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Authors

Singer, Elyse J
Thames, April D

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Neurobehavioral Manifestations of HIV/AIDS: Diagnosis and Treatment

Elyse J. Singer, M.D.[*] and

Professor of Neurology Director, NeuroInfectious Diseases Program, David Geffen School of Medicine at UCLA, 710 Westwood Plaza Room A129, Los Angeles CA 90095

April D. Thames, Ph.D.

Assistant Professor of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, 740 Westwood Plaza, C8-746, Los Angeles CA 90095

Elyse J. Singer: esinger@mednet.ucla.edu; April D. Thames: athames@mednet.ucla.edu

Synopsis

Behavioral disorders are common in HIV-infected (HIV+) persons. The differential includes pre-existing psychiatric diseases, substance abuse, direct effects of HIV infection, opportunistic infection (OI), and the adverse effects of medical therapies. Many patients have more than one contributing or co-morbid problem to explain these behavioral changes. The differential should always include consideration of psychosocial, genetic, and medical causes of disease. Treatment strategies must take into account the co-administration of antiretroviral therapy and the specific neurological problems common in the HIV+ population.

Keywords

Brain; infection; delirium; encephalitis; behavior; HIV; AIDS

Introduction

Over 34 million persons worldwide are infected with the Human Immunodeficiency Virus type-1 (HIV+) the cause of acquired immunodeficiency syndrome (AIDS). An estimated 20% of the more than one million HIV+ individuals in the United States are unaware of their HIV serostatus, and do not receive treatment with antiretroviral therapy (ART). Among those who are aware of their serostatus, over 50% receive no ART or receive only

[*]Corresponding author: Elyse J. Singer, M.D., Professor of Neurology, David Geffen School of Medicine at UCLA and Director, UCLA National, Neurological AIDS Bank, 710 Westwood Plaza, A-129, Los Angeles CA 90095, 310-794-1195, Fax 310-206-9416, esinger@mednet.ucla.edu.

April D. Thames, Ph.D. Assistant Professor of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, 740 Westwood Plaza, C8-746, Los Angeles CA 90095, 310-206-9296, Fax 310-206-8525, athames@mednet.ucla.edu

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inadequate treatment, which, places them at high risk for morbidity and mortality[1], including central nervous system (CNS) disorders.

HIV invades the CNS early, during the first days-weeks of primary infection. Approximately 24% of patients with primary HIV infection will have symptoms of an aseptic meningitis. HIV infection can result in progressive cognitive, motor, and behavioral abnormalities, particularly in persons who receive no ART, begin ART late in their disease, or receive inadequate ART that does not fully suppress HIV (1).

The neuropsychiatric effects of HIV can mimic idiopathic psychiatric disorders, delaying diagnosis and treatment of the underlying cause. The differential diagnosis of behavioral disorders in HIV+ persons includes pre-existing psychiatric disease, infectious, and medication-related causes. Because the processes that underlie such behavioral changes can be varied, we will first describe some important HIV–related behavioral symptoms (see Table 1) and then describe the clinical features of the most common underlying conditions.

Behavior Disorders Due to Pre-existing Psychiatric Illness

Behavioral disorders are common among both HIV+ and at-risk HIV- seronegative (HIV-) persons. Depression and anxiety receive the most attention, but delirium, apathy, mania, and severe mental illness (SMI) are also important. While the presence of pre-HIV psychopathology is the strongest predictor of psychiatric diagnosis after knowledge of seropositivity [2], it can be difficult to disentangle the effects of pre-morbid psychiatric illness from the biological effects of HIV, CNS opportunistic infections (OI), prescribed medications, or substance abuse. However, these distinctions are important in order to provide accurate diagnoses and treatment.

Severe Mental Illness

Individuals with severe mental illness (SMI), such as schizophrenia, bipolar disorder, and major depressive disorder (MDD), are at increased risk for contracting HIV. Once infected, they are at higher risk for suicide attempts, substance abuse, and failure to adhere to ART [3]. Adults with SMI are disproportionately at-risk because they are more likely to have multiple sexual partners, fail to use condoms, and engage in needle sharing. They are more resistant to risk reduction efforts because most of these programs assume that they have the cognitive capacity to make informed decisions about their behavior. Individuals with substance use disorders and victims of physical and sexual abuse also have specific risks for acquiring HIV [4].

Persons with a pre-morbid history of idiopathic SMI are characterized as having “primary psychosis”, whereas those with new SMI associated with medical illness, HIV disease, OI, or metabolic encephalopathies, are characterized as having “secondary psychosis” [5]. There are phenotypic differences between primary psychosis and the secondary psychosis associated with HIV. Persons with HIV-associated secondary psychosis are reported to show more disorders of consciousness, orientation, attention, and memory than patients with primary SMI [5]. They also tend to report less bizarre delusions, have a more variable course, and are more likely to have eventual remission of their psychosis [6].

Mood disorders and depression

Almost 50% of a large, nationally representative HIV+ sample screened positive for a mental health disorder, primarily major depressive disorder (MDD) and dysthymia[7]. In part, these high rates of MDD may be due to pre-morbid psychiatric illness. Some populations at high risk for HIV, such as men who have sex with men (MSM) or intravenous drug users (IDU), have high baseline rates of MDD. This may inflate the prevalence of MDD in HIV+ individuals. Alternatively, MDD may be a reaction to an HIV diagnosis, medical illness, HIV stigma, or the direct CNS effects of HIV as mediated by altered cytokine and neurotransmitter metabolism [8]. Identifying and treating MDD is important to long term management because prolonged MDD is associated with decreased adherence to ART [9].

The diagnosis of MDD in HIV+ persons may be difficult, because the neurovegetative symptoms of pre-morbid MDD (such as lack of energy, fatigue, anorexia, and sleep disturbances), may also be caused by the biological effects of HIV. HIV infection stimulates rising levels of pro-inflammatory cytokines such as interleukin-6, interleukin-1 beta, tumor necrosis factor-alpha and interferon-gamma, that are associated with “sickness behavior” (fever, hypersomnia, anorexia, decreased motor activity, and loss of interest in the environment)[10]. In differentiating between pre-existing MDD and the neurovegetative symptoms of HIV, it may be useful to remove the somatic depression symptoms included in diagnostic instruments such as the Beck Depression Inventory II (BDI-II)[11] and the Center for Epidemiologic Studies Depression Scale (CESD)[12]. For example, HIV+ persons may be screened using the “Beck Depression Inventory for Primary Care”, a tool that focuses on non-physical symptoms [13]. HIV+ patients are also at risk for hypothyroidism, adrenal insufficiency, and hypogonadism, which may present with neurovegetative symptoms[14].

Double-blind, randomized clinical trials (RCT) indicate that serotonin specific reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCADs) are useful in treating the symptoms of MDD in HIV+ patients[15]. Due to the lower incidence of anticholinergic side effects, SSRIs such as fluoxetine and paroxetine are typically used as first line agents while TCADs are sometimes used for patients with both depression and neuropathic pain. The atypical antidepressant bupropion, which has been studied in open label trials, can have significant interactions with the ART drugs ritonavir and efavirenz, and cannot be used in patients with seizure disorders [16]. Modafinil, a psychostimulant, reduced fatigue in HIV+ patients in a RCT [17], although its effects on other MDD symptoms was unclear. The monoamine oxidase inhibitor selegiline did not improve cognition in a RCT of HIV+ persons with neurocognitive deficits [18]. Use of other monoamine oxidase inhibitors in HIV+ patients is limited due to the potential for serious adverse effects.

Mania

Primary mania typically presents in young adulthood and is characterized by persistently elevated or irritable mood, increased physical activity, pressured speech, flight of ideas, racing thoughts, grandiosity, a decreased need for sleep, distractibility, and excessive high-risk activities. In contrast, secondary mania can present suddenly at any age in a previously normal person with no history of mood disorder, and it is frequently associated with brain disease [19]. HIV+ patients with secondary, or so-called “HIV mania”, are described as being

agitated, disruptive, sleepless, having high levels of energy, and being excessively talkative. They have a high rate of psychotic symptoms such as auditory or visual hallucinations and paranoia [20]. HIV mania is reported to be associated with irritability rather than euphoria. Unlike primary mania, cognitive deficits are usually present [20].

A first episode of HIV mania typically occurs in the context of a CNS disorder, such as HIV associated neurocognitive disorder (HAND) or a CNS OI. The mechanisms are poorly understood; however, the HIV *nef* protein is reported to alter CNS dopamine metabolism leading to hyperactive, "manic-like" behaviors in animal models [21].

Reports of HIV mania have dropped coincident with the widespread use of ART, but it remains a problem among untreated and under-treated persons.

The differential diagnosis of brain disorders underlying suspected "HIV mania" includes substance use (especially stimulants), alcohol withdrawal, metabolic abnormalities (e.g., hyperthyroidism), and CNS OI. Evaluations should include a neurological and mental status examination, brain magnetic resonance imaging (MRI) scan with and without contrast, serology for syphilis, urine toxicology, and CSF examination (if medically safe), including tests for OI and a quantitative HIV CSF PCR (viral load in CSF). The choice of psychotropic drug(s) to treat HIV mania is based on case reports, and open label studies, rather than RCT, as well as the desire to avoid adverse drug interactions, and the avoidance of HIV-specific side effects. HIV mania may improve with an approach that combines resolution of the underlying CNS process, use of a mood stabilizing drug, and/or addition of an anti-psychotic drug. For example, the mood stabilizer and anti-epileptic drug valproic acid has been used to successfully treat mania in HIV+ patients [16]. The disadvantages to valproic acid use are as follows: valproic acid is metabolized in the liver, and liver disease is common in HIV+ persons; further, valproic acid has interactions with many ART drugs [22,23]. This must be weighed against the potential disadvantages of other mood stabilizers, such as lithium, which can exacerbate renal disease, or carbamazepine, which can induce bone marrow suppression, hepatotoxicity, and induce the metabolism of ART (particularly protease inhibitors) [22,24,25]. Likewise, the older, high potency dopamine receptor 2 (DA2) blocking agents have been reported to cause serious extrapyramidal movement disorders and neuroleptic malignant syndrome in AIDS patients [26,27]. Atypical antipsychotics, such as risperidone, clozapine, ziprasidone, quetiapine and olanzapine are frequently used to manage psychosis in HIV+ patients [28,29]; however, they are associated with development of metabolic syndrome, cardiac problems and obesity, and may require dose adjustment if they are used with the protease inhibitor ritonavir[30,31]. Interactions between clozapine and ritonavir may increase clozapine levels leading to bone marrow toxicity[16].

Apathy Apathy is a common symptom of HIV and other neurodegenerative diseases. Apathy is characterized by a lack of interest in life activities, loss of interest in interacting with others, and decreased motivation. Apathy can be dangerous if it results in failure to pursue medical care [32]. This behavior is associated with impaired function of the subcortical regions and fronto-striatal circuits that are prime targets for HIV[33]. The emergence of apathy

in HIV+ is often associated with the onset of deficits in attention, working memory, learning, psychomotor, and executive function, such as characterize HAND.

Apathy may be diagnosed from a history, or by use of diagnostic inventories such as the Apathy Evaluation Scale [34], the apathy subscale of the Neuropsychiatric Inventory[35] and the Frontal Systems Behavioral Scale (FrSBe)[36]. Rivastigmine[37] and methylphenidate[38] have been studied in neurodegenerative disease as palliative treatments for apathy, but there are no studies in HIV+ patients.

Delirium

Delirium is an acute change in mental state characterized by fluctuating cognitive, perceptual and behavioral disturbances, altered level of consciousness, inattention, sleep-wake cycle disturbance, and delusions. Historically, delirium is associated with elderly, hospitalized patients. However, delirium is also common in HIV+ young adults and children, and is associated with increased mortality in HIV+ patients [39–41]. Risk factors include polypharmacy, substance use and withdrawal, and underlying CNS disease. Other factors that may trigger delirium include hypoxia, sepsis, thyroid disease, adrenal insufficiency, recent changes in medications, and end-organ failure.

The treatment of delirium includes environmental management to re-orient the patient and reduce agitation, and psychotropic medication to control aberrant behavior. There is only one controlled study of delirium treatment in AIDS, which dates to the pre-ART era. Breitbart et al., compared the use of low dose haloperidol, low dose chlorpromazine, and lorazepam in hospitalized AIDS patients with delirium [42]. The groups treated with low dose haloperidol and chlorpromazine demonstrated improvement (although mild extrapyramidal symptoms were noted) but patients treated with lorazepam suffered a significant increase in their delirium, to such a degree that the lorazepam arm of the study was terminated. Open-label studies and case reports suggest that the atypical antipsychotics clozapine, risperidone, and ziprasidone benefit AIDS patients with psychosis and/or delirium[16]. Some would argue that the use of older, D2-blocking antipsychotics should be avoided as first-line treatment in AIDS patients, due to reports of neuroleptic malignant syndrome and extrapyramidal movement disorders [26].

Anxiety

Anxiety is common in HIV+ patients, estimated to occur in 22–47% [43,44]. Posttraumatic stress disorder (PTSD) is a common anxiety disorder in HIV+ persons, estimated at 10–54% among populations such as MSM, minority women, and those with persistent pain[45,46] A study of HIV+ patients revealed that death anxiety was associated with overall PTSD symptom severity scores, as well as severity scores for re-experiencing, avoidance, and arousal symptoms of PTSD[47].

Generalized anxiety disorder (GAD) has been found to range between 6.5% and 20% in HIV + samples [7,48]. Physiological manifestations of anxiety, such as dyspnea, chest pain, tachycardia and dizziness, may be misattributed to HIV, cardiovascular disease or seizure disorder (due to syncope from hyperventilation) in HIV+ persons. Conversely, HIV-related infections, and substance intoxication or withdrawal, may mimic anxiety symptoms in

patients with tremors, rigors, or chills. The symptoms of anxiety may impact performance on cognitive testing, potentially leading to a misdiagnosis of HAND. Up to a 1 standard deviation drop in test performance has been documented in studies of healthy minority populations who have anxiety about test-taking [49,50]..

There is an emerging body of literature that has linked anxiety sensitivity (a fear of anxiety symptoms) to suicide [51,52]; in particular, cognitive concern (e.g., "I fear that I will lose my mind") is linked to suicidal thoughts [53]. Anxiety also interferes with ART adherence [5448].

Assessment of an anxiety disorder requires a history of symptoms (particularly prior to HIV infection), family history, substance use history (especially stimulants) and the use of over-the-counter medications, herbal supplements and caffeine. HIV+ patients with subclinical or overt neurocognitive impairment are more sensitive to the side effects of anxiolytic medications and should start at low doses [55]. Drug-drug interactions have been reported with anxiolytics and AIDS medications-for example, there are case reports of HIV+ patients on protease inhibitors who experienced prolonged sedation when given midazolam [56]. Buspirone, a popular anti-anxiety agent and 5HT1A agonist, has been reported to cause extrapyramidal signs when given with protease inhibitors such as ritonavir[57].

HIV–Associated Neurocognitive Disorder (HAND)

"HIV-associated neurocognitive disorder" or "HAND" (previously known as "HIV encephalopathy", "HIV–associated dementia", or "AIDS dementia complex") (2, 3) is the most common CNS disorder caused by HIV infection. It is characterized by the subacute onset of cognitive deficits, central motor abnormalities, and behavioral changes. Although cognitive decline is the defining feature in HAND, many patients have mild deficits that are detectable only by neuropsychological testing, and do not reach the functional criteria required to diagnose a dementia (e.g., inability to perform activities of daily living). The mildest form of HAND is classified as asymptomatic neurocognitive impairment (ANI), and is determined by a lack of significant cognitive complaints, neuropsychological test performance of which at least two cognitive domains fall greater than 1 standard deviation (SD) below the mean of demographically-adjusted normative scores, and no evidence of functional decline. The next is mild neurocognitive disorder (MND), classified by self or proxy-report of declines in at least 2 instrumental activities of daily living (IADLs; e.g., financial management); 2) unemployment or a significant reduction in job responsibilities due to reduced cognitive abilities; 3) decline in vocational functioning (e.g., increased errors, decreased productivity, or greater effort is required to achieve prior levels of productivity); 4) self-or proxy-report of increased problems in at least 2 cognitive ability areas in day-to-day life (this is not reliable among individuals with depression); or 5) scores at least 1 SD below the mean on a performance-based laboratory measure of everyday functioning (e.g., medication management). The most severe form of HAND, HIV associated dementia (HAD) is marked by at least moderate-to-severe cognitive impairment (i.e., at least 2 SDs below demographically-adjusted normative means) in at least two cognitive domains along with marked ADL declines that are not fully attributable to comorbidities or delirium. The neurocognitive profile of HIV has been characterized by deficits in attention, psychomotor slowing, episodic memory, working memory, executive

functions [58,59], reflecting frontal-subcortical compromise. For example, HAND patients frequently complain of slowed thinking and problems with learning new information.

The use of ART has attenuated the most severe aspects of HAND such as HAD[60], but cases still occur in HIV+ persons who are untreated, inadequately treated, or in persons who have "CNS escape" (a phenomenon where ART controls HIV in the periphery but not in the CNS [61]. Patients who develop HAND despite taking adequate ART are likely to have higher CD4+ counts, lower or undetectable plasma viral loads, and lower or absent CSF biomarkers of HAND than HAND patients in in the pre-ART era [62]. However, HAND is associated with a lower nadir (lowest ever) absolute CD4+ both pre-and post-ART.

In some HAND patients, cognitive deficits are overshadowed by behavioral/psychiatric features. Common behavioral symptoms associated with HAND include apathy, irritability, inertia, lack of spontaneity, social withdrawal, psychomotor slowing, complaints of diminished attention and concentration, emotional lability, and occasionally, "HIV mania". Many of these symptoms are not specific to HAND and occur in mood disorders and in other CNS diseases.

The differential diagnosis of behavioral changes associated with HAND includes an exacerbation of a pre-morbid psychiatric disease; neurosyphilis, CNS OI or tumor; adverse effects of medications; and the effects of substance abuse. The workup should include neuroimaging, preferably brain MRI with and without contrast. In most cases this will be normal or show cerebral atrophy with or without white matter changes, characteristic of HIV encephalitis. If not contraindicated, a CSF examination should be conducted to exclude OI, malignancy, and neurosyphilis. If available, an HIV quantitative PCR in CSF (a.k.a. a "CSF viral load") may point to CNS escape that may respond to a change in ART. Urine toxicology for drugs of abuse, screening for alcoholism and related disorders, and routine tests for thyroid disease, B12 deficiency, and folate deficiency, are essential. A neuropsychological examination is extremely useful in staging the degree of impairment and identifying any psychiatric disorders that confound the diagnosis of HAND,

HAND is treated by starting ART (if the patient is treatment naïve), and insuring that the patient fully adheres to the regimen and attains suppression of plasma and CSF viral load[63]. If the ART regimen is not controlling HIV replication, particularly in the CNS, it may be intensified by adding or substituting drugs with a higher CSF penetration effectiveness (CPE) score [64]. However, this approach is controversial [61,63], as higher CPE scores correlate with lower HIV RNA load in CSF but do not necessarily correlate with better cognition [65]. Individual case reports indicate that concurrent behavioral disorders may also improve with ART[66]. The results of small RCT indicate that psychostimulants such as methylphenidate may improve depression, neurocognitive test scores, and fatigue in HIV+ patients [67–69].

Cryptococcal meningitis (CM)

Cryptococcal meningitis (CM), caused by the fungus *Cryptococcus neoformans*, is the most common meningitis in AIDS. Typical patients with AIDS/CM have absolute CD4+ counts under 100 cells/μL and present with a subacute course of fever, malaise, and headache, with or without meningismus or photophobia. Behavioral symptoms such as personality changes,

psychosis or “AIDS mania” can also herald the onset of AIDS/CM[70]. The diagnosis of AIDS/CM is made by demonstrating Cryptococcal infection by Cryptococcal antigen testing or fungal culture in blood and/or CSF. India ink examination of CSF is also useful but is no longer performed by many labs. AIDS patients may have a minimal or no CSF lymphocytic pleocytosis, but increased opening pressure, elevated total protein, and low-normal CSF glucose are common. The preferred treatment of AIDS/CM includes either intravenous liposomal amphotericin B, in a dose of 3 to 4 mg/kg/daily, and flucytosine at a dose of 100 mg/kg daily in 4 divided doses for at least 2 weeks in patients with normal renal function[71]. Fluconazole can be used for induction therapy at a starting daily dose of 1200 mg day but is inferior to amphotericin and should be used only when standard treatment is unavailable or cannot be tolerated. Especially in low-resource settings, it may be necessary to delay ART treatment for AIDS/CM in order to avoid immune reconstitution inflammatory syndrome (IRIS). Most patients will require continued maintenance treatment with daily oral fluconazole until their CSF is sterilized and their CD4+ improves. Individual case reports indicate the amelioration of behavioral symptoms in AIDS/CM with atypical antipsychotics such as olanzapine[72]. A retrospective study indicates that substantial numbers of AIDS/CM survivors have persistent neurocognitive deficits [73].

Toxoplasmosis Encephalitis (TE)

Toxoplasmosis Encephalitis (TE), the most common cause of a CNS mass lesion in AIDS, is caused by the parasite *Toxoplasmosis gondii* [74]. This organism is usually acquired in early life and remains in latent (cystic) form within the brain. Toxoplasmosis encephalitis (TE) typically occurs when the cysts reactivate, e.g., in AIDS patients with CD4+ cell counts under 100 cells/μL. These TE lesions are highly inflammatory, producing cerebral edema and destruction of brain tissue. Typical symptoms of AIDS/TE include headache, seizures, fever, decreased cognition, altered level of consciousness, and focal neurological signs such as hemiparesis, visual field deficits, or aphasia [74]. Behavioral symptoms in AIDS/TE are of two types: non-focal symptoms such as delirium [75], psychosis[75,76] or mania[77]; and focal deficits such as aphasia [78], Parkinsonism [79], or unilateral movement disorders [80]. Of interest, latent toxoplasmosis in HIV-negative, immunologically intact patients has also been associated with psychiatric diseases and behavioral disorders[81].

The diagnosis of TE is supported when an AIDS patient presents with typical clinical symptomatology and brain neuroimaging demonstrates at least one contrast-enhancing mass lesion(s), often surrounded by a “ring” of edema[74]. These lesions are commonly found in the cerebral cortex, basal ganglia, cerebellum or brain stem [74]. The most important differential diagnosis is CNS lymphoma. Many patients with AIDS/TE are at-risk for cerebral herniation, so CSF studies may be unobtainable. When obtained, CSF typically shows a low-grade pleocytosis, elevated total protein, and sometimes elevated red blood cells. Toxoplasmosis cannot be cultured by conventional means. Direct molecular detection by polymerase chain reaction (PCR), while highly specific (96–100%), is not sensitive enough (50%) to reliably detect TE in CSF [71,82]. Detection of the organism requires a brain biopsy. Thus, CSF is important mainly to exclude alternative diagnoses. AIDS patients with typical clinical and imaging features of TE coupled with positive serum toxoplasmosis serology (serum IgG) and no alternative explanation for their symptoms are usually treated

empirically with anti-toxoplasmosis therapy, and followed carefully. The absence of toxoplasmosis antibodies makes a diagnosis of AIDS/TE unlikely (though not impossible)[71]. The typical choice of drugs includes pyrimethamine in combination with sulfadiazine and leucovorin, adjusted for body weight[71]. Pyrimethamine plus clindamycin plus leucovorin is the preferred alternative regimen for patients with TE who cannot tolerate sulfadiazine or do not respond to first-line therapy[71]. Atovaquone is an alternative in patients unable to tolerate either sulfonamides or clindamycin [83]. Steroids should not be administered unless needed to treat a mass effect causing increased intracranial pressure, as they may obscure the diagnosis. Improvement typically occurs within 14 days with anti-TE therapy and supports an empiric diagnosis of TE[83]. If the patient fails to improve or worsens, a brain biopsy may be needed to reach a diagnosis.

Neurosyphilis

Syphilis, caused by the spirochete *Treponema pallidum*, is a sexually transmitted infection, so co-occurrence with HIV is common. HIV causes impaired cell-mediated immunity, which accelerates the progression of syphilis, so that HIV+ persons have a greater frequency of neurosyphilis[84].

As with HIV, syphilis enters the CNS early in infection. Up to half of individuals with early syphilis will have CSF abnormalities indicative of neuroinvasion, and up to a quarter will have treponemes in their CSF. Most healthy patients clear the organisms. Failure to clear is the first step to neurosyphilis. Most neurosyphilis patients have asymptomatic infection of the CSF and meninges; only a fraction of those, who go untreated, will develop symptomatic neurosyphilis, and even fewer will develop general paresis (GP), the form of neurosyphilis most likely to present with behavioral changes. The host immune response is key to this process [84].

General paresis (GP) is caused by syphilitic infection of the brain parenchyma and is associated with neuronal loss. It typically occurs late in infection (20–30 years), although this process may be accelerated in HIV+ persons. Prior to the penicillin era, GP was a common reason for psychiatric hospitalization. Symptoms include dementia (which is not normally seen in primary psychiatric disease), emotional lability, anhedonia, grandiosity, paranoia, hallucinations, and mood changes that mimic mania and depression. Other features associated with general paresis include headache, seizures, pupillary abnormalities, and ataxia; patients with a concurrent tabes dorsalis (another form of late syphilis that affects the spinal cord) have loss of vibratory and position sense in the legs, incontinence, weakness, reflex changes, and lightning-like pains [85].

In GP, the MRI may be normal, or may show frontal and temporal atrophy due to neuronal loss. In HIV+ persons with GP, these changes may be overshadowed by concurrent HIV encephalitis. Gummas (syphilitic granulomas) may appear on MRI as space-occupying lesions.

The diagnosis of neurosyphilis can be challenging in HIV+ patients. Screening tests that use a nonspecific, nontreponemal antibody, such as the rapid plasma reagin (RPR), are usually reactive within 3–4 weeks of syphilis infection in HIV+ patients, although rare cases of

failure to develop antibodies have been reported in extremely immunocompromised persons[86]. The RPR is sensitive but not specific, so is confirmed with a more specific treponemal test e.g., the fluorescent treponemal antibody absorption (FTA-ABS), the microhemagglutination test for antibodies to *Treponema pallidum* (MHA-TP), or *Treponema pallidum* particle agglutination assay (TP-PA).

At a minimum, HIV+ patients with syphilis and ophthalmologic, otologic signs or neuropsychiatric symptoms should be screened for neurosyphilis with a CSF examination to determine if they have laboratory signs of neurosyphilis and to establish a baseline for treatment if this is the case. Unfortunately, *Treponema pallidum* is an obligate intracellular parasite and cannot be cultured by conventional means. Thus, laboratory diagnosis rests on two factors: the detection of CSF abnormalities (such as elevated CSF WBC, elevated total protein), and reactive serological testing (e.g. the CSF Venereal Disease Research Laboratory (VDRL) test). The CSF PCR is investigational and not currently recommended for the diagnosis of syphilis[71]. However, a study that used the laborious rabbit inoculation method to directly culture spirochetes from CSF found that 33% of patients with untreated primary and secondary syphilis who had a nonreactive CSF VDRL nonetheless had *Treponema pallidum* isolated from their CSF[87]. This and similar studies suggest that the CSF VDRL is a specific but not very sensitive for neurosyphilis. An alternative method of diagnosing neurosyphilis in a syphilis patient with a nonreactive CSF VDRL is to find CSF abnormalities, e.g., pleocytosis and elevated CSF protein, in a patient diagnosed with syphilis. However, a low grade lymphocytic pleocytosis and elevated CSF protein are common in asymptomatic HIV+ patients[88], thus reducing the value of these tests in HIV+ persons when the CSF VDRL is non-reactive. Some authors report an association between serum RPR titers of at least 1:32 and/or CD4+ counts under 350 cells/μl with neurosyphilis in HIV+ persons [89] although there are cases of neurosyphilis reported that do not meet this criteria.

Another proposal is that a CSF FTA should be performed in patients with a non-reactive CSF VDRL and suspected neurosyphilis; CSF FTA is very sensitive and is not as specific, so, a non-reactive CSF FTA is thought to exclude virtually all probability of neurosyphilis [90].

The treatment of choice for neurosyphilis in HIV+ patients is intravenous (IV) aqueous crystalline penicillin G, 18 to 24 million units daily, administered as 3 to 4 million units IV every 4 hours or by continuous infusion for 10 to 14 days or procaine penicillin, 2.4 million units intramuscularly (IM) once daily plus probenecid 500 mg orally 4 times a day for 10 to 14 days. HIV+ patients who are allergic to sulfa-containing medications should not be given probenecid because of potential allergic reaction[71]. Because neurosyphilis treatment regimens are of shorter duration than those used in late-latent syphilis, 2.4 million units benzathine penicillin IM once per week for up to 3 weeks after completion of neurosyphilis treatment can be considered to provide a comparable duration of therapy[71]. Ceftriaxone may be an alternative for those with penicillin allergy[71]. The response to antibiotic treatment is reported to differ in HIV+ persons, particularly if they have severe immunosuppression or are not treated with ART, as they are more likely to fail conventional treatment for neurosyphilis [87,91,92].

There is no consensus that antibiotic treatment of neurosyphilis produces a persistent improvement in cognition in persons with general paresis (note: most of the patients studied were HIV-negative)[93]. Further, although neurosyphilis remains associated with psychiatric and behavioral symptoms even in HIV-negative patients [94], there is no consensus or RCT describing how to best manage these symptoms. Sanchez et al., published a case series describing treatment of neurosyphilis with mood stabilizers and atypical anti-psychotic drugs[95]; however, these agents need to be used with caution in HIV+ patients receiving concurrent treatment with ART.

Herpes simplex virus 1 encephalitis

Herpes simplex virus 1 encephalitis (HSVE) is the most common encephalitis in the HIV-negative population and can also occur in HIV+ patients. It is hypothesized that HSV-1 enters the brain via the olfactory nerves and spreads into the limbic system, frontal, and temporal lobes[96]. Infected neurons and other cells can undergo cytolysis, causing hemorrhagic destruction of brain tissue. Particularly vulnerable areas include the fronto-orbital region, temporal lobes, hippocampus, cingulate gyrus and insular cortex[96].

The most common clinical presentation of HSVE includes fever, headache, seizures, altered level of consciousness, and culminates in stupor or coma[96]. However, HSVE patients can have a presentation dominated by behavioral symptoms, such as irritability, confusion, psychomotor retardation, anosmia, auditory, gustatory, or olfactory hallucinations, delusions, paranoia, or aggression. It is not unusual for an HSVE patient to be mistakenly referred to a psychiatric unit [97,98].

The diagnosis of HSVE is confirmed by brain MRI with/without contrast showing characteristic contrast-enhancing lesion(s) in the frontal and/or temporal areas, and/or by a positive HSV-1 PCR or elevated HSV-1 antibodies in CSF[99]. Occasionally the CSF studies are negative, and a repeat CSF examination or a brain biopsy is required to make the diagnosis. Treatment is intravenous acyclovir (60 mg/kg/day, given in three divided doses) for 21 days[100]. A repeat CSF exam should be performed at the end of therapy to assure that the virus has cleared. The use of continued outpatient treatment with oral valacyclovir is common but has not been shown to improve outcomes [101]. HSVE survivors often have behavioral sequelae [102] such as aphasia, memory deficits, visuospatial deficits, executive dysfunction, or Kluver-Bucy syndrome (hypersexuality, hyperoral behavior, and hyperphagia).

There are no RCT of treatment for the neurobehavioral sequelae of HSVE in HIV+ patients, but case reports describe the management of post-HSVE neurobehavioral deficits with anti-psychotics and mood stabilizers [103].

Progressive Multifocal leukoencephalopathy (PML)

The *John Cunningham virus* (JCV), a polyoma virus, is the cause of progressive multifocal leukoencephalopathy (PML), a serious and often fatal CNS demyelinating disease. The JCV is a ubiquitous virus transmitted by casual contact. World-wide, over 50% of adults are JCV- infected (JCV+) [104]. Once established, JCV takes up residency in a latent form in the

kidneys, and, possibly, in the brain[105]. Under conditions of immunosuppression, including HIV infection, JCV can reactivate and cause PML. HIV+ patients are doubly at risk, as JCV replication can also be increased by the HIV tat protein[106].

Pre-ART, most AIDS/PML patients presented with an absolute CD4+ cell count under 100 cells/μl. However, unlike some other CNS OI, PML can occasionally occur in HIV+ patients with absolute CD4+ cell counts over 200 cells/μl[107], in HIV+ patients who receive adequate ART, and in patients recently started on ART who experience immune reconstitution inflammatory syndrome uncovering an occult JCV infection[108]. However, the number of PML cases has declined overall in ART-treated populations.

The clinical presentation of PML can include cognitive decline, aphasia, acalculia, right-left confusion, agnosia, cortical blindness, akinetic mutism, emotional lability (pseudobulbar affect) apraxia, dysarthria, involuntary movements, catatonia, diplopia or seizures [109–113]. Other common features include visual field cuts, mono-or hemiparesis, gait disturbance, oculomotor palsy, sensory loss, tremors, incoordination, and ataxia [110]. Signs and symptoms are usually referable to the locations of the demyelinating lesion(s). Fever, headache, and stiff neck are rarely seen in uncomplicated AIDS/PML. The most common neuroimaging findings are one or more space-occupying white matter lesions that are non-enhancing, hyper intense on T2 and fluid-attenuated inversion recovery (FLAIR), hypointense on T1, and spare the cortical U-fibers. Virtually any brain area can be involved. Only 5–10% of cases have some degree of contrast enhancement.

A possible diagnosis of AIDS/PML should be considered in a HIV+ patient with one or more CNS signs/symptoms, an MRI that demonstrates at least one characteristic brain lesion(s), and no other CNS diseases explain the signs and symptoms. Historically, a diagnosis of definitive PML required a brain biopsy or autopsy showing demyelination, bizarre astrocytes, and enlarged oligodendroglial nuclei, along with histopathological or electron microscopy demonstration of JCV [114]. However, in 2013, this was expanded to include patients without a tissue diagnosis who had characteristic presentation, MRI, and a positive CSF JCV PCR [114].

The routine CSF examination in AIDS/PML is nonspecific, with mild or no pleocytosis, elevated total protein, and normal glucose, but is essential to exclude diagnoses that mimic the appearance of PML, such as other viral infections.

One potential problem in confirming the diagnosis of AIDS/PML is that the sensitivity of the CSF JCV PCR test, especially in ART-treated patients, is as low as 58% [115]. In addition, JCV has occasionally detected in the CSF of both immune suppressed persons, and in clinically and radiologically normal persons, without PML. For this reason, both clinical and laboratory features are necessary to establish a diagnosis of PML [114].

There is no specific drug that treats JCV infection. Multiple agents have been studied in RCT without success, including topotecan {131}, cytarabine {132, 133}, cidofovir {134}, and mefloquine[116]. The use of mirtazapine[117] and other 5HT2a receptor blockers (olanzapine, zisprasidone, mirtazapine, cyproheptadine, and risperidone) have been suggested because JCV may use the serotonergic 5HT2a receptor to enter glial cells in

culture systems, but, no RCT have been conducted. ART has improved the course of AIDS PML, decreasing the mortality rate, improving the neuroimaging features, improving survival, and decreasing CSF JCV viral load {135, 136} {125}, and should be optimized in all AIDS/PML patients[71].

Patients who survive AIDS PML are likely to have serious residual deficits {137}. There are no RCT trials that explore the appropriate medical treatment of behavioral abnormalities in AIDS/PML. Individual case reports have described the treatment of specific neuropsychiatric symptoms (such as pseudobulbar affect, agitation, movement disorders) in patients with PML with conventional psychotropic medications [118,119].

Adverse effects of medications used to treat HIV-1 and associated conditions

Antiretroviral therapy (ART) Toxicity—Antiretroviral therapy (ART) Toxicity: The ART drug efavirenz has been reported to cause CNS toxicity [120,121] manifested by neuropsychiatric symptoms and histopathological changes. Up to 60% of efavirenz-treated HIV+ patients experience the symptoms of mood disorders (mania or depression), suicidal thoughts, dizziness, confusion, lethargy, impaired concentration, hostile thoughts, aggression, psychosis, sleep disturbances (vivid dreams and insomnia), anxiety, catatonia, and hallucinations. This psychotropic effect is so well known that in some areas efavirenz is smoked as a recreational drug. The risk of suicide in HIV+ persons treated with efavirenz is also higher than in persons treated with other ART, particularly if there is a history of psychiatric disorder or substance abuse [122]. Behavioral disorders have been linked to elevated serum levels of efavirenz associated with genetic variations in drug metabolism. Efavirenz has also been linked to CNS mitochondrial [123] and neuronal toxicity[124].

Neuropsychiatric symptoms from efavirenz typically occur within the first few weeks of treatment. If the patient continues to take the drug, s/he may accommodate to these adverse effects but this may require up to 200 days of efavirenz use.

Individual cases of psychosis (with or without accompanying movement disorders) have been reported with other ART, including abacavir[125], and zidovudine[126].

Delirium has been reported as an idiosyncratic reaction to ART, catatonia has been reported in patients taking combination ART[127], and acute dystonia has been reported with lamivudine[128]. Various ART drugs such as zidovudine, abacavir, and efavirenz have been reported to trigger depressive episodes in susceptible persons[129]. Of interest, a larger study indicated that ART might actually improve depression in HIV+ persons[130]

Drugs Used to Treat Opportunistic Infections—Ganciclovir is an antiviral drug used to treat cytomegalovirus infections in AIDS patients. Psychosis, confusion, visual and auditory hallucinations, aphasia, incontinence and delirium have been reported [131]. These syndromes typically remit within 5 days after the drug is stopped. Ganciclovir is excreted by the kidneys, so that persons with impaired renal function may be at higher risk for this complication; lowering the dose may prevent this problem. Valacyclovir and acyclovir have also been associated with psychosis, especially in patients with renal insufficiency [132].

Sulfadiazine, a drug used extensively for the prophylaxis and treatment of TE in AIDS patients, has also been associated with psychoses, hallucinations, and tremor [133].

Anti-psychotic and Dopamine Blocking Drugs—HIV has a predilection for the basal ganglia and is associated with pathology affecting the dopaminergic (DA) systems [134]. Particularly in the pre-ART era, patients with HAND were noted to manifest Parkinsonian features including psychomotor and motor slowing, tremor, increased tone, cogwheeling, hypomimia and hypophonia[135]. However, most of these patients did not have a resting tremor nor did they respond well to typical Parkinson's drugs. The DA system is compromised in HIV as demonstrated by decreased levels of DA in the CNS of HIV+ patients [136,137]. Case reports indicate that HIV+ patients have developed Parkinsonism and other extrapyramidal disorders when treated with DA-blocking drugs [138].

Summary

In summary, patients with HIV/AIDS remain susceptible to significant and potentially life-threatening behavioral abnormalities even in the era of ART. These problems can be attributed to pre-existing psychopathology, underlying infection, or adverse medication effects, so that their physicians should consider whether new behavioral changes are the reflection of a new and unwanted brain infection or other serious process. The management of HIV+ remains challenging because many commonly used psychiatric medications can have unwanted adverse effects or potentially dangerous drug interactions. However, the development of psychiatric disease in the context of brain infection indicates the need to further explore the role of infectious agents in the pathogenesis of mental illness.

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Key Points

1. Behavioral disorders are an important problem in HIV/AIDS patients even in the current era of antiretroviral therapy (ART).
2. Behavioral pathology can be caused by pre-existing psychosocial problems, substance abuse, major psychiatric disorders, or by HIV infection itself, opportunistic infections, or effects of medications that treat HIV and related conditions.
3. Physicians who evaluate behavioral changes in HIV+ patients should screen for underlying medical disease, substance abuse, adverse effect of medications, and suicide risk.

Table 1

Presentation of Behavioral Pathology in HIV/AIDS Affected Persons

I	Pre-existing psychiatric disease
II	Depression
III	Anxiety
IV	Mania
V	Apathy
V I	Delirium

Table 2

Infectious disorders associated with behavioral pathology in HIV patients

1. HAND
II. Cryptococcal meningitis
III. Toxoplasmosis encephalitis
IV. Herpes Simplex Virus encephalitis
V. Neurosyphilis
VI. Progressive Multifocal Leukoencephalopathy (PML)

Table 3

Behavioral Disorders associated with HIV/AIDS treatment

I	Antiretroviral Drugs
II	Drugs Used to Treat Opportunistic Infections
III	Anti-Psychotic and Dopamine Blocking Drugs