

# Neuropsychiatric manifestations of HIV infection and AIDS

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As the life expectancy of people living with HIV infection has increased (through recent advances in antiretroviral therapy), clinicians have been more likely to encounter neuropsychiatric manifestations of the disease. Some patients present with cognitive deficits due to an HIV-triggered neurotoxic cascade in the central nervous system. However, more patients present with a depressive spectrum disorder during the course of their illness, the underlying pathogenesis of which is not as well understood. This category of psychiatric disorders presents diagnostic challenges because of the many neurovegetative confounding factors that are present in association with HIV illness. As quality of life becomes a more central consideration in the management of this chronic illness, better awareness of these neuropsychiatric manifestations is paramount. This article reviews these clinical issues and the available psychopharmacologic treatment options.

Comme l'espérance de vie des personnes vivant avec le VIH a augmenté (grâce aux progrès récents de la thérapie aux antirétroviraux), les cliniciens sont maintenant plus susceptibles de faire face à des manifestations neuropsychiatriques de la maladie. Certains patients se présentent avec des déficits de la cognition attribuables à une cascade neurotoxique déclenchée par le VIH dans le système nerveux central. Plus de patients se présentent toutefois avec un trouble du spectre dépressif pendant leur maladie, dont on ne comprend pas aussi bien la pathogénèse sous-jacente. Cette catégorie de troubles psychiatriques pose des défis diagnostiques en raison des nombreux facteurs confusionnels neurovégétatifs associés à l'infection par le VIH. Comme la qualité de vie devient un facteur plus central dans la prise en charge de cette maladie chronique, il est primordial d'être plus conscient de ses manifestations neuropsychiatriques. Dans cet article, les auteurs passent en revue ces enjeux cliniques et les traitements psychopharmacologiques possibles.

## Introduction

The Joint United Nations Programme on HIV/AIDS has estimated that, as of 2004, more than 40 million people worldwide were living with HIV virus type 1.<sup>1</sup> In North America, between 540 000 and 1.6 million adults and children are thought to be infected, and these are predominantly injection drug users and men who have sex with men. Far from over, this pandemic has also seen the number of women infected with HIV increase rapidly across the globe, and women now account for half of all people living with HIV worldwide. However, recent advances in the treatment of

this retrovirus have increased the life expectancy of seropositive people, which makes it more likely that clinicians will encounter patients with neuropsychiatric manifestations of the disease.

The most common neurologic manifestations are minor cognitive and motor disorder (MCMD) and HIV-associated dementia (HAD). The most common psychiatric manifestations are depressive spectrum disorders. In both cases, the impact of these syndromes on seropositive patients is significant and appropriate intervention is required, the key to optimal treatment resting with early diagnosis and aggressive treatment. In this paper, we describe the major neuropsychi-

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atric manifestations of HIV spectrum disease and also discuss the diagnosis and treatment of these types of conditions.

## Neurologic manifestations of HIV infection

The first cases of HIV-related infections were reported in 1981, and the virus was identified 2 years later.<sup>2</sup> Neurologic complications were recognized very early in the epidemic.<sup>3</sup> It is now known that HIV can be isolated from the cerebrospinal fluid (CSF) and can also be found in brain tissue, which suggests that the virus can cross the blood–brain barrier. Sacktor et al<sup>4</sup> reported that when monotherapy was a mainstay of treatment (between 1990 and 1992), the mean incidence of HAD was 21.1 cases per 1000 person-years, whereas when highly active antiretroviral therapy (HAART) became the norm (between 1996 and 1998), the mean incidence of HAD decreased significantly, to 10.5 cases per 1000 person-years.<sup>4</sup> These authors also noted a concurrent decrease in the incidence of opportunistic central nervous system (CNS) infections for the same observation periods.

Another team of researchers found a decrease in prevalence rates of opportunistic CNS infections over the same period; however, using autopsy data, they found an increase in the prevalence of HIV encephalopathy in the post-HAART years.<sup>5</sup> This would suggest that despite improved therapeutic options and an apparent decrease in neurologic complications, HIV seems to continue to infiltrate the CNS.

The presence and action of HIV in the CNS are now much better understood. HIV crosses the blood–brain barrier by a Trojan-horse-type mechanism using macrophages it infects.<sup>6</sup> Once in the brain, HIV targets and infects glial cells, from which it later secretes neurotoxins that lead to neuronal damage and death.<sup>7</sup> The extent of this neuronal damage is thought to be linked to the level of clinical neurologic deficits. Postmortem neuropathologic examinations of HIV-positive patients have revealed the presence of virus in cortical and subcortical structures, namely the frontal lobes, the subcortical white matter and the basal ganglia.<sup>8,9</sup> Some authors have suggested that the caudate nucleus and the basal ganglia are the primary areas of pathogenesis.<sup>10,11</sup>

The underlying mechanisms leading to neurocognitive impairment are now also better understood.<sup>6</sup> Recent evidence supports a mechanism by which neurotoxins released by periventricular macrophages and microglia trigger cytokine and chemokine release,<sup>12</sup> which in turn leads to modification of synaptic architecture in the cortex.<sup>13–15</sup> It is thought that apoptosis, or programmed cell death, is the most common mechanism resulting in cell loss.<sup>16,17</sup>

People with severe neurocognitive deficits or HAD usually have higher plasma HIV viral load; however, an elevated viral load does not always lead to HAD, and HAD has been documented in the absence of elevated viral load.<sup>7,18,19</sup> Hence, correlates have been identified in the CSF. Generally, HIV viral loads in the CSF are similar to those in the serum.<sup>20</sup> However, elevation of levels of certain substances in the CSF has been positively correlated with the presence of severe neurocognitive deficits. These substances

include  $\beta_2$ -microglobulin,<sup>21</sup> neopterin,<sup>22</sup> quinolinic acid<sup>23</sup> and Fas receptors and Fas ligands.<sup>24</sup> The latter finding is interesting since Fas is associated with the execution of apoptotic programs. Nevertheless, these findings currently have no diagnostic value.

Although HIV may remain dormant in the CNS for many years, its mere presence might lead to subtle deficits in cognitive functioning. However, these deficits are not found in all patients, which has led some authors to suggest that peripheral triggers might be involved.<sup>25,26</sup> Much more research is needed before it can be determined which individuals or subgroups of individuals are more vulnerable to neurologic complications.

Neurocognitive deficits are manifestations of both direct and indirect effects of HIV on the CNS.<sup>27</sup> While it is generally agreed that people with advanced disease present with deficits in many cognitive domains,<sup>28–31</sup> there is conflicting evidence regarding whether similar deficits occur in asymptomatic individuals. For example, some investigators have found neuropsychologic deficits in asymptomatic patients,<sup>32–36</sup> whereas others have found similar levels of neurocognitive impairment in seropositive and match-controlled seronegative individuals.<sup>37,38</sup> In a review of 57 studies examining neurologic functioning, the median rate of neuropsychologic impairment based on test performance was 35% for seropositive and 12% for seronegative patients.<sup>39</sup> However, in another review of 36 cross-sectional studies and 9 longitudinal studies, more than half of the studies showed no significant differences in the results of neuropsychologic testing between symptomatic and asymptomatic participants as well as no baseline impairment in seropositive patients.<sup>40</sup> Although methodologic differences might help to explain the discordant findings, research suggests that when deficits are present in asymptomatic patients, they are subtle and limited to fewer cognitive domains.<sup>28,40</sup> When depressive symptoms are also present, psychomotor slowing accompanies verbal memory deficits, whereas when depressive symptoms are absent, only verbal and nonverbal cognitive deficits are evident.<sup>41</sup>

As HIV disease progresses, additional cognitive domains often become impaired. Attention and concentration, as measured by dual task or divided attention paradigms, are decreased.<sup>42,43</sup> The presence of HIV in the fronto-subcortical circuitry and its deleterious impact on working memory means that executive function is also affected.<sup>44</sup> Learning and memory, as measured by information retrieval, are also impaired.<sup>31</sup>

The most prominent and common neurocognitive deficit is psychomotor retardation.<sup>7</sup> Cognitive slowing can be seen with or without normal motor function.<sup>29</sup> Thus, HIV-seropositive patients should be assessed for these types of neurocognitive impairments in the presence of subjective or behavioural indications.

### *Diagnosis and treatment of neurologic manifestations of HIV infection*

The American Academy of Neurology has put forth diag-

nostic criteria for HIV-associated MCMD (Box 1) and HAD (Box 2).<sup>45</sup> Whereas HAD is thought to represent neuronal death, MCMD is thought to be a lesser form of dementia on a continuum of cognitive deficits, representing neuronal dysfunction. The previous expression for this condition, AIDS dementia complex, has been dropped because seropositive patients not presenting with AIDS-defining criteria have presented with dementia.<sup>46</sup>

Both MCMD and HAD are diagnoses of exclusion, and CNS pathology must be ruled out. For example, CNS infectious pathogens or tumours as well as metabolic causes of encephalopathy must be investigated before the cognitive and motor deficits can be attributed to HIV infection. Among the more frequent CNS infections are toxoplasmosis and progressive multifocal leukoencephalopathy, which is caused by the papovavirus, whereas non-Hodgkins CNS lymphoma is the most common cancer associated with neurocognitive changes.<sup>47</sup>

Once opportunistic infections have been ruled out or treated if necessary, there are potentially 2 therapeutic options for neurocognitive deficits: diminish the effects of the virus on the CNS through better control of viral load or develop neuroprotective agents to shield the CNS from HIV-induced virotoxins. Unfortunately, antiretrovirals are not always successful in crossing the blood-brain barrier, but, as evidenced by the decrease in the incidence of HAD with the advent of HAART, they offer good results.<sup>48</sup> There are, in

#### Box 1: Diagnostic criteria for HIV-associated minor cognitive and motor disorder\*

- I. Acquired cognitive, motor or behavioural abnormalities (must have both A and B)
  - A. At least 2 of the following symptoms present for at least 1 month, verified by a reliable history:
    - (1) Impaired attention or concentration
    - (2) Mental slowing
    - (3) Impaired memory
    - (4) Slowed movements
    - (5) Incoordination
    - (6) Personality change, or irritability or emotional lability
  - B. Acquired cognitive or motor abnormality, verified by clinical neurologic examination or neuropsychologic testing
- II. Cognitive, motor or behavioural abnormalities causing mild impairment of work or activities of daily living (objectively verifiable or by report of key informant)
- III. Does not meet criteria for HIV-associated dementia (see Box 2)
- IV. Absence of another cause of the above cognitive, motor or behavioural abnormalities (e.g., active CNS opportunistic infection or malignancy, psychiatric disorders, substance abuse)

CNS = central nervous system.

\*Source: Working Group of the American Academy of Neurology AIDS Task Force.<sup>45</sup>

theory, neuroprotective agents against the virotoxins of HIV (Table 1),<sup>49,50</sup> including pentoxifylline,<sup>51,52</sup> nimodipine,<sup>53</sup> peptide T, memantine,<sup>53</sup> selegiline<sup>54</sup> and lexicapant.<sup>55</sup> However, supporting evidence is available only for selegiline as a potential therapeutic agent.

Traditional approaches to treating dementia in the course of HIV infection have also shown some success. Psychostimulants have been useful in treating both apathy and cognitive slowing in HAD.<sup>56-58</sup> Dopamine agonists have shown some success as well,<sup>59</sup> but there have been no controlled trials of cholinesterase inhibitors in treating dementia in HIV illness. Similarly, despite anecdotal evidence suggesting some success with agents such as donepezil, placebo-controlled trials have not yet been conducted.

Agitation and psychosis associated with dementia in HIV-infected patients are often treated with mood stabilizers and antipsychotics. In addition, the presence of cognitive slowing may be related to concurrent depressive symp-

#### Box 2: Diagnostic criteria for HIV-associated dementia\*

- I. Acquired abnormality in at least 2 of the following cognitive abilities, present for at least 1 month and causing impairment in work or activities of daily living:
  - (1) Attention or concentration
  - (2) Speed of information processing
  - (3) Abstraction or reasoning
  - (4) Visuospatial skills
  - (5) Memory or learning
  - (6) Speech or language
- II. At least 1 of the following:
  - (1) Acquired abnormality in motor functioning
  - (2) Decline in motivation or emotional control or change in social behaviour
- III. Absence of clouding of consciousness during a period long enough to establish presence of I, above
- IV. Absence of another cause of the above cognitive, motor or behavioural symptoms or signs (active CNS opportunistic infection or malignancy, psychiatric disorders, substance abuse)

\*Source: Working Group of the American Academy of Neurology AIDS Task Force.<sup>45</sup>

Table 1: Agents studied for their neuroprotective properties in HIV infection

Agent	Proposed mechanism
Pentoxifylline	Inhibits TNF alpha
Nimodipine	Decreases intracellular calcium
Peptide T	Blocks gp120 protein
Memantine	NMDA antagonist
Selegiline	Prodopaminergic, antioxidant and antipoptotic
Lexicapant	PAF antagonist

NMDA = N-methyl-D-aspartate; PAF = platelet-activating factor; TNF = tumour necrosis factor.

toms. As such, an underlying depressive illness should be ruled out. These concerns are reviewed in the next section, which examines the impact of depression and other psychiatric illnesses on HIV disease and outlines the treatment of these psychiatric disorders.

## Psychiatric manifestations of HIV infection

Recognizing the psychiatric manifestations of HIV disease can be complicated by the complex biologic, psychological and social circumstances associated with this illness, and psychiatric symptoms often go unrecognized and untreated.<sup>60</sup> The significance of these findings is magnified by emerging evidence that certain symptoms, such as depression, may be associated with an increase in mortality rate among HIV-seropositive women<sup>61</sup> and with disease progression in HIV-seropositive men.<sup>62</sup> Here, we examine the main psychiatric conditions observed among HIV-seropositive patients, including mood disorders and psychosis.

### Depression

Depression is one of the most common psychiatric disorders observed in people infected with HIV. Prevalence rates have shown wide variation, with estimates of between 4% and 22% for HIV-seropositive men and between 2% and 18% for HIV-seropositive women.<sup>63–65</sup> Earlier controlled studies found that the prevalence of major depression and other mood disorders was higher among asymptomatic HIV-seropositive men than in the general population<sup>66,67</sup> but was similar to that of HIV-seronegative gay men.<sup>63,68</sup>

Most prevalence studies have focused on HIV-seropositive men, even though it is estimated that women constitute 50% of new cases of HIV infection worldwide<sup>1</sup> and that women account for more than 16% of all cases of HIV infection in the United States;<sup>69</sup> moreover, women report higher rates of depression than men in the general population.<sup>70</sup> Current estimates of depression among HIV-seropositive women range from 1.9% to 35% in clinical samples<sup>71,72</sup> and from 30% to 60% in community samples.<sup>61,73</sup>

In addition, more recent studies with large sample sizes and controlled study designs have reported that HIV-positive women are at significantly greater risk for major depressive disorder than demographically matched HIV-negative women. Ickovics et al<sup>61</sup> reported chronic depressive symptoms in 42% and intermittent depressive symptoms in 35% of a sample of 765 HIV-positive women. In a clinical study of 93 HIV-seropositive women and 62 HIV-seronegative women, Morrison et al<sup>74</sup> found that the prevalence of major depressive disorders was significantly higher among HIV-positive women than among HIV-negative controls (19.4% v. 4.8%).

Whereas depression is increasingly recognized as a cause of increased morbidity and mortality in many chronic medical illnesses, it remains undiagnosed and untreated in the HIV-infected population.<sup>60,75</sup> In the context of HIV infection, the diagnosis of depressive disorders can be even more challenging because many vegetative symptoms of depres-

sion (e.g., fatigue, pain, anorexia and insomnia) are observed in many patients throughout the course of their HIV illness, even when depression is not present. However, in both the early and late phases of HIV disease, these symptoms correlate more closely with a mood disorder (when present) than with clinical correlates of infection.<sup>76</sup> The prominence of diminished mood in the morning coupled with anhedonia should alert clinicians to the presence of a major depressive disorder and should help distinguish it from demoralization or an adjustment disorder.<sup>77</sup> Clinical detection of depressive symptoms is even more important given a well-documented decrease in adherence to HAART in the context of depression.<sup>78–80</sup> Fortunately, recent studies have shown that the treatment of depressive symptoms in patients with HIV infection improves psychosocial functioning and quality of life.<sup>81</sup>

### Mania

Higher rates of mania have also been noted with progression of HIV infection. In early HIV infection, 1%–2% of patients experience manic episodes,<sup>76</sup> which is only slightly higher than the rate in the general population. However, after the onset of AIDS, 4%–8% of patients appear to experience mania.<sup>82,83</sup> This increased frequency of mania around the time of onset of AIDS has been closely associated with cognitive changes or dementia and is thought to be a secondary manic syndrome due to HIV infection of the CNS. In a 17-month chart review, among the 8% of patients with manic episodes, counts of helper/inducer lymphocyte (CD3+/CD4+) cells were significantly higher in those with a history of mood disorder, suggesting that mania may be a direct effect of HIV on the CNS.<sup>82</sup> In a case-control study of 19 patients with HIV-associated mania and 57 HIV-seropositive controls, AIDS dementia was significantly more common in patients with mania, which suggests a strong association between HIV neuropathology and manic symptoms.<sup>83</sup> Sometimes referred to as “AIDS mania,” this condition is phenomenologically different from the typical manic syndrome of bipolar disorder in both its symptom profile and severity,<sup>76</sup> and it is often characterized by irritability rather than euphoria.

### Psychosis

Psychosis is a recognized but — relative to the mood disorders — uncommon psychiatric manifestation of AIDS.<sup>84,85</sup> Even less commonly, antiretroviral therapy may precipitate psychosis. For example, there have been anecdotal reports of psychosis associated with ganciclovir<sup>86,87</sup> and efavirenz.<sup>88</sup> Psychosis was found more frequently in patients with AIDS-related neurocognitive impairments.<sup>69</sup> Using chart reviews, Navia and Price<sup>89</sup> found that 15% of 46 patients with HAD experienced psychotic symptoms. These findings were supported by data from the San Diego HIV Neurobehavioural Research Center suggesting that HIV-infected patients with psychosis exhibited greater neurocognitive impairments than HIV-positive controls without psychosis.<sup>84</sup>

### *Treatment of psychiatric manifestations of HIV infection*

Although a growing body of evidence supports the importance of treatment of mood disorders in HIV disease, controlled studies of somatic therapies are often lacking in this population, with polypharmacy and drug–drug interactions often presenting as complicating factors.

#### **Tricyclic antidepressants**

Numerous studies have reported the efficacy of tricyclic antidepressants (TCAs) for the treatment of HIV-seropositive patients with depressive disorders.<sup>90,91</sup> Rabkin et al,<sup>92</sup> in a double-blind, randomized, placebo-controlled trial of 97 HIV-seropositive patients, demonstrated the effectiveness of imipramine in the treatment of depression. At 6 weeks of treatment, 74% of the imipramine group and 26% of the placebo group showed improvement of depressive symptoms without changes in CD3+/CD4+ cell counts. It is important to note, however, that more than one-third of the subjects in that study discontinued treatment because of anticholinergic side effects. Elliott et al,<sup>93</sup> using a similar design, compared imipramine, paroxetine and placebo in 75 HIV-positive subjects. The 2 antidepressants were equally efficacious at 6, 8 and 12 weeks and were significantly more efficacious than placebo. Again, attrition due to side effects was 48% with imipramine, 20% with paroxetine and 24% with placebo.

#### **Selective serotonin reuptake inhibitors**

As suggested by the Elliott et al study described above,<sup>93</sup> selective serotonin reuptake inhibitors (SSRIs) are as effective as TCAs in the treatment of depression in HIV-seropositive patients, and they have a more favourable side effect profile. Rabkin et al, in an extension of their TCA study,<sup>92</sup> enrolled HIV-seropositive subjects with depression in whom treatment with imipramine had failed (because of lack of efficacy or intolerability of side effects) in a 12-week open-label trial of fluoxetine.<sup>94</sup> Although the baseline depression severity scores on the Hamilton Rating Scale for Depression (HAM-D) (mean 12.5) were lower than scores for the imipramine trial (mean 15.8), 83% of subjects treated with fluoxetine at 15–60 mg/day exhibited significant reductions in HAM-D scores. Although it did not alter CD3+/CD4+ cell counts, fluoxetine was well tolerated by subjects. In another study, Rabkin et al<sup>95</sup> used a randomized, placebo-controlled design to compare the efficacy of fluoxetine and placebo for treatment of depression in HIV-seropositive patients. Seventy-four percent of the subjects responded to fluoxetine, whereas 47% responded to placebo, but an intention-to-treat analysis showed that the differences between groups were less remarkable.

Ferrando et al<sup>96</sup> compared paroxetine, fluoxetine and sertraline in a 6-week open trial in 33 symptomatic HIV-seropositive subjects. Eighty-three percent of the subjects reported improvements in depression and somatic symptoms related to HIV disease. Only 73% of subjects completed the

study because of complaints of agitation, anxiety and insomnia at weeks 1 and 3. Because of the limited sample size, no differences in efficacy could be ascertained. In another 6-week trial of paroxetine in 10 HIV-positive patients with major depression, significant improvements in HAM-D scores were noted between weeks 2 and 6.<sup>97</sup> Overall, these studies seem to show that SSRIs are effective in reducing depressive symptoms in HIV-seropositive patients and may be better tolerated than traditional TCAs.

#### **Newer antidepressant agents**

Recent studies suggest that several of the newer antidepressant agents may be useful for the treatment of depression in HIV-seropositive patients. In an open trial of nefazodone in 15 outpatients, the response rate was 73% and there were few adverse effects.<sup>98</sup> However, reports of nefazodone-induced liver toxicity<sup>99</sup> may be relevant, given that many patients with HIV infection also have hepatitis B and C infection. Mirtazapine has also shown some benefit for patients with HIV infection, promoting weight gain and decreasing nausea; however, its sedating side effects can be problematic. In a recent 6-week open-label, flexible-dose trial of sustained-release bupropion in 20 HIV-seropositive depressed men and women, 12 patients attained remission at a mean dose of 265 mg/day. Fourteen of the patients reported some adverse events, and 5 patients discontinued the study because of side effects (panic attacks, agitation and irritability).<sup>100</sup>

Reboxetine, a selective norepinephrine reuptake inhibitor that is currently marketed in Europe, was studied in an open trial of 20 HIV-seropositive men with depression.<sup>101</sup> At 12 weeks, the 15 patients completing the trial showed at least a 50% reduction in symptoms at a dose of 8 mg/day. The 5 patients who discontinued the study did so because of side effects of insomnia, shivering and sweating. Overall, these open trials of newer antidepressants suggest efficacy similar to that observed in the controlled trials of TCAs and SSRIs, but controlled trials of the newer agents have lacked HIV-seropositive subjects.

#### **Psychostimulants and novel agents**

Methylphenidate and dextroamphetamine have been used in the treatment of depression in chronic medical illness, and both have been studied in placebo-controlled trials in patients infected with HIV. Fernandez et al<sup>98</sup> compared treatment response of desipramine and methylphenidate in 15 subjects, with both drugs leading to improvements of 50%. However, the desipramine-treated patients exhibited more side effects including dry mouth, anxiety and insomnia, consistent with previous studies of imipramine.<sup>92,93</sup>

Wagner et al,<sup>102</sup> in an open trial of dextroamphetamine treatment of 24 patients with AIDS and depression who exhibited debilitatingly low energy levels, found a response rate of 75%. Improvements in mood and energy coincided with significant reductions in HAM-D scores, which were noted as early as week 2. Although systematic follow-up evaluations were not available, the treatment effects were

maintained over 2 years. A placebo-controlled trial of dextroamphetamine showed a significant improvement in initiative and mood in 73% of depressed patients assigned to the drug and 25% of those receiving placebo.<sup>103</sup> These observations warrant further study.

HIV-associated reductions in testosterone levels have been correlated with changes in mood, appetite and sexual function.<sup>104</sup> Studies examining the effects of testosterone supplementation on depression<sup>104,105</sup> and the adrenal steroid dehydroepiandrosterone<sup>106</sup> have shown promise for improving mood as well as anabolic and androgenic parameters. Exercise may also augment improvement in psychologic and nutritional status in HIV-seropositive patients receiving testosterone therapy.<sup>107</sup>

### Mood stabilizers

Recent studies examining the efficacy of mood stabilizers for the treatment of manic symptoms in HIV-infected patients indicate that AIDS-associated manic states are responsive to available anti-manic agents, but patients are more prone to neurocognitive side effects.<sup>108,109</sup> The results of these mainly open trials should be interpreted with caution as they are limited by small sample sizes and other methodologic difficulties.

When mood stabilizers are used to treat HIV-infected patients, knowledge of the metabolic pathways of psychotropic agents and the influence of particular agents on overall drug metabolism is important. For example, carbamazepine may interact with antiretrovirals. As a potent inducer of CYP3A enzymes, carbamazepine may increase the metabolism of protease inhibitors such as indinavir<sup>110</sup> and non-nucleoside reverse transcriptase inhibitors such as delavirdine.<sup>111</sup> Conversely, because ritonavir is a potent enzymatic inhibitor of the CYP3A system that may raise serum levels of carbamazepine, carbamazepine toxicity is possible when these 2 drugs are used together.<sup>112</sup> In addition, medical conditions or treatments occurring during the course of HIV illness, such as hypoalbuminemia or administration of antibiotics, could elevate the free drug concentration of valproic acid.

In a case series of HIV-seropositive gay men, lithium was not well tolerated, and signs and symptoms of toxicity developed in 8 out of 10 patients, 7 of whom needed to stop treatment.<sup>108</sup> Dehydration and fluid shifts associated with diarrhea have also been reported.<sup>90</sup>

### Antipsychotic agents

The use of antipsychotic agents in the treatment of mood disorders and psychotic disorders in HIV-infected patients is less well studied. Reports indicate that HIV-seropositive patients may be more sensitive to the extrapyramidal side effects associated with dopamine receptor antagonists. This may be related to the psychomotor slowing associated with HIV infection.<sup>84</sup> In a case series of 21 patients with psychotic symptoms (12 of whom had mania with psychotic features), risperidone was efficacious and produced fewer side effects

than conventional neuroleptics, although some studies have reported increased sensitivity to both older and newer antipsychotic agents.<sup>113</sup> An open-label study using clozapine reported improvements in psychotic symptoms in HIV-infected patients without extrapyramidal symptoms.<sup>114</sup> Clearly, controlled trials are needed in this area.

### Psychopharmacology summary

The studies reviewed above point to the need for more controlled trials of psychopharmacologic agents for psychiatric disorders in people living with HIV, but they also provide support for the efficacy of these agents in the treatment of mood disorders. A recent study by Vitiello et al,<sup>115</sup> however, points out that even when psychiatric disorders are recognized, they may remain untreated. In a study of the prevalence and patterns of use of psychotropic medications, for which these authors used a probability sample of 1561 HIV-seropositive patients with a diagnosis of major depression or dysthymia, only 43% of subjects reported ever receiving antidepressant medication. They also noted that African-American HIV-seropositive patients with depression were less likely to receive antidepressant medications than any other ethnic group. This is especially concerning given that this group is overrepresented in the HIV-infected population.

In the treatment of HIV-infected patients, strategies similar to those that apply for treatment of psychiatric disorders in the general population should be followed. Knowledge of the metabolic pathways of psychotropic agents as well as the major antiretrovirals are useful because of potential adverse drug–drug interactions. Reassuringly, there are no absolute contraindications specific to this patient population other than an increased sensitivity to side effects, which has been widely reported.<sup>90,116</sup>

The use of nontraditional agents (such as herbal agents) to treat psychiatric symptoms must also be monitored in HIV-seropositive patients. An open-label study revealed that the serum concentration of the protease inhibitor indinavir, metabolized by the 3A4 isoenzyme system, was markedly reduced by the administration of St. John's wort, a 3A4 inducer.<sup>117</sup> This reduction in indinavir levels was significant enough to potentially cause drug resistance and treatment failure. Similar caution should be exercised with concomitant use of alcohol or recreational drugs such as Ecstasy: alcohol can increase the risk for pancreatitis,<sup>118</sup> and Ecstasy has proven nearly fatal in combination with ritonavir.<sup>119</sup>

### Psychoneuroimmunology of HIV infection

Despite the development of effective combination antiretroviral therapies for HIV that have lengthened the life expectancy of HIV-infected patients, there continues to be wide variability in the course of HIV disease, specifically in the length of time before diagnosis of AIDS or death. These findings have prompted investigators to look at other factors that might influence the disease, such as stress, depression and other psychosocial factors.

Evidence has been mounting that chronic stress and dys-

functional coping may affect the immune system, exerting potentially harmful effects on cellular immunity,<sup>120-123</sup> but studies assessing the effects of depression on immunity in HIV-positive patients have yielded conflicting results.<sup>124-126</sup> One research group has shown significant effects of stress on cellular immune parameters,<sup>127</sup> and depressive symptoms (especially in the presence of severe stress) were related to declines in several lymphocyte subsets (NK cells and CD16, CD56 and CD8 cytotoxic suppressor cells) over a 2-year period in HIV-seropositive men.<sup>128</sup>

Additional evidence is emerging from longitudinal studies to suggest that depression is associated with disease progression or death in HIV-infected subjects. Among 7 prospective studies with long-term follow-up, 6 studies found that depression was associated with HIV disease progression<sup>62,129,130</sup> and death.<sup>61,131,132</sup> However, no relation was found between baseline depression and progression to AIDS or decline in CD4 lymphocytes in the Multicenter AIDS Cohort Study.<sup>133</sup> Other major longitudinal studies with shorter follow-up periods have shown no relation of stress and depression to changes in CD4 cell counts.<sup>124,125</sup>

While most studies have focused on men, recent data support the negative impact of depressive symptoms on immunity in women. Ickovics et al<sup>61</sup> have shown that depression among women infected with HIV is associated with HIV disease progression and mortality. Furthermore, depressive symptoms have been shown by another group to be significantly associated with higher counts of activated T cells (CD8+, CD38+, DR+) and higher viral loads, all of which are associated with advancing HIV disease.<sup>134</sup> Major depression was also associated with reductions in NK cell activity.<sup>134</sup>

## Conclusions

People infected with HIV have a better life expectancy today than in the early days of the epidemic, mostly because of recent advances in antiretroviral therapy. Although the relations among neuropsychiatric symptoms, neuroendocrine peptides and the immune system remain unclear, the emergence of neuropsychiatric complications during HIV infection or AIDS can have serious effects if they are not identified promptly. Whether these complications are due to the direct or indirect effects of HIV on the brain or to the effects of stress and depression, careful diagnosis and treatment are necessary. Continued investigation to elucidate potential causal mechanisms holds the promise of refinement of existing therapies and development of new treatment options.

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