

5-step psychiatric workup of HIV patients

Differentiate AIDS-related and antiretroviral effects from psychiatric disorders

Mr. G, a 28-year-old heterosexual Puerto Rican man, is admitted to the hospital's infectious diseases (ID) unit after 3 weeks of worsening bifrontal headaches. He has been treated as an outpatient for several years since becoming HIV-positive and was diagnosed with AIDS after an intracranial toxoplasmosis infection. Although he has not taken antiretrovirals for several months, Mr. G has adhered intermittently to his antiretroviral regimen and previously developed other opportunistic infections, including thrush and bacterial pneumonia.

Three days after Mr. G is admitted, ID clinicians become concerned that he appears severely depressed and request a psychiatric evaluation.

Psychiatric evaluation and diagnosis in patients with HIV can be a challenge because of:

- the myriad ways HIV can impact the CNS
- the proliferation of antiretroviral medications
- patients' increasing lifespan as a result of highly active antiretroviral therapy (HAART)¹
- the psychological repercussions of living with HIV infection.

In this case-based review, we outline a rational, 5-step approach to evaluating and diagnosing psychiatric symptoms in patients with HIV.

A wide differential diagnosis

Patients who are HIV-positive have disproportionately high rates of psychiatric disorders. One study of approximately 2,800 adults receiving care for HIV found that



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HIV patients

Clinical Point

Be vigilant for deficits in attention or orientation that might indicate an acute brain syndrome

Table 1

HIV-associated CNS infections

More common

Cryptococcus neoformans meningitis
Progressive multifocal leukoencephalopathy (polyomavirus JC)
Toxoplasma gondii

Less common

Aspergillosis
Coccidioidomycosis
Cytomegalovirus
Herpes simplex or varicella-zoster encephalitis
Histoplasmosis
Leptomeningeal tuberculosis

Source: References 5-8

nearly one-half screened positive for major depression, dysthymia, generalized anxiety disorders, or panic attacks.² Some psychiatric morbidity may be related to:

- the stress of having HIV
- stressors related to risk factors for acquiring HIV, including low socioeconomic status, homelessness, and discrimination and social stigma based on race and sexual orientation
- substance abuse, which is common among patients with HIV.²

Other “psychiatric” symptoms may be the result of HIV infection in the brain, either acutely (as seen in HIV encephalopathy³) or cumulatively (as seen in AIDS-associated dementia⁴). Psychiatric symptoms may be the result of intracranial opportunistic infections in immunocompromised AIDS patients (Table 1).⁵⁻⁸ Antiretroviral medications commonly used to treat HIV also can cause psychiatric symptoms (Table 2).^{9,10}

Because of the range and variety of psychopathology encountered in HIV disease, keep a wide differential diagnosis in mind when evaluating patients with HIV.

A 5-step process can help you determine if symptoms in any patient—regardless of HIV status—are caused by a primary psychiatric disorder or CNS impairment (Box, page 64).

STEP 1 Perform initial exams

A careful diagnostic exam that includes a mental status examination with gross cognitive functioning testing is necessary to differentiate primary psychiatric disorders from HIV-related CNS pathology, including:

- HIV-associated dementia
- HIV-associated minor cognitive motor disorder (a less severe form of HIV-related cognitive and psychomotor impairment)
- opportunistic infections.

CASE CONTINUED

Mr. G sits in a chair alone in his room, looking out the window. He responds minimally to your initial greetings and has a staring expression and flat affect. Mr. G is calm and cooperative with the exam but has almost no spontaneous speech, answering questions with slow, imprecise 3- or 4-word responses. He is relaxed and does not seem guarded or paranoid.

Mr. G denies depressed mood or suicidal thinking and appears surprised to be asked about these symptoms. He also denies a history of manic or psychotic symptoms or problems with sleep, appetite, or energy. Bedside cognitive exam—focusing on alertness, orientation, attention, and memory—does not demonstrate any gross deficits.

Cognitive workup. Be vigilant for deficits in attention and orientation that might indicate an acute brain syndrome. In addition, look for discrepant patterns of symptoms or other features that may suggest CNS pathology. For example, Mr. G’s impoverished speech and lack of motivation—combined with a clear sensorium and lack of obvious patterns of mood, anxiety, or psychotic symptoms—suggest that a primary psychiatric disorder might not explain his presentation.

Although commonly used, the bedside Mini-Mental State Examination may be insensitive to cognitive deficits in HIV-associated dementia. The HIV-Dementia Scale is more sensitive to HIV’s typical subcortical features.

Physical workup. When evaluating symptoms in an immunocompromised patient at risk for opportunistic infections, it is important to conduct a comprehensive

physical exam. Pay attention to evidence of secondary infection and to neurologic signs. Fever may suggest an opportunistic infection that could contribute to psychiatric symptoms. Immunocompromise in HIV may be associated with a variety of infectious meningitis forms, such as:

- cryptococcus
- aseptic meningitis (which may be caused by HIV)
- histoplasmosis
- coccidioidomycosis.

A stiff neck or positive Kernig's and Brudzinski's signs (pain elicited upon passive extension of the knee with the hip flexed, or with flexion of the neck) specifically indicate an infection or other inflammatory process within the meninges that may lead to mental status changes. Motor, sensory, and cranial nerve examinations can detect evidence of intracranial mass lesions resulting from CNS neoplasms or infections to which immunocompromised patients are vulnerable.

CASE CONTINUED

Physical exam reveals that Mr. G has a low-grade fever (100.2° F) and penile erosion consistent with herpes simplex infection. He has no meningeal signs and an otherwise normal neurologic examination.

STEP 2 Evaluate lab results

Use laboratory testing to search for potential medical causes of the patient's presentation. Include a complete blood cell count, electrolytes, blood urea nitrogen and creatinine, and liver function tests to look for underlying metabolic problems.

CASE CONTINUED

Complete blood count, electrolytes, kidney function, and liver function tests are all within normal limits, and rapid plasma reagin (RPR) for syphilis is negative. Cerebrospinal fluid (CSF) analysis demonstrates normal opening pressures, protein, and glucose. India ink stain is negative for *Cryptococcus neoformans*, but 1 week later CSF cultures are positive for *Cryptococcus*. The patient has a CD4 count of 15 and a viral load of approximately 44,000.

Table 2
Neuropsychiatric side effects of antiretroviral medications

Medication	Potential side effect(s)
Abacavir	Depression, anxiety, psychosis
Amprenavir	Mood changes
Didanosine	Lethargy, nervousness, anxiety, confusion, sleep disturbances, mood disorders, psychosis
Efavirenz	Agitation, depersonalization, hallucinations, disturbed dreams, mood disorders, depression, suicidality, antisocial behavior, psychosis, catatonia, delirium
Enfuvirtide	Anxiety, depression
Indinavir	Mood changes
Lamivudine	Insomnia, mood disorders
Lopinavir+ Ritonavir	Mood changes, agitation, anxiety
Nevirapine	Depression, cognitive impairment, psychosis
Ritonavir	Anxiety
Saquinavir	Depression, anxiety, sleep disturbances
Stavudine	Sleep disorders, mood disorders, delirium
Zalcitabine	Somnolence, impaired concentration, mood disorders, delirium
Zidovudine	Sleep disturbance, vivid dreams, agitation, mania, depression, psychotic symptoms, delirium

Source: References 9,10

In patients with HIV, CD4 count can reveal the degree of immunocompromise, whereas viral load shows the extent of viral activity. Typically, patients with a CD4 count >500 are not at risk for opportunistic infections. A count <50 indicates a high risk for infections. In an antiretroviral-adherent patient, a detectable viral load suggests that viral activity is not being suppressed by the medication regimen.

Clinical Point

Fever might suggest an infection that could be contributing to psychiatric symptoms



HIV patients

Clinical Point

Consider ordering a test for syphilis because syphilis can mimic psychiatric symptoms and worsen the course of HIV infection

Box

New-onset symptoms: Psychosis or CNS impairment?

The stepwise approach this article describes to evaluate and diagnose psychiatric symptoms in HIV-positive patients can be used in any patient to determine if psychiatric symptoms are the result of a primary psychiatric disorder or CNS impairment. This approach may be particularly helpful when evaluating patients with new-onset or unusual symptoms, as described in the following case.

Ms. K, 34, has a diagnosis of ophthalmic herpes and is hospitalized to control severe pain in her left eye. On the second day, she appears moderately anxious and somewhat restless. Although it is possible to recognize some words and connections between a few ideas, her speech is otherwise incomprehensible. The ophthalmologist requests a psychiatric consultation, concerned that the change in mental status represents emerging psychosis.

Because Ms. K is unable to provide information coherently, the psychiatrist carefully reviews her medical, social, and psychiatric histories and medications. Ms. K's history includes tonsillectomy at age 2, arthroscopic knee surgery after a skiing accident in college, and the use of oral contraception.

STEP 1 During Ms. K's mental status exam, she appears alert, attentive, and cooperative, although moderately anxious. Rather than tangentiality or loosening of associations, her speech is notable for pervasive word substitutions and paraphasic errors, such as saying "chair" when asked to identify the nightstand in her room.

Aside from her ocular lesion, Ms. K's physical exam is normal.

STEP 2 Laboratory testing reveals normal electrolytes, renal functioning, liver function tests, thyroid functioning, and B12 and folate levels. Rapid plasma reagin for syphilis is negative.

STEP 3 The psychiatrist feels that her exam demonstrates aphasic features rather than psychotic thought process abnormalities and orders neuroimaging. Brain CT with contrast reveals that Ms. K has a ring-enhancing lesion in the left temporal-parietal area, consistent with toxoplasmosis or a glioblastoma. Biopsy confirms toxoplasmosis.

STEPS 4/5 Neuropsychological testing was not performed in this case. It would have revealed the aphasia. Putting all of the data together resulted in clarifying that the patient was not psychotic.

Because toxoplasmosis often develops in patients with severely compromised immune systems, the healthcare team advises Ms. K to undergo HIV testing. Her enzyme-linked immunoadsorbent assay is positive for HIV antibodies, and her HIV infection is confirmed with a Western blot test.

Treatment with pyrimethamine and sulfadiazine rapidly resolves her neurologic symptoms. When she is no longer aphasic, Ms. K gives a history of several sexual relationships in the last 4 years. She typically used condoms during sexual activity but recalled instances when the condom had ruptured during intercourse. She denies any other risk factors for contracting HIV. Ms. K fully recovers from toxoplasmosis with no signs of cognitive impairment. She is started on antiretroviral therapy and followed as an outpatient.

Carefully evaluate patients with a CD4 count <200 for HIV-related CNS disease. In general, the lower the CD4 count, the higher the suspicion for secondary causes of psychiatric symptoms.

Strongly consider ordering the RPR test for syphilis because:

- HIV and syphilis share sexual risk factors

- having syphilis increases the likelihood of comorbid HIV infection 7- to 9-fold¹¹
- syphilis may worsen the course of HIV infection¹²
- syphilis can mimic psychiatric symptoms.^{13,14}

CSF analysis may reveal evidence of

meningitis, and special stains may be used to detect meningitis-causing organisms that are characteristic of AIDS. CSF also may be tested directly for CNS syphilis.

STEP 3 Order neuroimaging

Neuroimaging is an essential part of the workup of a patient for whom your clinical examination raises suspicion for CNS impairment. In patients with longstanding HIV infection, brain imaging may reveal cerebral atrophy, which may accompany the cognitive changes found in HIV-associated dementia. In addition, immunocompromised patients, particularly those with a CD4 count <50, are at risk for CNS lymphoma and CNS toxoplasmosis infection. Both of these AIDS-associated entities demonstrate ring-enhancing lesions on brain CT or MRI and may be difficult to differentiate radiographically.¹⁵

CASE CONTINUED

Brain MRI shows moderate cerebral and cerebellar atrophy, which ID clinicians attribute to the long-term effects of HIV infection. No evidence of focal or mass lesions is seen.

By further investigating Mr. G's medical records, you find a brain MRI performed when Mr. G initially presented with toxoplasmosis in 2001. This scan reveals a large ring-enhancing mass in the right frontal lobe. Although the patient had refused a brain biopsy, the radiologist determined the lesion was most consistent in appearance with intracranial toxoplasmosis.

STEP 4 Perform neuropsychological testing

When physical exam, mental status exam, or neuroimaging suggests a possible CNS cause for a patient's psychiatric presentation, neuropsychological testing can help characterize which of the patient's brain functions are compromised and determine their anatomic source. This testing allows for a more complete and precise assessment of brain function than can be achieved by a bedside cognitive exam. It typically includes the Trail Making Test Parts A and B and the Grooved Pegboard

Test to evaluate executive and psychomotor functioning, as well as the Controlled Oral Word Association Test to evaluate cognitive speed.

CASE CONTINUED

A search of medical records reveals that Mr. G had recently undergone a brief neuropsychological assessment at the hospital's outpatient HIV mental health clinic. The psychologist found evidence of frontal lobe dysfunction, including problems with shifting sets, verbal fluency, and naming the months of the year backwards. Mr. G's performance demonstrated a subcortical dementia pattern that included prominent fine motor impairment.

In HIV-positive patients with evidence of cognitive impairment, neuropsychological testing can help determine if the pattern of deficits is consistent with HIV-associated dementia. Such deficits typically follow the pattern of a subcortical dementia characterized by apathy, amotivation, psychomotor retardation, and slowing of general information processing. This differentiates it from Alzheimer's dementia, which is typically characterized by short-term memory impairment, personality changes, and affective changes such as depression.

STEP 5 Synthesize all data to make a diagnosis

Psychiatric illness in HIV-positive patients may involve factors at multiple biopsychosocial levels, including problems with social support, psychological stress, primary psychiatric illness, immunocompromise, and CNS disease. Consider data from all of these levels to arrive at a diagnosis.

CASE CONTINUED

After carefully considering Mr. G's history, physical and mental status examinations, laboratory data, current and past neuroimaging, and neuropsychological testing, you and ID clinicians conclude that Mr. G's neuropsychiatric presentation primarily represents the residual deficits from his large frontal lobe toxoplasmosis lesion diagnosed in 2001, with possible contribution from an underlying HIV-associated dementia. You feel that a

Clinical Point

Brain imaging in patients with longstanding HIV infection may reveal cerebral atrophy

Table 3

Staging system for HIV-associated dementia

Stage	Degree of severity	Clinical characteristics
0	Normal	Normal mental and motor function
0.5	Equivocal	Minimal or equivocal symptoms characteristic of cognitive or motor dysfunction, or mild signs (snout response or slowed extremity movements); no impairment of work or ADLs; gait and strength normal
1	Mild	Unequivocal evidence of functional, intellectual, or motor impairment (including symptoms, signs, or neuropsychological testing); can walk without assistance and perform all except more demanding aspects of work or ADLs
2	Moderate	Able to perform basic activities of self care but unable to work or maintain the more demanding ADLs; ambulatory but may require a single prop
3	Severe	Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all outputs) or motor disability (unable to walk unassisted, requires walker or personal support, usually slowed and accompanied by clumsiness of arms)
4	End stage	A nearly vegetative state; intellectual and social comprehension and output are rudimentary; patient is nearly or absolutely mute and paraparetic or paraplegic, with urinary and fecal incontinence

ADLs: activities of daily living
Source: References 9,16



HIV patients

Clinical Point

Neuropsychological testing can help determine if a pattern of cognitive deficits is consistent with HIV-related dementia

depressive disorder can be ruled out with a high degree of certainty because the patient denied abnormalities of mood or hedonic tone, did not demonstrate deficits in neurovegetative functioning such as appetite, energy, and sleep, and did not show evidence of suicidality. You attribute the flat affect and amotivation that had prompted the psychiatric consult to his secondary neuropsychiatric deficits.

In the absence of another neurologic diagnosis, Mr. G would likely be classified as having Stage 1 HIV-associated dementia. (Table 3).^{9,16} However, it is difficult to determine which of his deficits are due to an underlying HIV-related dementing process and which are related to his more focal frontal lobe compromise demonstrated on neuropsychological testing.

CASE CONTINUED

Because Mr. G had no evidence of a mood syndrome, you do not recommend antidepressants. You note that although a stimulant might improve the patient's cognitive function and apathy, Mr. G's history of heavy cocaine use is considered a contraindication.

Mr. G's cognitive and motivation deficits will complicate the management of his complex medical condition and medications. You recommend that he be referred to a structured outpatient living and care environment to support his HAART adherence. Despite the primary team's efforts in discharge planning, however, the patient does not keep his clinic appointments and is lost to follow-up.

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Related Resources

- Aidsmap information on AIDS and HIV. www.aidsmap.com.
- America Psychiatric Association AIDS Resource Center. www.psych.org/AIDS.

Drug Brand Names

Abacavir • Ziagen	Nevirapine • Viramune
Amprenavir • Agenerase	Pyrimethamine • Daraprim
Didanosine • Videx	Ritonavir • Norvir
Efavirenz • Sustiva	Saquinavir • Invirase
Enfuvirtide • Fuzeon	Stavudine • Zerit
Indinavir • Crixivan	Sulfadiazine • Microsulfon
Lamivudine • Epivir	Zalcitabine • Hivid
Lopinavir/Ritonavir • Kaletra	Zidovudine • Retrovir

Disclosure

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Bottom Line

Screen patients for HIV risk factors, and remain vigilant for potential neuropsychiatric sequelae in at-risk individuals. Diagnosing psychiatric symptoms in HIV-positive patients who are immunocompromised requires a stepwise approach that considers the complex matrix of psychological, neuropsychiatric, and general medical factors found in HIV disease.

Clinical Point

In your diagnosis, consider patients' social support, psychological stress, CNS disease, and other factors

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The Neuroleptic Malignant Syndrome Information Service (NMSIS) announces a competition to recognize promising new investigators based on a scholarly paper addressing **"New insights on psychotropic drug safety and side effects."**

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