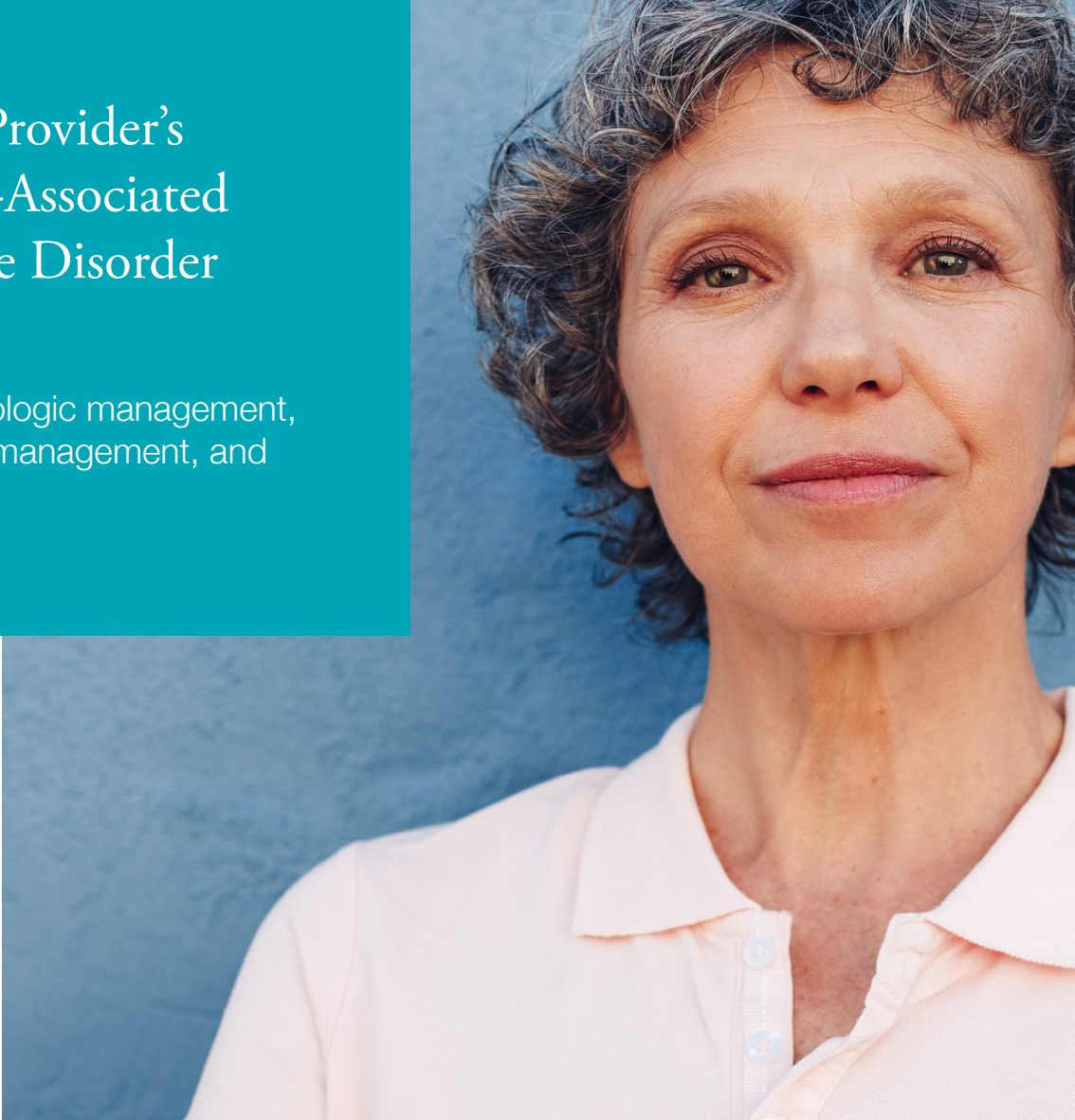


A Healthcare Provider's Guide to HIV-Associated Neurocognitive Disorder (HAND):

Diagnosis, pharmacologic management,
non-pharmacologic management, and
other considerations

This material is provided
by UCSF Weill Institute
for Neurosciences as an
educational resource for
health care providers.



UCSF Weill Institute for Neurosciences
Memory and Aging Center



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Diagnosis

Definition

People living HIV may develop a spectrum of cognitive, motor, and/or mood problems collectively known as HIV-Associated Neurocognitive Disorder (HAND). Typical symptoms include difficulties with attention, concentration, and memory; loss of motivation; irritability; depression; and slowed movements. Previously known as *AIDS Dementia Complex*, HAND is categorized into three levels of functional impairment. *Asymptomatic Neurocognitive Impairment* (ANI) is a mild form of HAND with impaired performance on neuropsychological tests, but affected individuals report independence in performing everyday functions. *Mild Neurocognitive Disorder* (MND) is a common form of HAND that mildly interferes with everyday function. In its most severe form, HAND can manifest as *HIV-Associated Dementia* (HAD), where there is an inability to complete daily tasks independently. HAND is not necessarily a progressive disorder that worsens with time.

Epidemiology and Etiology

Before the arrival of anti-retroviral therapy (ART), HAD was frequent in late-stage disease. Although the advance in HIV treatments in the mid 1990s has shifted the severity of HAND away from the more severe HAD, effective antiretroviral therapy and viral suppression cannot entirely prevent the development of HAND. Currently, up to 30–50% of people living with HIV may suffer from HAND, most of whom have mild forms.¹ The etiology of HAND is currently being studied by researchers. HAND may in part be caused by residual injury from unsuppressed HIV viral replication in the brain in the time prior to starting ART. Persistent immune activation is also a theorized cause of HAND, as even patients on virally suppressive ART can have persistent immune activation in the plasma and cerebrospinal fluid (CSF).

Risk Factors

Risk factors for developing HAND include lack of viral suppression, low nadir CD4 count, and increasing age.^{2,3,4} Additional risk factors may include medical comorbidities such as hypertension, hyperlipidemia, diabetes, and possible co-infections like hepatitis C.⁵ There may also be host factors that make certain individuals more vulnerable to develop HAND.

Course

There is no typical course of HAND, and it is not typically thought to be a progressive disorder inevitably leading to dementia. Most of the time, HAND symptoms remain mild in patients on ART with an undetectable viral load. Some people experience only issues with attention, concentration, irritability or apathy, while others struggle with a combination of cognitive, motor, and mood changes. How much these changes disrupt a person's daily life differs from one individual to the next. Cognitive symptoms are often—although not always—the first problem to become apparent to a person with HAND and their family members, friends, caregivers, and health care providers.

Differential Diagnosis

For any HIV patient with new onset neurologic or neurocognitive (approximately within the previous year), it is critical to rule out the process of central nervous system (CNS) viral escape. CNS viral escape is the presence of replicating HIV virus in the CSF when there is very low or undetectable HIV RNA in the blood. This can occur, as HIV mutates rapidly in a given environment and may uniquely “compartmentalize” within the CNS. The clinical presentation of CNS viral escape is quite variable, and clinicians should have a low threshold for performing a lumbar puncture to measure CSF HIV RNA for any new onset neurologic

or neurocognitive symptoms.^{6,7} Simultaneous plasma HIV RNA should also be ordered, and genotyping for drug resistance patterns should be performed if there are detectable levels of HIV RNA. Any identified drug resistance patterns can then guide alterations of the ART regimen.

In addition to considering CNS viral escape, patients should be screened for symptoms of obstructive sleep apnea that can cause cognitive changes. A sleep study should be ordered if there are any suspicions of obstructive sleep apnea. Practitioners should also screen for reversible causes of cognitive change, such as low vitamin B12 (lower than 400), abnormal TSH, or a positive RPR. It is also possible that older people living with HIV may independently develop a neurodegenerative process, such as Alzheimer's disease, which may cause cognitive changes.

Diagnostic Criteria

The National Institute of Mental Health and the National Institute of Neurological Diseases and Stroke directed a working group to develop a standardized diagnostic classification of HAND. The results were published in 2007.⁸

HIV-1-associated mild neurocognitive disorder (MND)

If there is a prior diagnosis of MND, but currently the individual does not meet criteria, the diagnosis of MND in remission can be made.

Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 standard deviation (SD) below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills. Typically, this would correspond to a Memorial Sloan Kettering (MSK) scale stage of 0.5 to 1.0.

The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):

- Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning.
- Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.
- The cognitive impairment does not meet criteria for delirium or dementia.
- There is no evidence of another preexisting cause for the MND.

If the individual with suspected MND also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of MND should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use.

1. HIV-1-associated dementia (HAD)

If there is a prior diagnosis of HAD, but currently the individual does not meet criteria, the diagnosis of *HAD in remission* can be made.

- a. Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (Note that where neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used, but this should be done as indicated in algorithm; see below). Typically, this would correspond to an MSK scale stage of 2.0 or greater.
- b. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities).
- c. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature), or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.
- d. There is no evidence of another, preexisting cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse compatible with CNS disorder).
 - i. If the individual with suspected HAD also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of HAD should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least one month has elapsed following cessation of substance use. Note that the consensus was that even when major depression and HAD occurred together, there is little evidence that pseudodementia exists and the cognitive deficits do not generally improve with treatment of depression

Pharmacologic Management

Medications to Use

The primary medical intervention at this time is to achieve viral suppression and a CD4 count >200 with ART. Lack of treatment is the biggest risk factor for cognitive decline. A small number of studies suggest that adding a CCR5 inhibitor, such as maraviroc, may improve cognition in HAND.^{9,10} However, this is not currently a universally accepted practice.

Expected benefits may be mild improvement in alertness, concentration, and memory. If the patient has vascular disease, they should receive management and education regarding tight control of cardiovascular risk factors.

Medications to Avoid

Medications with strong anticholinergic side effects, such as sedating antihistamines, barbiturates, narcotics, benzodiazepines, gastrointestinal and urinary antispasmodics, CNS stimulants, muscle relaxants, and tricyclic antidepressants should be avoided. Antipsychotics should be used with caution. If used, carefully evaluate effectiveness of medication and consider discontinuing if there is no improvement in six weeks.^{11,12,13}

Non-pharmacologic Management

Healthy Lifestyle

Research suggests that the combination of good nutrition, vigorous physical activity, and mental and social engagement may provide benefit for people with cognitive disorders.^{14,15} More research is needed to determine the actual mechanisms behind these effects. A heart-healthy diet (lower in sugar and fat and higher in vegetables and fruit) is considered to be good for both the body and the brain. An example is the Mediterranean diet that promotes nutrition based on fruit, vegetables, nuts, and grains with limits on consumption of red meat and saturated fats. Vigorous physical exercise has been associated with improvement of mood and mobility, and a decrease in the risk for falls.^{16,17} Socially engaging physical activities (e.g., swimming with a friend, participating in exercise groups) can be especially enjoyable. Engagement in activities that are mentally stimulating (crossword puzzles, Sudoku, computer games) is encouraged as long as the activity is enjoyable.

The Alzheimer's Association has more information on tips for maintaining your health: alz.org/we-can-help-brain-health-maintain-your-brain.asp

Sleep

Disrupted sleep can negatively impact memory and thinking, though the mechanisms are not well understood.¹⁸

Components of sleep hygiene include:

- Avoid napping during the day
- Avoid stimulants such as caffeine, nicotine, and alcohol too close to bedtime
- Get regular exercise
- Avoid eating right before sleep

Other Considerations

Support Resources

- The AIDs Education and Training Center: aidsetc.org/guide/hiv-associated-neurocognitive-disorders
- POZ: poz.com/basics/hiv-basics/hiv-brain-hiv-associated-neurocognitive-disorder
- Family Caregiver Alliance: caregiver.org/hiv-associated-neurocognitive-disorder-hand
- Alzheimer's Association: alz.org
- Family Caregiver Alliance: caregiver.org
- National Institute of Health/National Institute on Aging: nia.nih.gov/alzheimers
- US Dept. of Health and Human Services Health Resources and Services Administration: hab.hrsa.gov/deliverhivaidscares/neurocognitiveimpairment.pdf
- Alzheimer's Australia Vic: fightdementia.org.au/sites/default/files/20140723_-_NAT_-_Professional_resources_-_HAND_booklet_for_workers%5b1%5d.pdf
- Mind Exchange Working Group: ncbi.nlm.nih.gov/pubmed/23175555

Research and Clinical Trials

The National Institutes of Health maintains an extensive listing of clinical trials at clinicaltrials.gov. Academic medical centers may be engaged in research and clinical trials.

Driving

Most patients with HAND have no impairments in driving. Reporting to the department of motor vehicles should be consistent with state laws. Some states have mandatory reporting requirements: the diagnosis is reported to local health departments who then report to the DMV. Individual state requirements can be found at: dmvusa.com.



Living Situation and Environment

It is important to determine if the patient's residential setting best meets his or her functional and cognitive abilities. Areas of concern may include personal safety (e.g., ability to manage medications safely, nutritional requirements, personal hygiene) and quality of life (e.g., activities and engagement that match the person's needs and abilities). HIV-positive elders may face unique difficulties living alone with minimal support structures due to social isolation, stigma of the disease, and the HIV epidemic taking the lives of friends and partners.

Elder Abuse

Patients with cognitive issues and their caregivers are vulnerable to abuse. Refer to Adult Protective Services (APS) if there is concern for the well-being of the patient or the caregiver.

To locate an APS office in your state, see: napsa-now.org/get-help/help-in-your-area/.

Legal Planning

It is always wise to provide information about advance directives and durable power of attorney. Make referrals for legal and financial advice, especially if there are concerns about the patient's judgment, decision-making, or vulnerability. A formal evaluation for capacity may be warranted in some circumstances. The Alzheimer's Association provides a brochure that covers legal planning: alz.org/national/documents/brochure_legalplans.pdf.

- Advanced Directives**
 These documents allow individuals to state their preferences for medical treatments and to select an agent or person to make health care decisions in the event they are unable to do so or if they want someone else to make decisions for them.
- Power of Attorney**
 A Power of Attorney (POA) is a legal document that gives someone of an individual's choosing the power to act in his or her place. POAs can be for medical or financial matters.
- Living Will**
 A living will is a written, legal document that spells out medical treatments that an individual would and would not want to be used to keep them alive, as well as other decisions such as pain management or organ donation.

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