

EDITORIAL REVIEW

Neurologic and psychiatric complications of antiretroviral agents

Glenn J. Treisman^{a,b} and Adam I. Kaplin^{a,c}

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Introduction

Much progress has been made in treating HIV infection in the last several years. In the USA, mortality among people infected with HIV decreased from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in 1997 [1], and people infected with HIV are now living longer, healthier lives [2]. What was once considered a progressive, ultimately fatal disease has become, in developed countries, a chronic condition that often can be managed long term.

In large part, this change has resulted from the introduction of protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), and non-nucleoside reverse transcriptase inhibitors (NNRTI) in highly active antiretroviral treatment (HAART) regimens [3]. Now, carefully selected combinations of these agents can bring viral loads below detectable levels, increase CD4 T-lymphocyte counts, and improve immune function.

However, investigators have begun to realize that HIV cannot be completely eradicated with the treatments that are currently available and that long-term HAART may have side-effects that are severe or health-

complicating enough to require modification or temporary cessation of treatment. Even when the virus is virtually undetectable in the blood, it appears to remain sequestered in host reservoirs that are inaccessible to HAART [4] and may provide a source for viral rebound if therapy is withdrawn [5]. With the treatments currently available, HAART will probably need to continue for the patient's lifetime, and clinicians need a thorough understanding of the health implications associated with long-term HAART, the potential complications of HIV infection even in the absence of overt illness, and the strategies for maintaining treatment adherence and minimizing treatment side-effects.

Unfortunately, complications of HAART and complications of HIV infection, particularly in patients with advanced disease and AIDS, overlap significantly. Among health risks that may be associated with HIV or HAART are neurologic complications (such as myelopathy, neuropathy and neuropathic pain, changes in cognition, and dementia), and psychiatric complications (such as mania, depression, schizophrenia, and substance abuse and dependence). The purpose of this review is to identify specific neurologic and psychiatric symptoms and disorders that may arise in adult HIV patients as a result of both HIV infection and antire-

From the ^aDepartment of Psychiatry and Behavioral Sciences, ^bthe Department of Internal Medicine and the ^cDepartment of Neuroscience, at the Johns Hopkins University School of Medicine, 720 Rutland Avenue Baltimore, Maryland 21205-2196, USA.

Correspondence to: G. J. Treisman, Johns Hopkins University School of Medicine, Meyer 4-119, Baltimore, MD 21205-2185, USA.

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troviral treatment, to discuss current theory about the etiology of these disorders, and to suggest strategies for their diagnosis and management.

Neurologic complications associated with HIV/AIDS

HIV enters the central nervous system (CNS) early in the course of infection. If the infection progresses to symptomatic disease and AIDS, various nervous system pathologies may appear, including opportunistic infections of the CNS (e.g., toxoplasmosis, cryptococcal meningitis), primary CNS lymphoma, progressive multifocal leukoencephalopathy (PML), peripheral or sensory neuropathy and HIV-associated dementia [6,7].

HIV-associated dementia is a progressive subcortical dementia that prior to the development of antiretroviral therapies was almost always fatal [8]. Symptoms of HIV-associated dementia include slowing of motor and mental function with memory loss and language deficits, which are less prominent [9]. Risk factors for developing HIV-associated dementia include older age, decreased body mass, and persistent physical symptoms [6]. In patients with more advanced HIV disease, HIV-associated dementia may have an incidence of 4–7% and an estimated cumulative prevalence of 15% [10], and may severely impair patients' daily functions [11].

HIV may also cause cognitive changes early in the course of infection, as suggested by Grant et al. [12]. These investigators observed neuropsychologic changes not only among patients with AIDS or with AIDS-related complex, but also in patients who were HIV-seropositive only. Common alterations included problems with abstract reasoning, learning difficulties, and slowed information processing [12]. Other studies have suggested that CNS involvement early in HIV infection produces mild cognitive impairment in people who are otherwise asymptomatic [13,14]. Although mild cognitive or motor impairment does not necessarily progress to more severe HIV-associated dementia, even mild cognitive impairment may affect work performance and result in unemployment [15]. Because the Mini-Mental State Exam used to assess cognitive impairment is not a sensitive screen for cognitive deficits early in the course of HIV-associated dementia, alternative screening exams have been developed [16]. Sustained psychomotor slowing is associated with HIV-associated dementia, AIDS, and death [17].

Peripheral neuropathies have been reported in 15–50% of people with AIDS. They are among the most common neurologic manifestations seen in patients infected with HIV and may appear soon after infection or later in the disease process [18,19]. Treatment with

the dideoxynucleosides didanosine, zalcitabine, and stavudine may exacerbate or trigger HIV-associated neuropathy [7].

Some patients develop myelopathy as a later consequence of HIV infection. HIV-associated myelopathy, which involves the degeneration of nerves in the middle and lower thoracic spinal cord, occurs in 22–55% of patients with HIV [20,21].

Psychiatric complications associated with HIV/AIDS

HIV infection increases the patient's risk for various psychiatric disorders, including depression, mania, psychosis, and substance abuse [22]. Antiretroviral therapy may precipitate or worsen psychiatric disorders [23–25].

Mania may appear in patients with AIDS who have mild cognitive impairment, and is observed in both early- and late-stage disease [26]. Mania has also been observed shortly after initiation of zidovudine treatment in patients with no prior psychiatric history.

Other mood disorders, including depressive disorders, have been associated with HIV infection. Although findings from several studies have suggested that depression is no more prevalent in patients with HIV than in patients at risk for HIV infection, a large-scale meta-analysis of 10 studies has shown a twofold increased risk for depression among patients with HIV relative to patients at risk for infection [27]. In addition, a study by Bing and colleagues has shown an increased prevalence of major depression among patients receiving treatment for HIV infection [28]. These findings may reflect an increased vulnerability to develop depression associated with groups at risk for HIV or may be explained, in part, by depression leading to carelessness or increased high-risk behavior predisposing to infection with HIV. Depression also may be a consequence of HIV-induced brain injury or antiretroviral treatment [6,26,29–31]. Lyketsos et al. have shown an increased prevalence of major depression in association with late-stage HIV disease [32].

Accumulating evidence suggests that HIV infection may be directly linked to the onset of psychosis, a term used to describe patients with gross distortions of reality, thought disorders, hallucinations, and delusions. Psychosis can be a manifestation of psychiatric conditions such as delirium, affective disorders, or schizophrenia, but it also may occur in the absence of these conditions. Estimates of the prevalence of new-onset psychosis in patients with HIV range from 0.5 to 15% (which is considerably higher than would be expected

in the general population) [33,34]. One study that compared 20 HIV-positive patients with new-onset psychosis (and no prior psychotic episodes or current substance abuse) with 20 non-psychotic HIV-positive patients found that the former group showed a trend toward greater global neuropsychological impairment [34]. The authors suggested that new-onset psychosis in these patients may be one manifestation of HIV-associated encephalopathy. History of substance abuse also was more common among patients with psychosis, suggesting an increased brain vulnerability; however, they also had significantly higher mortality at follow-up, suggesting that they had more advanced HIV disease [34].

HIV infection may exacerbate psychiatric conditions, including major depression, bipolar disorder, and schizophrenia. One study of patients who had schizophrenia before they were diagnosed with HIV infection found that the patients had more severe depressive episodes and reduced tolerance to psychopharmacologic medications (including benzodiazepines and neuroleptics) after infection than before [35]. Although methodological issues make such studies difficult, more research is needed to understand better the role of HIV infection in worsening pre-existing psychiatric disorders.

Various complications of HIV infection – including opportunistic infections of the CNS, tumors, systemic disease, and adverse effects of medications – may mimic psychiatric illnesses, producing symptoms that resemble mania, depression, psychosis, or drug intoxication. In all cases, any underlying medical problem should be addressed. The acute onset of psychiatric symptoms in a patient with no such prior history should prompt a complete neuropsychiatric evaluation, toxicology and laboratory screens, and when appropriate, neuroimaging studies and lumbar puncture, to help identify possible causes.

Etiology of neurologic and psychiatric complications in HIV/AIDS

The pathogenesis of HIV infection within the brain and its relationship to neurologic and psychiatric complications remains obscure, but there is evidence that cellular and molecular components of the immune system are involved [11].

Several different mechanisms may explain the effects of HIV on the CNS. Researchers have hypothesized that pathogenesis begins with viral penetration of the CNS and associated loss of integrity of the blood–brain barrier. This may allow cellular and non-cellular inflammatory components of the immune system to enter the CNS, resulting in damage to neurons and non-

neuronal support cells [3]. There is controversy over the separate roles of the virus, immune mediators, opportunistic infections, and medications in causing direct CNS injury, and as yet, there is little evidence that any single mechanism explains all CNS injury.

Some studies have examined viral load and CD4 cell counts, measures typically used to monitor immunologic function in patients with HIV infection, as potential markers of CNS injury and vulnerability to CNS complications. A study that followed viral loads and CD4 cell counts in a large cohort of HIV-infected men without AIDS found that relatively high plasma HIV RNA (> 3000 copies/ml) and low CD4 T-lymphocyte counts ($< 500 \times 10^6$ cells/l) were predictive of both dementia and neuropathy [36]. The authors suggested that effective suppression of HIV may reduce the risk of developing these neurological complications.

Based on evidence of basal ganglia dysfunction in HIV-associated dementia [37], Berger *et al.* proposed that microvascular abnormalities would be found in the basal ganglia of patients with this condition [38]. Using time-course magnetic resonance imaging, these investigators observed increased enhancement – both immediate and late – in basal ganglia of individuals with HIV infection and moderate-to-severe dementia, relative to HIV patients without dementia. These data suggested that increases in regional cerebral blood volume and disruption of the blood–brain barrier have an etiologic role in the development of HIV-associated dementia.

Most HIV DNA in the brain has been found in macrophages/microglia, often near apoptotic neurons, suggesting that cytokines produced by the infected cells might contribute to neuronal destruction [39]. Macrophages may infiltrate the CNS by interacting with the endothelial cells that form the blood–brain barrier, causing endothelial cell damage and disrupting the barrier [40]. Chemokines (cytokines that act as macrophage attractants) and their receptors on neurons and glial cells appear to play a central role in HIV entry into the CNS and eventual cellular destruction [41,42].

Synaptic damage, without neuronal loss, has been observed in patients with mild HIV-associated cognitive disorders. Using synaptic density as an indicator of damage in post-mortem brain samples from HIV-infected patients, Everall and colleagues found that reduced synaptic density correlated significantly with ante-mortem neuropsychological functioning, and stressed that early diagnosis and treatment could potentially reverse synaptic damage and prevent cognitive decline [43].

Evidence is accumulating to suggest roles for several HIV proteins, including glycoprotein 120 (gp120),

HIV-1 negative factor (Nef), and transactivating protein (Tat), in HIV-induced neuropathogenesis. For example, the viral envelope protein gp120 appears to bind to rat dorsal root ganglia and human neuroblastoma cells [44], and in rats exposure to gp120 has been shown to cause swelling and increase tumor necrosis factor in the sciatic nerve trunk, induce astrocyte and microglial infiltration into the spinal cord, and cause neuropathic pain behaviors [45]. *In vitro*, studies have shown that Nef induces macrophage chemotaxis [46] and acts as a potent neurotoxin [47]. Astrocytes treated with Tat *in vitro* produced pro-inflammatory cytokines and chemokines that may contribute to neuronal injury [48]. Tat also stimulates macrophage production of metalloproteinases, enzymes that are expressed at increased levels in certain neurologic diseases and in the brain tissues of patients with AIDS [49]. Although the significance of these laboratory findings for patients with HIV or AIDS remains to be clarified, it is probable that many of these mechanisms combine to produce the neurologic and psychiatric changes seen with HIV infection and AIDS. Identifying and characterizing the mechanisms involved may open new avenues for prevention and treatment.

Antiretroviral agents associated with neurologic complications

CNS complications in patients with HIV, including psychiatric syndromes, delirium, seizures, and cognitive impairment, may in some cases reflect consequences of treatment with antiretroviral drugs that penetrate the CNS. For example, zidovudine and efavirenz, both considered attractive choices for patients with CNS complications because they have good CNS penetration, are themselves associated with potentially significant neuropsychiatric complications. In contrast, treatment with interferon, which has poor CNS penetration, is also associated with a high rate of CNS complications. Peripheral neurologic complications including neuropathic pain, neuropathic weakness, and denervation syndromes have been attributed to various toxic and metabolic factors in association with antiretroviral treatment. In managing neurologic complications, it is important to distinguish, when possible, between symptoms related to the HIV disease process and side-effects of HAART. To make such distinctions, clinicians need to understand which antiretroviral agents may cause neurologic and psychiatric symptoms.

NRTI

Zidovudine, a nucleoside analogue that inhibits replication of HIV by interfering with viral reverse trans-

criptase, was the first agent to significantly reduce mortality and opportunistic infections in HIV-infected patients [50]. Zidovudine has been found effective, at high doses, in slowing the progression of AIDS dementia, and can penetrate the blood-brain barrier [51]. Zidovudine is therefore an attractive choice in HAART regimens targeting dementia and other CNS complications of HIV. However, its CNS penetration may also explain the confusion, agitation, and insomnia in up to 5% of people who took zidovudine for 1 year [23].

In addition, there are anecdotal reports of psychiatric symptoms, including mania and depression, in patients treated with zidovudine. Several case reports document manic episodes in association with zidovudine treatment, even in patients with no previous psychiatric history [9,52,53]. In some patients, mania was severe enough to necessitate hospitalisation [9,52,53]. In recent years, fewer problems have been reported, in part because zidovudine is now used in lower doses—approximately 600 mg/day (or 300 mg twice a day) versus the up to 2000 mg/day doses used in the pre-HAART era.

The mechanisms involved in zidovudine-associated psychiatric effects are unknown. For some patients, dose reduction is beneficial, but for others, discontinuation may be necessary. Discontinuing zidovudine treatment has been shown to rapidly reduce manic symptoms (and symptoms returned upon reintroduction of the drug, suggesting a causal relationship) [9]. However, patients have been able to resume zidovudine treatment if they also received treatment for mania [9,52].

Other adverse neurologic effects of zidovudine treatment are insomnia, myalgia, and severe headaches [54]. Zidovudine also has been associated with seizures, particularly in cases of overdose, that have on rare occasions been fatal [55–58]. Because HIV infection is associated with similar neurological problems, it is important to exclude other causes before attributing them to zidovudine treatment. However, the severity of these side-effects suggests the need to closely monitor patients taking this drug.

Neurologic symptoms associated with other NRTI may include headache, malaise, and fatigue; [59] for most patients, these symptoms are not severe enough to discontinue HAART. A more serious side-effect, peripheral neuropathy, may be seen with didanosine, zalcitabine, or stavudine treatment but not with zidovudine treatment [24,25]. The mechanism is unknown, but *in vitro* studies have shown that zalcitabine, stavudine, and didanosine – but not zidovudine – inhibit nerve growth factor (NGF)-stimulated differentiation of a neuronal cell line [60].

For patients with peripheral neuropathy, symptomatic

treatment with ibuprofen or topical analgesic creams can sometimes be effective. Tricyclic antidepressants have been used to manage pain in patients with HIV-associated peripheral neuropathy; however, one controlled trial found that these drugs were no more effective than placebo in relieving symptoms of neuropathy [61]. In clinical practice, we have found tricyclic antidepressants and other treatments can be partially effective, but for many patients, the pain of neuropathy can be severe, irreversible, and debilitating. Therefore, patients with HIV who develop neuropathy require careful evaluation to determine the risks and benefits of continuing NRTI treatment. In some cases, decreasing dosage may help, but in others, the contributing drug must be discontinued.

NNRTI

Three NNRTIs – efavirenz, delavirdine, and nevirapine – are currently available for the treatment of HIV infection. They are usually prescribed in combination with NRTI. Clinical trials of delavirdine and nevirapine revealed few adverse events affecting the CNS; therefore, the relatively more substantial CNS side-effects seen in clinical trials of efavirenz were unexpected.

CNS side-effects observed with efavirenz include dizziness, headache, confusion, stupor, impaired concentration, agitation, amnesia, depersonalization, hallucinations, insomnia, and abnormal or vivid dreams [62–64]. For most patients, these side-effects resolve within 6–10 weeks of starting treatment, but for some patients, symptoms seem to wax and wane long term. In pivotal clinical trials, more than 50% of patients taking efavirenz experienced some CNS effects, although few patients discontinued treatment as a result [65]. CNS disturbances were seen immediately after efavirenz treatment began [64]. For most patients, these disturbances diminished or resolved within 2 months. Neither dose reduction nor dose splitting shortened or reduced the intensity of symptoms [64].

In a study of 48 patients designed to decrease efavirenz-associated CNS side-effects, efavirenz was titrated up over a 2-week period to a maximum dose of 600 mg (taken once daily at bedtime) [66]. Interim results revealed that 17 patients (35%) experienced at least one moderate or severe CNS side-effect; another 12 patients (25%) reported mild CNS side-effects. Two patients discontinued treatment because of CNS side-effects.

Psychiatric effects also have been noted with efavirenz, though they occur less frequently than neurologic effects. However, when efavirenz-associated psychiatric

effects occur, they may be serious and may include anxiety, depression, and suicidal ideation [62–64]. A small study comparing patients who took efavirenz or PI for a mean of 45 weeks documented higher scores on psychometric scales of anxiety and hostility in the efavirenz group than in the PI group—effects that were subtle but persistent [67].

With continued treatment, most overt efavirenz-associated CNS effects typically diminish or disappear. In our clinical experience, many patients learn to manage the symptoms within 2–4 weeks of onset. Some patients find that bedtime dosing makes symptoms more tolerable. A small dose of sedative-hypnotic medication may help to prevent disturbing dreams [64]. A recent study by Marzolini *et al.* demonstrated the value of monitoring plasma efavirenz levels in patients with persistent CNS side-effects. The study found that CNS toxicity was three times more frequent in patients with high, compared to low, plasma efavirenz [68]. Patients taking efavirenz who have a history of depression or other mental health problems should be monitored closely. If symptoms of depression are treated aggressively, patients may be able to continue efavirenz treatment.

Clinicians should advise patients of possible CNS effects of efavirenz, and should watch for changes in behavior, cognition, or mood. If side-effects persist or patients find them intolerable, a switch in HAART regimen may be appropriate. Although efavirenz is often a first-line treatment, many patients receive it after experiencing treatment failure on earlier HAART regimens. Therefore, patients who switch to efavirenz and then experience neurologic or psychiatric side-effects may have limited options for future antiretroviral treatment. It is important to carefully consider risks and treatment alternatives for these patients.

PI

The combination of HIV PI with the older antiretroviral agents brought about substantial decreases in viral loads and opportunistic infections with concomitant increases in CD4 T-cell counts. As a result, HIV-associated morbidity and mortality has declined dramatically in recent years [1,69].

Although PI may have neurologic side-effects, they tend to be variable and less prominent than those seen with NRTI or NNRTI. Neurologic symptoms may occur more often with ritonavir or ritonavir/saquinavir combination treatments than with indinavir treatment [70]. One study has correlated higher plasma concentrations of ritonavir with a higher risk of (unspecified) neurologic side-effects [71].

Management of neurologic and psychiatric complications associated with HIV/AIDS

Because some of the neurologic symptoms of HIV infection, such as cognitive impairment, HIV-associated dementia, and peripheral neuropathy, may result directly from the effects of viral infection on the nervous system [12–14], researchers have hypothesized that the use of HAART to reduce viral load might ameliorate these and other neurologic and psychiatric symptoms. In addition, other symptom-specific treatments are being used to manage the symptoms and pathology of HIV-related neurologic and psychiatric complications.

Effects of suppressing viral load

Not long after zidovudine was proven effective in decreasing viral load, researchers began investigating its effects on HIV-associated neurologic symptoms. Before combination treatments were available, several studies reported successful treatment of AIDS dementia with zidovudine monotherapy. Early data suggested that high doses of zidovudine might decrease the development of HIV-associated dementia by decreasing viral load in the CNS; [72] a subsequent double-blind, placebo-controlled study found that zidovudine treatment partially reversed HIV-associated cognitive defects in patients with AIDS and AIDS-related complex [73]. However, a long-term study of HIV-infected men found that zidovudine, when given at doses used in clinical trials in the USA, did not prevent development of HIV-associated dementia [7].

Because PI have limited CNS penetration, their ability to affect CNS viral load and effectively treat neurologic and psychiatric components of HIV infection was thought to be limited [74]. However, there is now evidence that PI-containing HAART regimens are extremely effective for the treatment of several neurologic complications of HIV/AIDS. For example, PI-based HAART increased survival among patients with PML [75] and can reverse white matter abnormalities in patients with HIV-associated encephalopathy [76]. PI-based HAART also reversed neurodevelopmental and neuroradiologic abnormalities in an HIV-infected child [77].

An open-label prospective study of 26 patients with neurocognitive impairment on HAART regimens consisting of one PI and two NRTI revealed significant progressive decreases in neurocognitive impairment, with parallel decreases in plasma viral load, after 6 and 15 months of treatment [78]. Over time, these patients improved significantly on tests of concentration, speed of mental processing, memory, fine motor functions, and visual/spatial ability. In another study, Chang et al. used proton magnetic resonance spectroscopy to measure cerebral metabolites in the frontal lobes and basal

ganglia of patients with mild HIV-associated dementia before and after HAART [79]. They found that PI-containing HAART improved cognitive symptoms in these patients; these improvements were reflected in magnetic resonance imaging measures and paralleled declines in systemic viral load.

Martin et al. have examined the impact of HAART (mostly indinavir-based) on neuropathy-associated pain and viral load in 49 patients with HIV [80]. After 8 months, patients whose viral loads decreased in response to treatment also had significant improvements in pain threshold.

A study by d'Arminio-Monforte et al. examined the effects of several antiretroviral regimens on the development of CNS complications, including brain toxoplasmosis, cryptococcal meningitis, PML, and AIDS dementia complex, in a group of patients with AIDS [81]. At enrollment, patients had CD4 cell counts $\leq 200 \times 10^6/l$ and no CNS complications. The patients were monitored every 3 months. Because the study was carried out between 1993 and 1998, antiretroviral treatment was variable: some patients received no treatment; some were on a single antiretroviral agent, and some received a combination of two or three agents (two NRTI plus a PI or a NNRTI). Analysis of the data revealed a significant decrease in the overall incidence of CNS complications over time, and the decrease was inversely correlated with the number of antiretroviral agents used. CD4 T-lymphocyte counts and antiretroviral treatment were significant predictors of the development of CNS complications.

To determine whether PI-based HAART could reverse depression in patients with HIV, Low-Beer et al. measured depressive symptoms in a group of men and women before and 1 year after treatment with PI-containing triple combination therapy. The investigators found that of 453 participants, 234 (52%) were depressed before HAART began. After 1 year, the rate of depression declined (to 207, or 46%; $P = 0.085$). Although this change was not statistically significant, patient scores on a total depression scale and on many subscales improved significantly. Specifically, the investigators observed improvements in total scores ($P = 0.001$), depressive mood ($P = 0.002$), and positive affects ($P = 0.005$) on the Centre for Epidemiologic Studies-Depression scale. Improvements in depression paralleled improvements in CD4 cell counts [82].

Effects of symptom-specific treatments

Peripheral neuropathy

The discomfort experienced by people with HIV-associated peripheral neuropathy is often refractory to standard treatments for pain [18]. For example, a placebo-controlled study of amitriptyline and mexiletine in patients with HIV-associated peripheral

neuropathy found no significant improvement in pain intensity, relative to placebo, with either treatment [83]. Similarly, a randomized, placebo-controlled study of the efficacy of acupuncture, amitriptyline, and a combination of the two treatments for pain relief in patients with HIV-associated peripheral neuropathy found that none of the treatments worked better than placebo [61].

Recently, newly devised approaches to pain treatment have shown promise for patients with HIV-associated neuropathic pain. For example, a recent pilot study showed that lamotrigine, an anticonvulsant, worked significantly better than placebo to decrease neuropathic pain in patients with HIV [84]. However, severe rash, a known side-effect of lamotrigine treatment, occurred more frequently than in studies of lamotrigine treatment in epilepsy. Another study examined the effects of NGF, a neurotrophic growth factor that stimulates regeneration of damaged nerve fibers, on HIV-associated peripheral neuropathy [85]. Results showed that twice-weekly injections of NGF reduced neuropathic pain in these patients. In addition, NGF was generally well tolerated, although some patients complained of injection-site pain.

Impaired cognition, attention, and concentration

Data from a recent pilot study suggest that a monoamine oxidase inhibitor, selegiline, may improve HIV-associated cognitive impairment [86]. Psychostimulants (e.g., methylphenidate) have been used to counter some symptoms of HIV-associated dementia—in particular, impaired attention and concentration [6].

Psychiatric complications

Experience with a wide range of psychiatric symptoms in patients with HIV suggests that these symptoms are amenable to treatment. Several studies now suggest that HIV-infected individuals with major depression can be successfully treated with various antidepressants [87,88]. Clinical trials of specific agents, including paroxetine [89], fluoxetine [90], and trazodone [91] show that these agents work better than placebo to relieve symptoms of anxiety and depression. Surprisingly, a recent study has shown that several new drugs – specifically, *cis*(Z)- and *trans*(E)-flupentixol, which are structural isomers of the neuroleptic flupentixol, and several derivatives of the antidepressants paroxetine and fexofenadine – can inhibit HIV replication. Additional research is needed, but the findings suggest that these agents may be useful in antiretroviral regimens for patients with HIV-related psychiatric complications [92].

In addition, several reports suggest that low doses of neuroleptics may be useful in treating HIV-associated psychosis [6,93]. However, treatment with standard neuroleptics may lead to drug-induced Parkinsonism.

Clozapine, an atypical anti-psychotic, was used successfully to treat HIV-associated psychosis in six patients who had developed drug-induced Parkinsonism previously, while taking typical neuroleptics [94]. However, clozapine is associated with a significant risk for bone marrow toxicity and aplastic anemia, and should be used with caution. In our experience, newer atypical neuroleptics, such as risperidone, olanzapine, and quetiapine are easier to use, have fewer associated toxicities, and may be as effective as clozapine for the treatment of HIV-associated psychosis.

General recommendations for pharmacologic treatment of psychiatric conditions in patients with HIV include: (i) start doses low and titrate up slowly; (ii) choose the simplest dosing schedule possible; and (iii) select drugs with side-effect profiles that can be used to therapeutic advantage (e.g., agents with sedating properties may be helpful for patients with insomnia). Although treatments must be chosen carefully and side-effects monitored closely, treatment of comorbid psychiatric disorders can have a positive impact on patients' quality of life.

Drug interactions

Most current literature on drug interactions describes the potential for interactions based on studies of cytochrome P450 activity and related mechanisms of drug metabolism. Data from controlled clinical trials correlating blood levels with clinical outcomes tend to be scarce; practical clinical experience is more likely to be documented as case studies or case series. Reports of clinically significant drug interactions may represent a common problem or reflect unique P450 expression in an individual. Therefore, simple reduction of drug interactions to tables may be misleading, and it is imperative that clinicians read the literature critically.

All currently recommended HAART regimens include at least three different antiretroviral drugs [95,96] with some regimens combining up to six different agents [97]. Given that many HIV patients take medications for comorbid disorders, the potential for multiple drug-drug interactions is great. In fact, two large retrospective studies of inpatients with HIV showed that approximately half of patients who were taking a PI were taking at least one other drug that could result in a drug interaction [98,99]. In the second study, about half of the drug interactions were considered potentially serious or even life-threatening [99]. Because our knowledge of drug interactions is far from complete, medications with great potential value for managing HIV-associated psychiatric and neurologic disorders may be unnecessarily avoided [3].

Many neuropsychotropic drugs and antiretroviral agents are metabolized via cytochrome P450 pathways [3]. Interactions among these agents are largely the result of induction or inhibition of cytochrome P450 enzymes. For example, among the PI, ritonavir has been shown to have the greatest inhibitory action on CYP 3A4 and has been associated with many drug interactions—including inhibitory effects on the metabolism of other antiretroviral agents, a property that is now being exploited to enhance the half-life and decrease dosing frequency of these drugs.

In addition to having effects on shared metabolic pathways, *in vitro* data suggest that some anticonvulsants, in particular, valproate, may increase viral replication [100–102]. However, the clinical implications of these findings are unclear, and a recent retrospective evaluation of 11 patients with HIV infection who were taking valproate for manic syndromes did not appear to increase viral load, so long as their antiretroviral treatment was adequate [103].

Interactions between anticonvulsants and antiretroviral agents can be complex. For instance, despite theoretical concerns that some PI may elevate circulating levels of anticonvulsants, one report has described a patient who experienced a seizure recurrence when circulating phenytoin levels dropped shortly after he began indinavir treatment [104].

Fundamental challenges in preventing harmful drug–drug interactions include the considerable individual variation observed in the degree to which cytochrome P450 enzymes can be induced or inhibited and the degree to which antiretroviral agents and other drugs induce or inhibit cytochrome P450 enzymes. These complexities are compounded when patients take multiple drugs, which makes predicting clinical drug interactions difficult in most circumstances.

Methadone interactions

Many people become infected with HIV through injecting drug use, and many patients on HAART may take methadone as well, as part of drug abuse treatment. The use of methadone may be programmatic, and health care providers in methadone clinics or similar environments may have limited experience with HAART regimens. Conversely, in hospital settings, methadone is generally prohibited, and because many HIV clinics are hospital-based, communication between HIV care providers and methadone clinics may be limited. In view of these difficulties and because maintaining therapeutic levels of methadone and HAART agents is critical, clinicians who treat these patients need to be aware of potential interactions.

Methadone metabolism is complex. Multiple cytochrome P450 enzymes are thought to be involved, and

circulating methadone concentrations can be affected by cytochrome P450 inhibitors or inducers. Interactions may also occur through effects on renal clearance and glucuronidation. Complicating our understanding of these interactions are the individual, idiosyncratic changes in methadone metabolism and excretion that cannot be predicted based on current knowledge.

Several studies have noted that people on methadone maintenance therapy may experience withdrawal symptoms following introduction of an NNRTI (i.e., efavirenz or nevirapine) [105–107]. In two of the three studies, concentrations of methadone were substantially reduced in the presence of the NNRTI [105,107]. These findings suggest the need to carefully monitor patients on methadone if NNRTI are introduced [107].

A small study examining methadone-zidovudine interactions found that blood concentrations of methadone were unaffected by zidovudine, but zidovudine concentrations were affected by methadone [108]. Specifically, circulating zidovudine levels rose enough to prompt concern about side-effects and toxicity. Based on these results, toxicity should be closely monitored in patients receiving methadone and zidovudine; the dose of zidovudine may need to be reduced [108].

Although methadone does not appear to affect PI levels, PI may have complex effects on methadone levels. In healthy volunteers, ritonavir decreased methadone levels only slightly [109]. However, there is one report of ritonavir causing withdrawal symptoms in a patient on methadone maintenance therapy [110]. In another study, nelfinavir reduced circulating methadone concentrations, but had no apparent clinical impact [111]. Although similar effects might be expected for other NRTI, in one study, methadone decreased concentrations and area-under-the-curve for didanosine and stavudine, possibly by reducing bioavailability [112]. Therefore, patients who take these antiretroviral agents with methadone may need to adjust the dose to maintain viral suppression.

Interactions with illicit/recreational drugs

Patients with HIV may also use illicit or recreational drugs, many of which may be metabolized via cytochrome P450 enzymes, and antiretroviral agents may affect blood concentrations of these drugs. For example, PI have been shown to slow the metabolism of methylenedioxymethamphetamine (MDMA or 'ecstasy'), which is metabolized via cytochrome enzyme P450 2D6, leading to increases in serum concentrations and potentially toxic effects [3]. There has been at least one report of a death thought to result from ritonavir–MDMA interactions [113]. Ritonavir affects mainly the 2A4 isozyme, but is also a substrate for 2D6, which

may explain the increased concentrations of MDMA in the patient who died. Another report describes a patient treated with ritonavir and saquinavir who experienced prolonged effects of MDMA and a near-fatal reaction from a small dose of gamma-hydroxybutyrate, a CNS antidepressant used recreationally for its

euphoric effects and ability to stimulate muscle growth [114].

Interactions with sildenafil

We often prescribe sildenafil (Viagra) for HIV-positive patients who are experiencing sexual dysfunction,

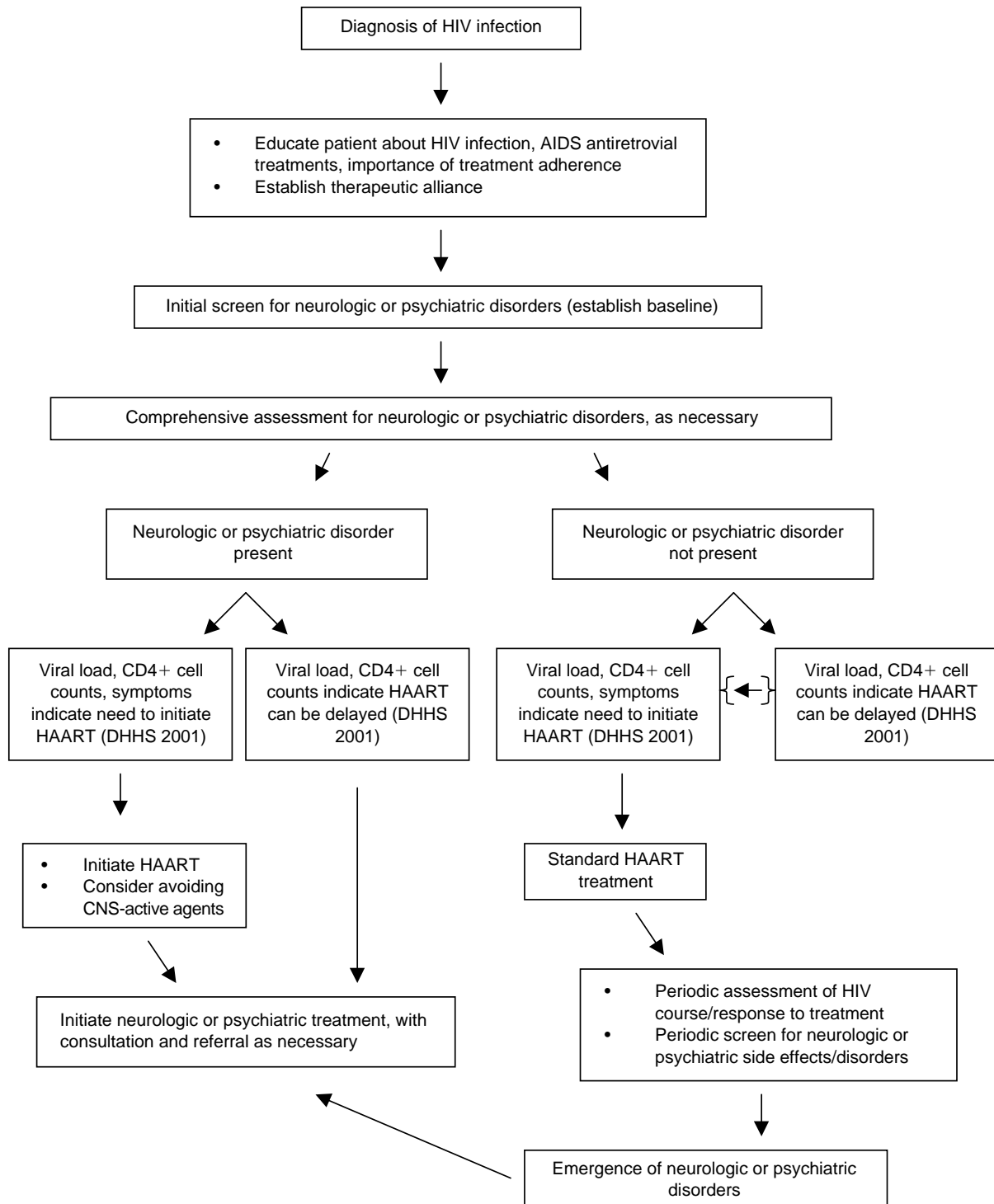


Fig. 1. Proposed strategy for monitoring and managing comorbid neurologic or psychiatric disorders in patients with HIV.

including patients with antidepressant-induced sexual dysfunction. Sildenafil also is metabolized by cytochrome P450 2A4 enzymes, and therefore may interact with antiretroviral agents. A recent study has demonstrated that indinavir, saquinavir, and ritonavir increase circulating levels and decrease clearance of sildenafil. This may be of particular concern in view of potential cardiac side-effects associated with sildenafil [69].

Guidelines for rational use of antiretroviral therapy in patients with comorbid psychiatric disorders

The main consideration in managing patients with HIV and comorbid neurological or psychiatric complications is to weigh the risks and benefits of continuing, altering, or stopping antiretroviral treatment. As we suggest in Fig. 1, psychiatric problems can often be treated without altering HAART regimens, but some conditions are severe enough to make a change in HAART desirable or necessary. Furthermore, patients on HAART who have exhausted most or all anti-

retroviral treatment options therapy should continue their current regimen and begin aggressive intervention for the complicating psychiatric disorder, whereas patients who have many potential treatment options may be changed to an alternate HAART regimen with less risk.

Patients who are taking medications known to affect psychiatric functioning, such as steroids, interferons, zidovudine, efavirenz, or other antiretroviral agents, should be monitored closely for psychiatric morbidity, side-effects, and toxicity. Some psychiatric side-effects of antiretroviral drug treatment may be transient or mild, while others may be severe or prolonged. For example, in our clinic, we find that depression occurs more frequently among patients taking efavirenz than with any other antiretroviral agent. Although depression resolves rapidly and spontaneously for many patients, for some, it may become a serious and even life-threatening problem. Thus, for some patients, it may be worthwhile to wait before considering changes in antiretroviral treatment; for others, immediate adjustments may be necessary.

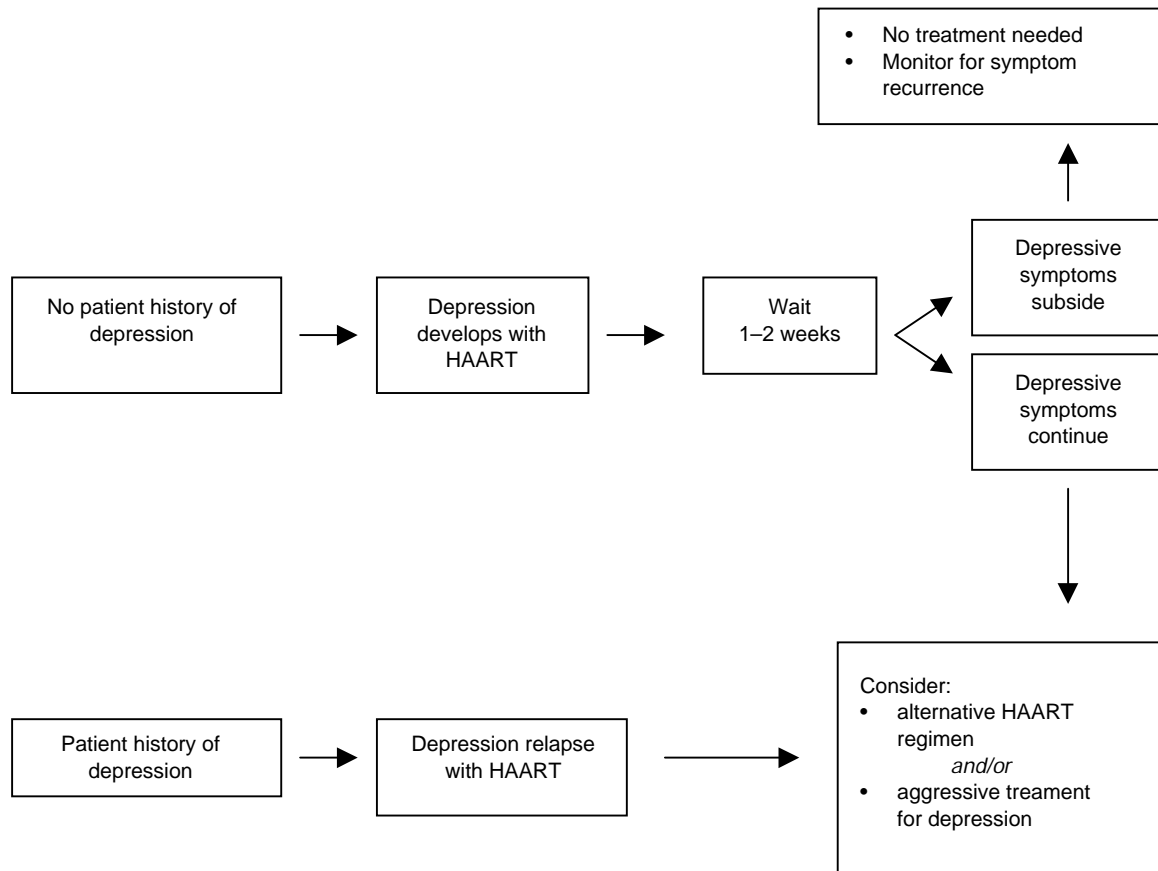


Fig. 2. Proposed strategies for managing depression in patients with HIV who have begun HAART.

Because patients with depression often respond well to treatment, they should, in general, receive such treatment before HAART begins or concurrently with the initiation of HAART. Brief guidelines for the treatment of depression in HIV patients have been published [90,105]. For patients who develop depression after beginning HAART, changes in HAART regimens may be unnecessary if symptoms resolve (Fig. 2). For patients with a history of depression prior to HIV infection, treatment issues are more complex. If a relapse of depression occurs after HAART initiation, a change in antiretroviral treatment may be necessary. For patients with severe depression before HAART begins, treatment to resolve or improve depressive symptoms may need to precede antiretroviral treatment (Fig. 3).

Studies have shown that people with psychiatric disorders often have very low rates of adherence to antiretroviral treatment regimens [115], and that conversely, treatment for psychiatric disorders improves adherence [30]. Thus, appropriate screening, prevention, and treatment of psychiatric disorders prior to or concurrent with HAART can enhance patient compliance.

Summary

Dramatic advances over the last decade have transformed HIV infection from a short-term, inevitably fatal disease to a chronic condition amenable to medical

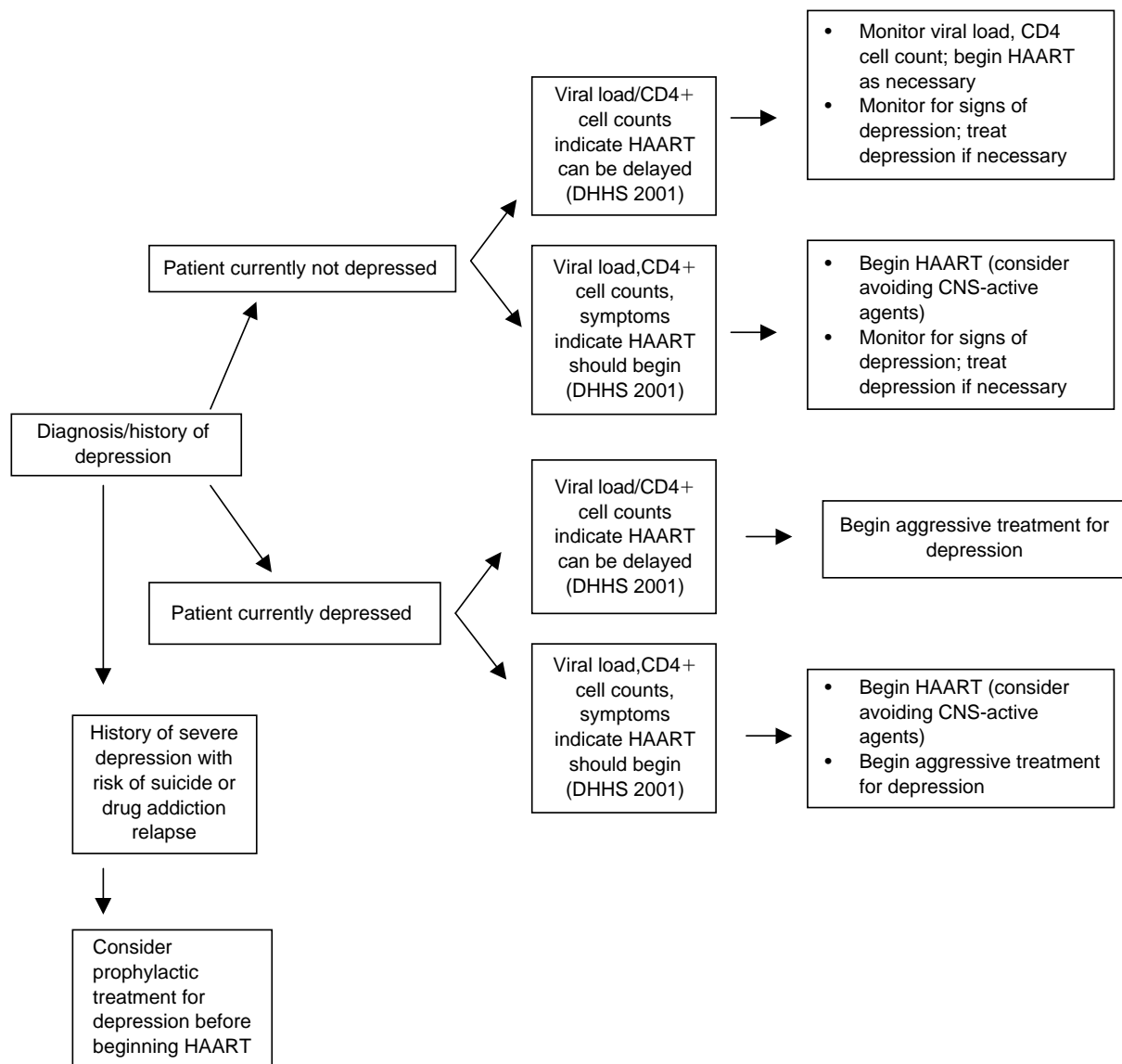


Fig. 3. Proposed strategies for managing depression in patients with HIV who have not started HAART.

management, similar to diabetes or congestive heart failure. The ability to monitor treatment and disease status by quantifying plasma viral load and CD4 T-lymphocyte counts has contributed to this transformation, but the most important contribution to this transformation has been the development of HAART.

However, experience has shown that both HIV infection and its treatment have neurologic and psychiatric consequences. In addition, a major challenge currently is the dramatic difference between predicted and actual percentages of patients whose HIV levels can be brought under control. Although research predicts that most patients should be able to attain persistent undetectable viral loads with HAART, only a minority actually do so.

Among barriers to successful treatment are psychiatric disorders that may place patients at risk for infection in the first place, contribute to the spread of infection by influencing high-risk behaviors, and compromise adherence to antiretroviral treatment. Patients with HIV and comorbid psychiatric disorders tend to require more time, effort, and resources than do other HIV-infected patients, at a time when the health care system is already beleaguered by cost containment measures. For the indigent HIV-infected population, mental health resources and illicit drug treatment resources are scarce.

People with psychiatric illness respond to medication and adhere to HIV treatment regimens better after treatment. Furthermore, it is possible that effective treatment of psychiatric disorders may curb risky behaviors that may contribute to transmission of HIV. Thus, it is important to recognize neurologic and psychiatric symptoms, to distinguish, when possible, between HIV-associated and HAART-related symptoms, and to implement appropriate treatment for comorbid neurologic or psychiatric disorders.

Despite the complexity of the patient population in the USA, we find that effective treatment for psychiatric disorders, when delivered in collaboration with effective HIV care, dramatically improves outcomes and quality of life. Successful treatment may also allow patients to achieve levels of function they may never have considered to be within their reach subsequent to their diagnosis of HIV. As new developments become available to help patients live more normal lives, it is essential for clinicians to have the skills and resources to assess and manage the disorders that hinder treatment of patients with HIV. This is critical not only in terms of cost containment and outcome measures, but as a matter of doing what is right for the vulnerable, underserved, and disenfranchised patients who currently get and transmit HIV at epidemic rates.

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