COGNITIVE DISORDERS AND HIV/AIDS

I. INTRODUCTION
HIV enters the central nervous system (CNS) soon after initial infection and is responsible for a range of neuropsychiatric complications. Although HIV is neuroinvasive, it does not directly infect neurons. The major brain reservoirs for HIV infection and replication are microglia and macrophages. Astrocytes can be infected but are not a site of active HIV replication. Accordingly, HIV-associated neurologic complications are indirect effects of viral neurotoxins (viral proteins gp120 and tat) and neurotoxins released by infected or activated microglia, macrophages, and astrocytes.

In addition to HIV-associated dementia (HAD), other HIV-associated neuropsychiatric complications include the following:

- Minor cognitive motor disorder, which differs from HAD in severity and degree of functional disability but may progress to HAD
- Neurobehavioral impairments (e.g., apathy, depression, anxiety/agitation, sleep disturbance, hypomania)
- Myelopathy, which is functional disturbance and/or pathologic change to the spinal cord
- Aseptic meningitis

Despite the decreasing incidence of HAD in recent years, cognitive impairment is the most common CNS complication in people with HIV/AIDS. Delirium is the most common cognitive disorder in hospitalized patients with AIDS. The prompt diagnosis of cognitive impairment/dementia and delirium may significantly decrease morbidity and mortality.

**Key Point:**
Early stages of dementia and delirium are often subtle, difficult to recognize, and may resemble primary psychiatric disorders.

II. HIV-ASSOCIATED DEMENTIA
Greater degree of immunodeficiency and age are significant risk factors for HAD. However, the incidence of HAD has decreased since the introduction of HAART. After initiation of HAART, some people with HAD have shown marked improvement in cognitive status. This has been postulated to be due to an improvement in immune status, as evidenced by increased CD4 cell count and a decrease in plasma viral load and cerebral spinal fluid (CSF) viral load. Early studies, particularly in the pre-HAART era, have indicated that CSF HIV viral load correlates with severity of cognitive dysfunction, particularly in patients whose CD4 count is <200 cells/mm³. At this time, measurement of viral load in CSF is predominantly a research tool, rather than routine standard of care.

A. Presentation
HAD produces a highly variable clinical course and a spectrum of signs and symptoms, ranging from subtle cognitive and motor impairments to profound dementia (see Table 1). Common early symptoms include word-finding difficulty, forgetfulness, psychomotor slowing, and diminished writing or visual/motor skills. Simple strategies, such as written reminders, can be used to compensate for early deficits.
Table 1
Clinical Manifestations of HIV-Associated Dementia

<table>
<thead>
<tr>
<th>Type of Impairment</th>
<th>Manifestations</th>
</tr>
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<tbody>
<tr>
<td>Affective</td>
<td></td>
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<tr>
<td></td>
<td>- Apathy (depression-like features)</td>
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<td></td>
<td>- Irritability</td>
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<td></td>
<td>- Mania, new-onset psychosis</td>
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<tr>
<td>Behavioral</td>
<td>- Psychomotor retardation (slowed speech or response time)</td>
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<tr>
<td></td>
<td>- Personality changes</td>
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<tr>
<td></td>
<td>- Social withdrawal</td>
</tr>
<tr>
<td>Cognitive</td>
<td>- Lack of visuospatial memory (misplacing things)</td>
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<tr>
<td></td>
<td>- Lack of visuomotor coordination</td>
</tr>
<tr>
<td></td>
<td>- Difficulty with complex sequencing (difficulty in performing previously learned complex tasks)</td>
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<tr>
<td></td>
<td>- Impaired concentration and attention</td>
</tr>
<tr>
<td></td>
<td>- Impaired verbal memory (word-finding ability)</td>
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<tr>
<td></td>
<td>- Mental slowing</td>
</tr>
<tr>
<td>Motor</td>
<td>- Unsteady gait, loss of balance</td>
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<tr>
<td></td>
<td>- Leg weakness</td>
</tr>
<tr>
<td></td>
<td>- Dropping things</td>
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<tr>
<td></td>
<td>- Tremors, poor handwriting</td>
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<tr>
<td></td>
<td>- Decline in fine motor skills</td>
</tr>
</tbody>
</table>

Common psychiatric symptoms include depressed mood and hypomania (see Depression And Mania In Patients With HIV/AIDS). Some patients experience a gradual mental decline, whereas others deteriorate rapidly over a relatively short period of time. Seizures, global cognitive deterioration, mutism, incontinence, and severe confusion are common clinical features of late-stage HAD.

B. Diagnosis

**Recommendations:**
Clinicians should exclude other treatable, reversible causes of change in mental status before a diagnosis of HAD can be made (see Table 2).

Clinicians should conduct neuroimaging studies and a lumbar puncture as part of a complete evaluation for HAD.
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Differential Diagnosis of Symptoms Presenting As Possible HAD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS disease</strong></td>
<td>Infectious</td>
</tr>
<tr>
<td></td>
<td>• Cytomegalovirus encephalitis</td>
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<tr>
<td></td>
<td>• Neurosyphilis</td>
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<tr>
<td></td>
<td>• Cryptococcal meningitis</td>
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<tr>
<td></td>
<td>• Tuberculous meningitis</td>
</tr>
<tr>
<td></td>
<td>• CNS toxoplasmosis</td>
</tr>
<tr>
<td></td>
<td>• Progressive multifocal leuencephalopathy*</td>
</tr>
<tr>
<td></td>
<td>• HIV minor cognitive motor disorder</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td>CNS lymphoma</td>
</tr>
<tr>
<td></td>
<td>Metastatic disease</td>
</tr>
<tr>
<td><strong>Vasculitis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic/metabolic/endocrine disease</strong></td>
<td>B12 deficiency</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Thyroid disease</td>
</tr>
<tr>
<td></td>
<td>Addison’s disease</td>
</tr>
<tr>
<td><strong>Primary psychiatric illness</strong></td>
<td>Mood disorders (major depression,* hypomania, dysthymia)</td>
</tr>
<tr>
<td></td>
<td>Delirium</td>
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<tr>
<td><strong>Substance withdrawal or intoxication</strong></td>
<td>Chronic methamphetamine</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Opioids</td>
</tr>
<tr>
<td></td>
<td>Chronic cannabis</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td>Psychotropics (antipsychotics, sedative-hypnotics, sedating antidepressants)</td>
</tr>
<tr>
<td></td>
<td>Antiretroviral therapy</td>
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<tr>
<td></td>
<td>Drug-drug interactions (see Appendix II)</td>
</tr>
</tbody>
</table>

*Cognitive impairment may occur as an accompanying feature of a depressive episode. The term *pseudodementia* is used to describe this clinical presentation, which resolves with appropriate treatment of the depressive disorder.

Substance use disorders/intoxication, CNS opportunistic infections, and malignancies should always be included in the differential diagnosis, particularly when cognitive changes are acute and/or progress rapidly. Although computed tomography (CT) and magnetic resonance imaging (MRI) scans may be nonspecific, they are useful to exclude other CNS disorders. MRI is preferable to CT. Magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have been used to evaluate HAD, but they are primarily used in research settings at this time. For further discussion of the advantages and disadvantages of each, see *Criteria for the Medical Care of Adults With HIV Infection: Neurologic Complications of HIV Infection*. 

3
When early-stage HAD is suspected, the usual screening tests used for cognitive disorders are of limited value, including abbreviated forms of the mental status examination such as the Folstein Mini-Mental State Exam. Although not effective for identifying early-stage cognitive dysfunction, the following tests have been used to identify and stage HAD:

- **HIV Dementia Scale:** screens for the memory and attention deficits and psychomotor slowing that are typical of HIV dementia; requires training to administer and, therefore, may not be ideal for a clinic setting (see Appendix A).

- **Modified HIV Dementia Scale:** designed specifically for use by non-neurologists and, therefore, may be more ideal than the HIV Dementia Scale for the clinic setting; requires approximately 5 minutes to administer (see Appendix B).

- **Mental Alternation Test:** useful for assessing patients with early dementia who will show impairments in timed trials (see Appendix C).

- **Memorial Sloan Kettering (MSK) Scale:** can be used for assessing severity (see Appendix D); it combines the functional impact of both cerebral (dementia) and spinal cord (myelopathy) dysfunction. The two entities can be separated and staged independently.

- **Trail Making Test, Parts A and B (from the Halstead-Reitan Neuropsychological Battery):** may be used as a screening tool, but results require interpretation by a neuropsychologist. However, it may be used at the bedside to track a patient’s response to ARV treatment over time (to order the test, see http://www.reitanlabs.com/catalog/default.php).

In addition to screening tests, reports from caregivers or family members may also be useful when assessing patients for possible symptoms of HAD.

**Key Point:**
HAD may be incorrectly diagnosed as Alzheimer’s disease. Early HAD differs from Alzheimer’s disease in that it is more likely to present with behavioral changes, progresses more rapidly, may be associated with abnormal CSF findings, and is rarely associated with aphasia.

C. Management of Patients With HAD

1. Referral

**Recommendations:**
Clinicians should refer patients with HAD who present with accompanying depression, mania, psychosis, behavioral disturbance, or substance use for psychiatric consultation to assist in psychopharmacologic treatment and management.

Clinicians should refer patients who require treatment with multiple psychotropic medications and/or are using illicit substances for psychiatric consultation because of the risk of drug-drug interactions and toxicity.
Psychiatric consultation may assist in differentiating between HAD and pseudodementia associated with depression and between HAD and cognitive impairment attributable to mania, psychosis, delirium, substance use, or psychotropic or HIV-related medications. Neuropsychological testing may also be helpful with diagnostic assessment.

2. Treatment
In centers with neuro-AIDS expertise, the treatment of HAD is a multidisciplinary approach that involves infectious disease specialists, neurologists, and psychiatrists. A psychologist, nurse practitioner, or social worker may also help with behavioral strategies for the management of patients with HAD.

Three therapeutic modalities exist for management of patients with HAD:
- ARV therapy
- Pharmacologic treatment of symptoms
- Nonpharmacologic management

The MSK scale (described above; Appendix D) may be useful in developing a management plan and determining the level of assistance a patient may need.

a. Antiretroviral Drugs

**RECOMMENDATIONS:**
Clinicians should assess the efficacy of the HAART regimen when patients receiving HAART present with symptoms of HAD.
Clinicians should initiate HAART when patients not receiving HAART present with symptoms of HAD.

Early, small studies have shown that HAART that includes drugs that penetrate the blood-brain barrier, particularly zidovudine, lead to improvement and, at the very least, to a partial return of functioning in patients previously diagnosed with HAD. However, more recent data suggest that when HAART results in viral suppression, it will improve patients’ cognitive performance, independently of its theoretical ability to efficiently cross the blood-brain barrier. Therefore, it is probable that if viral load is suppressed systemically, it will be suppressed in the CNS. Accordingly, the prevailing goal may be to achieve viral suppression, rather than using a regimen that is superior only in crossing the blood-brain barrier. Future research may help elucidate the optimal ARV regimens for treatment of HAD.

b. Pharmacologic Treatment of Symptoms

Patients with HAD may also benefit from psychotropic medications used to target specific symptoms, such as psychomotor slowing, agitation, anxiety, depression, mania, and psychosis. However, HIV-infected patients are more likely than the non-infected population to develop extrapyramidal side effects with antipsychotic agents and hepatotoxicity with drugs that are metabolized primarily by the liver. In addition, drug-drug interactions between PIs and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs) with psychotropic drugs may lead to increases in adverse drug reactions (see Appendix II).
c. Nonpharmacologic Management

**RECOMMENDATIONS:**
Clinicians should involve members of the patient’s primary support system, such as family or friends, in both medication management and attending appointments and should educate them about HAD and its course.

Clinicians should assess patients’ ability to function independently at home and arrange for assistance in the form of family support, nursing case management, and nursing home care services when indicated. Clinicians should refer patients who are unable to be safely cared for at home for placement in a skilled nursing facility.

Clinicians should discuss advance directives such as a living will, healthcare proxy, or durable power of attorney early in the course of illness, while patients have the capacity to make decisions about their treatment. Clinicians should clearly document the content of these discussions in the medical record and include copies of advance directives as part of the medical record.

Clinicians should consult with a psychiatrist if questions exist about a patient’s mental capacity to make decisions about his or her treatment.

Patients with HAD may lose decision-making capacity due to either acute illness, such as delirium, or progression of underlying cognitive deficits. Loss of decision-making capacity may be either temporary and reversible or permanent. Determination of a patient’s ability to make decisions about his or her treatment should always refer to a specific clinical situation, for example, the capacity to refuse a lumbar puncture. Clinically, determination of decisional capacity may arise more often with regard to a patient’s capacity to *refuse* a medical procedure or treatment. Therefore, attention to both advance directives and family involvement may be particularly important in the management of patients with HAD.

In the nonpharmacologic management of patients with HAD, clinicians should do the following:
- **When giving instructions:**
  - Simplify complex tasks, especially drug regimens
  - Suggest use of pill boxes, diaries, and time tables
  - Repeat information
  - Write instructions to provide structure for patient and caregiver
- **When presented with patients who are confused, agitated, or challenged by their experience:**
  - Maintain orientation cues, and structure activities appropriately
  - Try to keep the environment familiar and prepare patients for change
  - Redirect or distract patients from inappropriate behavior
  - Maintain calm when patients become confused or agitated and refrain from confronting an agitated patient
  - Depending on the severity of the case, explain the benefits of structured routines and activities, such as attending day programs, church, and family gatherings and spending time outdoors
Because the term *dementia* and the awareness of cognitive decline can be frightening to HIV-infected patients and to their families, educating patients and their families is crucial.

### III. Delirium Associated With HIV

**Recommendation:**
Clinicians should immediately refer patients who present with signs and symptoms of delirium to the hospital.

Delirium is the most common neuropsychiatric complication in hospitalized patients with AIDS. Delirium may be life-threatening and requires immediate medical attention. Occasionally, patients may present with early signs of delirium in the primary care setting. Thus, it is essential that clinicians be able to recognize the signs and symptoms and refer patients to the hospital immediately. In these cases, the clinician should then contact the emergency department to follow-up with the disposition of the patient.

The following patients are at risk for developing delirium:
- Those in advanced stages of immunosuppression
- Those with a history of opportunistic infections, substance use, head/brain injuries, or episodes of delirium
- Those with HAD or infections and malignancies of the CNS

#### A. Presentation and Diagnosis

**Recommendation:**
Clinicians should assess for delirium when there is a sudden change in a patient’s cognitive functioning, consciousness, or behavior.

The hallmarks of delirium are an impairment of consciousness, with a reduced ability to focus or sustain or shift attention, and changes in cognition or development of perceptual disturbances that are not explained by a preexisting dementia. These disturbances may develop over a short period of time, and the symptoms may fluctuate in severity. Delirium is generally a direct physiologic consequence of a medical condition. Table 3 summarizes manifestations of delirium in patients with HIV/AIDS.
### Table 3
Clinical Manifestations of Delirium in HIV-Infected Patients

- Impairment of memory, orientation, prefrontal “executive” functions
  - Difficulty with abstraction
  - Difficulty with sequential thinking
  - Impaired temporal memory
  - Impaired judgment

- Disturbances in thought and language
  - Decreased verbal fluency

- Disturbances in perception
  - Hallucinations (primarily visual)
  - Illusions (misinterpretation of visual cues, e.g., mistaking shadows for people)

- Disturbances in psychomotor function
  - Hypoactive
  - Hyperactive
  - Mixed hypo- and hyperactive

- Disturbances in sleep-wake cycle
  - Daytime lethargy
  - Nighttime agitation

- Delusions*

- Affective lability

- Neurologic abnormalities
  - Tremors
  - Ataxia
  - Myoclonus
  - Cranial nerve palsies
  - Asterixis
  - Cerebellar signs
  - Nystagmus

* Delusions are usually paranoid but more disorganized than those seen in psychoses.

Delirium is often difficult to diagnose. When patients appear hypoactive, depression is a frequent misdiagnosis for delirium. Possible causes of delirium are listed in Table 4. Clinicians should maintain a high index of suspicion for delirium related to CNS infections and substance use in HIV-infected patients. It is important to note that the combination of HIV infection and methamphetamine use is associated with significant brain structure alterations and cognitive impairment.
Table 4
Possible Causes of Delirium

<table>
<thead>
<tr>
<th>Possible Causes of Delirium</th>
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</thead>
<tbody>
<tr>
<td>Metabolic abnormalities</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Hypoxemia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>CNS infections and malignancies</td>
</tr>
</tbody>
</table>

B. Management of Patients With Delirium

**RECOMMENDATION:**
Treatment should be aimed at correcting the underlying conditions that have led to delirium.

Treatment of delirium in patients with HIV/AIDS is based on the same principles used for treatment of delirium in patients with other medical illnesses. Correcting the underlying conditions that have led to delirium is the primary treatment. Symptoms such as confusion or agitation can be treated by using low doses of neuroleptics (e.g., haloperidol or risperidone; see Appendix II). If symptoms of agitation put the patient or others at risk and are not controlled by low doses of antipsychotics, adding low doses of lorazepam may achieve sedation. Psychiatric consultation may be helpful in management.

**Key Point:**
HIV-infected patients may be more sensitive to the side effects of psychotropic medications. Older patients and those with more advanced disease are at highest risk for side effects.

**References**


**FURTHER READING**


### Appendix A

**HIV Dementia Scale***

<table>
<thead>
<tr>
<th>Max Score</th>
<th>Score</th>
<th><strong>Memory-Registration</strong> Give four words to recall (dog, hat, green, peach) - 1 second to say each. Then ask the patient all 4 after you have said them.</th>
</tr>
</thead>
</table>
| 4         | ( )   | **Attention†** Anti-saccadic eye movements: 20 (twenty) commands.  
            |       | ____errors of 20 trials.  
            |       | ≤3 errors = 4; 4 errors = 3; 5 errors = 2; 6 errors = 1; >6 errors = 0 |
| 6         | ( )   | **Psychomotor Speed** Ask patient to write the alphabet in upper case letters horizontally across the page (use back of this form) and record time: ____seconds.  
            |       | ≤21 sec = 6; 21.1 - 24 sec = 5; 24.1 - 27 sec = 4; 27.1 - 30 sec = 3; 30.1 - 33 sec = 2; 33.1 - 36 sec = 1; >36 sec = 0 |
| 4         | ( )   | **Memory Recall** Ask for 4 words from Registration above. Give 1 point for each correct. For words not recalled, prompt with a "semantic" clue, as follows: animal (dog); piece of clothing (hat); color (green); fruit (peach). Give 1/2 point for each correct after prompting. |
| 2         | ( )   | **Construction** Copy the cube below; record time: ____seconds.  
            |       | (<25 sec = 2; 25 - 35 sec = 1; >35 sec = 0) |


A score of <10 points would be an indication of possible HAD.

* Because of the Attention category, this scale requires training to administer and, therefore, may not be preferable for use in a clinic setting. The Modified HIV Dementia Scale (Appendix B) omits the Attention category, making the modified scale more ideal for administration by the clinician.

† Attention: Hold both hands up at patient's shoulder width and eye height, and ask patient to look at your nose. Move the index finger of one hand, and instruct patient to look at the finger that moves, then look back to your nose. Practice until patient is familiar with task. Then, instruct patient to look at the finger which is NOT moving. Practice until patient understands task. Perform 20 trials. An error is recorded when the patient looks towards the finger that is moving.
### Appendix B

**Modified HIV Dementia Scale***

- After omitting the “Attention” category in the HIV Dementia Scale, perform the scale as described in Appendix A.
- With the omission of the “Attention category,” the maximum score totals 12 points.
- A score of <7.5 points would be an indication of possible HAD.


### Appendix C

**Mental Alternation Test***

- Patients are asked to count to 20, say the alphabet, and then alternate between the numbers and letters in the following fashion: “1-A, 2-B, 3-C...”
- Progressing from the most recent number or letter to the next letter or number in the sequence is one alternation.
- The number of correct alternations in 30 seconds, discounting any errors, determines the score.
- The maximum score is 52 points.
- A score of ≤15 indicates the need for more extensive cognitive testing.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Degree of Severity</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>0.5</td>
<td>Equivocal or subclinical</td>
<td>Absent, minimal, or equivocal symptoms, without impairment of work or capacity to perform activities of daily living (ADL); mild signs, such as snout reflex and slowed ocular or extremity movements, may be present (gait and strength are normal)</td>
</tr>
<tr>
<td>1.0</td>
<td>Mild</td>
<td>Able to perform all but the more demanding aspects of work and ADL, but with unequivocal evidence of intellectual or motor impairment, which may include impaired performance on neuropsychologic testing (tandem gait may be impaired but patient can walk without assistance)</td>
</tr>
<tr>
<td>2.0</td>
<td>Moderate</td>
<td>Able to perform basic activities of self-care but cannot work or maintain the more demanding ADL (ambulatory but may require single prop, e.g., cane)</td>
</tr>
<tr>
<td>3.0</td>
<td>Severe</td>
<td>Major intellectual incapacity—cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output—or motor disability (cannot walk unassisted, requiring walker or personal support, usually with slowing and clumsiness of arms as well)</td>
</tr>
<tr>
<td>4.0</td>
<td>End-stage</td>
<td>Nearly vegetative, intellectual and social comprehension and output are at a rudimentary level, nearly or absolutely mute (paraparetic or paraplegic with urinary and fecal incontinence)</td>
</tr>
</tbody>
</table>


* Myelopathy staging is in parentheses.