or substance abuse that may have been significant confounders.

The manufacturer and published data report a neuropsychiatric event rate of 5% associated with zidovudine therapy.[33,34]

2.2 Abacavir

Published reports include several cases that suggest abacavir as the antiretroviral responsible for the observed CNS adverse effects.[21,22] The patients presented with depression, migraines, mood changes that progressed to suicidal ideation and auditory hallucinations. The authors use the fact that

Table I. Selected case reports of antiretroviral-induced neuropsychiatric reactions

Antiretroviral	Psychiatric manifestation	Weeks post initiation	Notes	Reference
Zidovudine	Delusions, auditory hallucinations	1	Monotherapy, symptoms return with rechallenge	18
	Agitation, bizarre behaviour, psychosis	60	Occurred with coadministration of acyclovir, symptoms return only after reintroduction of zidovudine	19
	Mania	28	Symptoms do not return after restarting zidovudine by 3-month follow-up	20
Abacavir	Headache, depression, anxiety, auditory hallucinations	2	Both co-infected with hepatitis C, no evidence of abacavir hypersensitivity	21
	Mutism, catatonia, homicidal behaviour, persecutory delusions	4	No previous evidence of post partum depression or psychosis, no return of symptoms at 1-year follow-up when same regimen except for abacavir restarted	22
	Headache, night terrors	2	Symptoms appear abruptly once abacavir substituted for didanosine	23
Nevirapine	Cognitive impairment, impulsive suicide attempts, persecutory delusions	2	Nevirapine overdose precedes suicide attempt in one patient	24
	depression		Rapid resolution of symptoms once nevirapine changed to abacavir	25
Efavirenz	Irritability, suicidal ideation, aggression, antisocial behaviour	4	Severity of symptoms require psychiatric hospitalisation	26
	Excitability, anxiety, insomnia	2	Symptoms resolve with dose reduction of efavirenz	26
	Mental confusion, amnesia	8	Symptoms resolve with dose reduction of efavirenz	26
	Mania, disinhibition, grandiosity	4	No family or personal history of psychiatric disorder	27
	Mania		Occurred in the setting of overdose of 90 efavirenz tablets	28
	PTSD, intrusive recollections	4	Previous history of PTSD	29
	PTSD	1	Symptoms subside within 4 weeks while continuing efavirenz-containing regimen	29
	Severe psychosis, confusion, aggression	4	Originally attributed to interaction with fluconazole	30
	Disorientation, paranoid delusions, violent behaviour	1	Improved mental status observed within 7 days after discontinuation of efavirenz	31
	Suicidal ideation, anhedonia, agitation	4	History of previous psychiatric hospitalisation, patient refused to restart antiretroviral therapy	32

PTSD = post-traumatic stress disorder.

these symptoms did not return once abacavir was switched to nevirapine as proof of causality.

Another case attributed to abacavir involved an antiretroviral-experienced patient with a history of depression.[23] In contrast to the previous cases, this patient's depression was controlled on citalopram and they had a CD4 count of >500 cells/μL at the time that abacavir was substituted for didanosine because of metabolic complications. Within days, the patient complained of migraine headaches, night terrors and mood disturbances, which all resolved immediately after abacavir was discontinued. Foster et al.[23] suggest that the presence of headache and mood changes may be early indicators of abacavir-induced neuropsychiatric sequelae. None of the published case reports document the development of abacavir-associated psychiatric manifestations in the setting of an abacavir hypersensitivity syndrome. Nevertheless, nucleoside neuropsychiatric adverse events remain uncommon. The manufacturer reports a neuropsychiatric event rate of 2% associated with abacavir therapy.[35]

2.3 Nevirapine

Nevirapine has been associated with neuropsychiatric complications in a small number of published case reports.[24,25] Wise et al.[24] described three cases in patients without a prior history of mental illness, all of whom manifested symptoms within 2 weeks of initiating treatment with nevirapine. The patients developed a delirium, an organic affective state, and an organic psychosis with persecutory delusions. Unfortunately, the brief report fails to report the antiretrovirals that nevirapine was used in conjunction with or other coadministered medications that may have contributed to the symptoms.

Another case of mania and cognitive impairment occurred unexpectedly in a patient who was tolerating nevirapine.[36] The symptoms began with the introduction of clarithromycin for a respiratory infection and resolved after the withdrawal of the macrolide. The authors suggest that since both nevirapine and clarithromycin are metabolised by the same hepatic cytochrome P450 (CYP) isoenzyme, it is likely that a pharmacokinetic interaction was the underlying aetiology of the CNS disturbance.

2.4 Protease Inhibitors

There are few case reports of neuropsychiatric disorders developing in patients taking a protease inhibitor-based ART regimen in which the protease inhibitor is thought to be the antiretroviral responsible for the observed behaviours.[37] The manufacturer's product insert for ritonavir reports <2% incidence of psychiatric disorders including depression, hallucinations and abnormal thinking, and it is not clear whether these may be the result of interactions with other medications.[38]

2.5 Efavirenz

Efavirenz has a long half-life permitting once-daily administration, and is the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) for combination regimens for antiretroviral naive patients.[39] The majority of neuropsychiatric complications related to ART have been associated with the use of the NNRTI, efavirenz.[26]

Efavirenz has a wide range of neuropsychiatric effects, with published reports suggesting that 40–70% of patients experience some form of CNS disturbance.[39-42] CNS adverse effects from efavirenz-containing regimens are reported more than three times as often as from protease inhibitor regimens. The most common CNS adverse effects reported by patients are sleep disturbances, ranging from insomnia to vivid dreams and night terrors. Dizziness, vestibular complaints and difficulty concentrating are frequently reported and tend to appear soon after initiation of therapy.[43,44] These complaints usually last for the first 2–4 weeks of treatment. In cases where efavirenz-associated sleep disturbances persist, the majority report that the effects are mild enough to tolerate and continue with the prescribed regimen. Preliminary data from AACTG study 5097s reported that the majority of patients slept better after the initial exposure to efavirenz.[45] Only 4% of patients discontinued efavirenz as part of their treatment regimen because of CNS-associated adverse effects.[45]

More serious neuropsychiatric disorders have been documented with efavirenz use. Depression, aggressive behaviour, paranoia and psychosis including hallucinations are rare complications induced by efavirenz (see table I). Manic episodes

have also been reported; in one case, secondary efavirenz intoxication following an overdose of 90 tablets.[27,28]

The literature contains only two case reports of recurrences of post traumatic stress disorder (PTSD) predicated by initiation of efavirenz in antiretroviral naive patients.[29] Each reported a history of PTSD and depression that had not been present at the time immediately prior to starting treatment. Within 1 week of starting efavirenz in combination with zidovudine and lamivudine, both patients reported intense intrusive recollections, flashbacks and physiological distress when exposed to cues resembling previous torture. In these cases, the decision was made to continue efavirenz and the symptoms of PSTD subsided within 4 weeks.

Reports have suggested that psychiatric manifestations are more likely to occur in patients with a pre-existing history of a psychiatric diagnosis or substance abuse.[46-48] A case-control study from the Swiss HIV cohort reported that intravenous drug users were more likely than non intravenous drug users to stop efavirenz during the first 2 months of therapy as a result of intolerance of adverse effects. A retrospective study of HIV-positive patients who abused cocaine, alcohol, or marijuana showed that they were no more at risk of exhibiting CNS adverse effects than patients who denied substance abuse.[49] The study cited that the most common reason for discontinuation of efavirenz was virological failure and not adverse effects. Of the patients failing efavirenz, 79% were non-injection substance abusers who did not report CNS adverse effects. A review by Halman determined that pre-existing psychiatric history was not an independent risk factor for the development of neuropsychiatric adverse effects with efavirenz use.[50]

2.5.1 Pharmacogenetics

Efavirenz is metabolised by the hepatic CYP system, primarily by CYP isoenzyme 2B6, a mixed function oxidase, with some involvement of CYP3A4. Efavirenz has been demonstrated to cross the blood-brain barrier. Efavirenz concentrations in CSF have been documented to reach up to 1.2% of the corresponding plasma concentrations.[51]

Marzolini et al.[52] investigated the relationship between efavirenz plasma concentrations and the development of neuropsychiatric symptoms. Plasma serum samples from 130 patients who received efavirenz as part of combination ART were analysed for drug concentration. The researchers also recorded concomitant medications used, as well as duration of efavirenz use, body mass index, CD4 and HIV viral load measurements and CNS adverse effects at the time of sampling. The study found a large variability of the efavirenz concentrations between patients and these differences were not influenced by the age, sex, ethnicity or body mass index of patients. Data showed that 50% of patients who had low efavirenz concentrations had documented virological failure. Twenty-four percent of patients who had efavirenz concentrations higher than the optimal range developed neuropsychiatric adverse effects compared with only 9% of patients with concentrations in the recommended therapeutic range. No patients with low efavirenz concentrations developed CNS manifestations. While the authors factored protease inhibitor coadministration into the analysis, they failed to mention if there were associations between other medications taken that effect the plasma efavirenz concentrations. The report mentions only one patient in the low concentration group in which the concomitant use of phenobarbital is suggested as aetiology of the low plasma concentrations. The anticonvulsant is a known CYP3A4 inducer and the inference is that the increased rate of efavirenz clearance is responsible for the lower observed concentrations.

The influence of genetic factors that alter the hepatic metabolism of efavirenz has been increasingly addressed in the recent literature. Pharmacogenomic investigations have suggested that genetic variations may play a significant role in neuropsychiatric disorders with efavirenz use. The single nucleotide polymorphism *CYP2B6* G516T mutation is associated with significantly reduced function of the CYP2B6 enzyme.[53,54]

AACTG study 398 noted that the clearance of efavirenz was 28% higher in non-Hispanic Caucasians than in African Americans and Hispanics.[55] The slower elimination in these populations becomes increasingly important as HIV morbidity and mortality disproportionately affects non-White races worldwide. The single nucleotide polymorphism G516T of *CYP2B6* associated with loss of function

has been reported to directly affect efavirenz concentrations in Caucasian and African-American individuals.

Impaired hepatic metabolism of efavirenz in patients with the G516T polymorphism has been indicated as the cause of psychosis.[30] In this case the patient developed confusion, aggression and behavioural changes 1 month after initiation of an efavirenz-containing regimen.[30] Symptoms were originally thought to be secondary to the known interaction efavirenz with fluconazole, but they persisted after the antifungal dose was appropriately reduced. The patient's plasma concentration of efavirenz was discovered to be >30 times the normal limit. Efavirenz was discontinued with resolution of the psychiatric manifestations. Efavirenz was restarted at 200mg once daily, a third of the recommended daily dose, with no recurrence of symptoms. The patient achieved virological suppression and adequate CD4 count recovery at 6 months. Genetic investigation demonstrated that the patient was homozygous for the *CYP2B6* G516T allele.

AACTG study A5097s further analysed the relationship between the single nucleotide polymorphisms that affect efavirenz metabolism.[53,54] The study investigated whether allelic variants previously associated with altered plasma efavirenz concentrations (*CYP2B6*, *CYP3A4*, *CYP3A5* and multidrug transporter P-glycoprotein [MDR-1]) were associated with neuropsychiatric adverse effects. The 24-week randomised cohort included 154 patients, 32% of whom were African American and 10% of whom were identified as Hispanic.

The study revealed that significant alterations in efavirenz concentrations as measured by areas under the concentration-time curve (AUCs) were only significant for variations in the *CYP2B6* genotype. The *CYP2B6* G516T allele was associated with higher plasma efavirenz concentrations. It was determined that patients who were homozygous for the *CYP2B6* G516T variation (T/T) had statistically significant median efavirenz AUCs nearly three times as high as those with wild type (G/G), and more than twice that of patients heterozygous for the allele (G/T). Homozygotes for *CYP2B6* G516T were more common in African Americans than in Caucasians, 20% versus 3%, respectively. Too few Hispanic patients were included in the study to be evaluated as a separate population in terms of prevalence of *CYP2B6* G516T homozygotes.

Among all patients in AACTG A5097s, the presence of the *CYP2B6* G516T allele was associated with adverse CNS symptoms at 1 week. None of the other CYP450 alleles nor MDR-1 were associated with these symptoms. Nearly one third of subjects developed treatment-limiting CNS toxicities or prematurely discontinued efavirenz, but the investigation revealed that there was no statistically significant association between tolerability of efavirenz and the presence of the *CYP2B6* G516T allele. There were no differences in either virological or immunological responses in T/T patients homozygous for the allele as compared to G/G or G/T patients at 24 weeks.

A more recent investigation conducted by the Swiss HIV Cohort Study substantiated the association of the *CYP2B6* G516T allele and alterations in both efavirenz and nevirapine concentrations with the CNS toxicity of the antiretrovirals.[56] It was determined that the T/T variant was associated with both increased plasma and intracellular efavirenz concentrations, and plasma concentrations of nevirapine. The intracellular drug concentration and the *CYP2B6* genotype were strong predictors of efavirenz neuropsychiatric manifestations.

2.5.2 Long-Term Neuropsychiatric Manifestations

Two independent European teams of researchers have recently published data on the neuropsychiatric manifestations with efavirenz in patients who have been on an efavirenz-based regimen for ≥3 months. A cross-sectional study compared 60 patients on an efavirenz-based regimen with the same number of patients on a protease inhibitor-based regimen for at least 1 year.[57] Quality of life and psychological status were assessed via standardised questionnaires. No significant difference in psychological status or quality of life was demonstrated between the efavirenz or protease inhibitor groups. It did reveal that neuropsychiatric disorders persisted in more than half of HIV-infected patients on long-term therapy, but these disturbances were usually mild and well tolerated clinically. The study did not find any association between efavirenz plasma concentrations and the presence of neuropsychiatric disorders. A limitation of the study was that patients

who had previously discontinued efavirenz because of moderate or severe adverse effects or who had supra-therapeutic plasma concentrations were excluded.

Lochet et al.[58] developed a self-administered questionnaire to assess quality-of-life issues, specifically addressing sleep disturbances, cognitive changes and mood disorders in 174 consecutive patients who had all received efavirenz for ≥3 months. The most common disorders noted were abnormal dreams, memory disorders, nocturnal walking and sadness. Twenty-three percent of patients reported moderate to severe global neuropsychiatric discomfort.

Recent reports addressed the influence of antiretrovirals associated with CNS adverse effects on neurocognitive performance. In a large randomised controlled trial comparing the use of protease inhibitor-sparing ART regimens in treatment naive patients, the improvement in neuropsychological performance was comparable in patients receiving efavirenz with those who were not, at 6 months.[59] In a treatment-experienced cohort with virological suppression, neurocognitive impairment was associated with increased age and nadir CD4 count, but not with current ART regimen nor the relative CSF penetration of the individual antiretrovirals.[60]

3. Conclusions

The evolution of HIV disease management makes a comparative review of early published reports of antiretroviral-associated neuropsychiatric manifestations more problematic. Updated dose recommendations, coformulations and changes in the accepted criteria on when to initiate therapy are likely to eliminate cofounders that may have contributed to adverse outcomes. Pharmacokinetic interactions secondary to the coadministration of medications may promote higher plasma concentrations, predisposing patients to CNS manifestations.

Practitioners should be aware that although uncommon, significant neuropsychiatric manifestations can be associated with ART. Most commonly reported with the use of efavirenz, reports have attributed symptoms to all classes of antiretrovirals. The definitive mechanism of efavirenz associated with CNS adverse effects has not been delineated. Recent reports suggest that pharmacogenomic factors may contribute to altered metabolism of efavirenz, predisposing the patient to slower elimination and higher plasma concentrations. These genetic factors may disproportionately affect African American and Hispanic populations. However, it is important to note that it is not recommended that practitioners reduce efavirenz doses in certain populations in an effort to avoid or diminish neuropsychiatric manifestations. There is no established direct correlation of efavirenz concentrations and symptoms, and patients may be placed at risk of virological failure and resistance if they receive suboptimal doses of efavirenz.

Therapeutic drug monitoring, the process of documenting peripheral blood-drug concentrations to ensure therapeutic levels, is used in practice to adjust medication doses to reach the desired target concentrations. This option, although attractive, has inherent pitfalls when applied to HIV therapy. For antiretrovirals, the practice is expensive and not readily available in the US. More importantly, it does not measure the intracellular or CSF drug concentrations nor the amount of tissue penetration for individual medications. These drug concentrations are of particular importance in relation to the propensity of an individual agent to cause or treat HIV-associated neuropsychiatric manifestations.

It is important for practitioners to obtain detailed medication and psychiatric histories from patients prior to the initiation of therapy. Our growing armamentarium of antiretrovirals and other medication classes increases the possibility of significant pharmacokinetic interactions. Despite the possibility of neuropsychiatric complications of efavirenz, it remains a potent option in treating HIV-infected patients regardless of psychiatric history, history of substance abuse or ethnicity.

Acknowledgements

This work was supported in part by a grant from the National Institutes of Health/National Institutes of Allergy and Infectious Disease AIDS Clinical Trials Group U01 – AI -27665. Michelle Cespedes has no potential conflicts of interest that are directly relevant to the contents of this paper to disclose. Judith Aberg has received research support and/or honorarium from GlaxoSmithKline, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Merck and Roche Pharmaceuticals.

References

1. Palella FJ, Delaney KM, Moorman AC, et al. The Outpatient Study Investigators. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998; 338: 853-60
2. Mauri MC, Fabiano L, Bravin S, et al. Schizophrenic patients before and after HIV infection: a case-control study. Encephale 1997; 23 (6): 437-41
3. Sewell DD, Jeste DV, Atkinson JH, et al. HIV-associated psychosis: a study of 20 cases. San Diego HIV Neurobehavioural Research Center Group. Am J Psychiatry 1994; 151 (2): 237-42
4. Dube B, Benton T, Cruess DG, et al. Neuropsychiatric manifestations of HIV infection and AIDS. J Psychiatry Neurosci 2005; 30 (4): 237-46
5. Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. Am J Psychiatry 2001 May; 158 (5): 725-30
6. Blanch J, Martinez E, Rousaud A, et al. Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. J Acquir Immune Defic Syndr 2001; 27 (4): 336-43
7. Molina JM, Ferchal F, Rancinan C, et al. Once-daily combination therapy with emtricitabine, didanosine, and efavirenz in human immunodeficiency virus-infected patients. J Infect Dis 2000; 182: 599-602
8. Langford D. Chronic exposure of the blood-brain barrier to highly active antiretroviral therapy. Infect Dis Clin Pract 2004; 12: 158-62
9. Neuenburg JK, Brodt HR, Herndier BG, et al. HIV-related neuropathology, 1985 to 1999: rising prevalence of HIV encephalopathy in the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2002; 31: 171-7
10. Berger JR, Nath A, Greenberg RN, et al. Cerebrovascular changes in the basal ganglia with HIV dementia. Neurology 2000; 54 (4): 921-6
11. Zheng J, Ghorpade A, Niemann D, et al. Lymphotropic virions affect chemokine receptor-mediated neural signaling and apoptosis: implications for human immunodeficiency virus type 1-associated dementia. J Virol 1999; 73: 8256-67
12. Enting RH, Hoetelmans RM, Lange JM, et al. Antiretroviral drugs and the central nervous system. AIDS 1998 Oct 22; 12 (15): 1941-55
13. Langford D, Grigorian A, Hurford R, et al. Altered P-glycoprotein expression in AIDS patients with HIV encephalitis. J Neuropathol Exp Neurol 2004; 63: 1038-47
14. Antinori A, Perno CF, Giancola ML, et al. Efficacy of cerebrospinal fluid (CSF)-penetrating antiretroviral drugs against HIV in the neurological compartment: different patterns of phenotypic resistance in CSF and plasma. Clin Infect Dis 2005; 41: 1787-93
15. Kandanearatchi A, Vyakarnam A, Landau S, et al. Suppression of human immunodeficiency virus replication in human brain tissue by nucleoside reverse transcriptase inhibitors. J Neurovirol 2004; 10: 136-9
16. Wendel KA, McArthur JC. Acute meningoencephalitis in chronic human immunodeficiency virus (HIV) infection: putative central nervous system escape of HIV replication. Clin Infect Dis 2003; 37: 1107-11
17. Marra C, Sinha S, Evans S, et al. ACTG 736: CSF HIV-1 and Cognitive Function in Individuals receiving potent ART [abstract no. 361]. Denver (CO): 13th Conference on Retroviruses and Opportunistic Infections; 2006 Feb 5-8;
18. Maxwell S, Scheftner WA, Kessler HA, et al. Manic syndrome associated with zidovudine. JAMA 1988; 259 (23): 3406-7
19. O'Dowd MA, McKegney F. Manic syndrome associated with zidovudine [letter]. JAMA 1988; 260 (24): 3587
20. Schaerf FW, Miller R, Pearlson GD, et al. Manic syndrome associated with zidovudine [letter]. JAMA 1988; 260 (24): 3587-8
21. Colebunders R, Hilbrands R, De Roo A, et al. Neuropsychiatric reaction induced by abacavir. Am J Med 2002; 113: 616
22. Foster R, Olajide D, Everall IP. Antiretroviral therapy-induced psychosis: case report and brief review of the literature. HIV Med 2003; 4: 139-44
23. Foster R, Taylor C, Everall IP. More on abacavir-induced neuropsychiatric reactions. AIDS 2004; 18 (18): 2449
24. Wise MEJ, Mistry K, Reid S. Neuropsychiatric complications of nevirapine treatment. BMJ 2002; 324: 879
25. Colebunders R, Florence E. Neuropsychiatric reaction induced by clarithromycin. Sex Transm Infect 2002; 78: 75-6
26. Peyriere H, Mauboussin JM, Rouanet I, et al. Management of sudden psychiatric disorders related to efavirenz. AIDS 2001; 15: 1323-4
27. Shah MD, Balderson K. A manic episode associated with efavirenz therapy for HIV infection. AIDS 2003; 17 (11): 1713-4
28. Blanch J, Corbella B, Garcia F, et al. Manic syndrome associated with efavirenz overdose. Clin Infect Dis 2001; 33: 270-1
29. Moreno A, Labelle C, Samet JH. Recurrence of post-traumatic stress disorder symptoms after initiation of antiretrovirals including efavirenz: a report of two cases. HIV Med 2003; 4: 302-4
30. Hasse B, Gunthard F, Bleiber G, et al. Efavirenz intoxication due to slow hepatic metabolism. Clin Infect Dis 2005; 40: e22-3
31. de la Garza CL, Paoletti-Duarte S, Garcia-Martin C, et al. Efavirenz induced psychosis. AIDS 2001; 15: 1911-2
32. Puzantian T. Central nervous system adverse effects with efavirenz: case report and review. Pharmacotherapy 2002; 22 (7): 930-3
33. GlaxoSmithKline. Retrovir (zidovudine) tablets, capsules, and syrup: prescribing information. Research Triangle park (NC): GlaxoSmithKline Company 2005 Nov.
34. Rachlis A, Fanning MM. Zidovudine toxicity. Clinical features and management. Drug Safety 1993; 8: 312-20
35. GlaxoSmithKline. Ziagen (abacavir) tablets and oral solution: prescribing information. Research Triangle Park (NC): GlaxoSmithKline Company 2006 Mar.
36. Prime K, French P. Neuropsychiatric reaction induced by clarithromycin in a patient on highly active antiretroviral therapy (HAART). Sex Transm Infect 2001 Aug; 77 (4): 297-8
37. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. AIDS 2002; 16: 1201-15
38. Abbott Laboratories. Norvir (ritonavir) capsules and oral solution: prescribing information. North Chicago (IL): Abbott Laboratories, 2006 Jan
39. Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents - October 6, 2005. Panel on Clinical Practices for Treatment of HIV Infection, Department of Health and Human Services [online]. Available from URL: http://AIDSinfo.nih.gov [Accessed 2006 Sep 6]
40. Blanch J, Martinez E, Rousaud A, et al. Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. J Acquir Immune Defic Syndr 2001 Aug 1; 27 (4): 336-43
41. Goldenberg D, Boyle B. Psychiatric Safety of efavirenz [abstract WePeB4238]. Presented at the XIII Conference on AIDS. Durban, 2000 Jul 9-15
42. Puzantian T, Lee J, Lee RJ, et al. Psychiatric effects associated with efavirenz: a retrospective study [poster 481]. Presented at the 40th Annual Meeting of the Infectious Diseases Society of America. Chicago, 2002 Oct

43. Bristol-Meyers Squibb Company. Sustiva™ (efavirenz) capsules and tablets: prescribing information. Princeton (NJ): Bristol-Meyers Squibb Company, 2005 Feb

44. Fumaz CR, Tuldra A, Ferrer MJ, et al. Quality of life, emotional status, and adherence of HIV-1 infected patients treated with efavirenz versus protease inhibitor-containing regimen. J Acquir Immune Defic Syndr 2002; 29: 244-53

45. Ribaudo H, Clifford D, Gulick R, et al. Relationships between efavirenz pharmacokinetics, side effects, drug discontinuation, virologic response, and race: results from ACTG A5095/A5097s [oral abstract no. 132]. San Francisco (CA): 11th Conference on Retroviruses and Opportunistic Infections; 2004 Feb 8-11

46. Lucas GM, Gebo K, Chaisson RE, et al. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. AIDS 2002; 16: 767-74

47. Mocroft A, Madge S, Johnson A, et al. A comparison of exposure groups in the EuroSIDA study: starting highly active antiretroviral therapy, response to HAART, and survival. J Acquir Immune Defic Syndr 1999; 22: 369-85

48. Hirschel B, Flepp M, Bucher H, et al. Switching from protease inhibitors to efavirenz: differences in efficacy and tolerability among risk groups: a case control study from the Swiss HIV cohort. AIDS 2002; 16: 381-5

49. Juethner SN, Seyfried W, Aberg JA. Tolerance of efavirenz-induced central nervous system side effects in HIV infected individuals with a history of substance abuse. HIV Clin Trails 2003; 4 (3): 145-9

50. Halman M. Management of depression and related neuropsychiatric symptoms associated with HIV/AIDS and antiretroviral therapy. Can J Infect Dis 2001; 12: 9C-19C

51. Tashima KT, Caliendo AM, Ahmad M, et al. Cerebrospinal fluid human immunodeficiency virus type 1 (HIV-1) suppression and efavirenz drug concentrations in HIV-1-infected patients receiving combination therapy. J Infect Dis 1999; 180 (3): 862-4

52. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1 infected patients. AIDS 2001; 15: 71-5

53. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 2004; 18: 2391-400

54. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. Clin Infect Dis 2006; 42: 401-7

55. Pfister M, Labbe L, Hammer SM, et al. Population pharmacokinetics and pharmacodynamics of efavirenz, nelfinavir, and indinavir: Adult AIDS Clinical Trail Group Study 398. Antimicrob Agents Chemother 2003; 47 (1): 130-7

56. Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenet Genomics 2005; 15 (1): 1-5

57. Fumaz CR, Munoz-Moreno JA, Molto J, et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. J Acquir Immune Defic Syndr 2005; 38 (5): 560-5

58. Lochet P, Peyriere H, Lotthe A, et al. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. HIV Med 2003; 4: 62-4

59. Clifford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med 2005; 143: 714-21

60. Giancola ML, Lorenzini P, Balestra P, et al. Neuroactive antiretroviral drugs do not influence neurocognitive performance in less advanced HIV-infected patients responding to highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2006; 41: 332-7

Correspondence and offprints: Dr *Michelle S. Cespedes*, AIDS Clinical Trials Unit, New York University, 550 First Avenue, C & D Building Room 558, New York, NY 10016, USA.
E-mail: michelle.cespedes@med.nyu.edu