



Prevalence

Diagnosis

What to do About HAND

Conclusion

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS IN THE COMBINATION ANTIRETROVIRAL THERAPY ERA

Since the beginning of the epidemic, HIV infection has been associated with neurologic and neurocognitive complications.¹ HIV-associated neurocognitive disorders (HAND), the term used to describe these manifestations, describes a spectrum ranging from mild, asymptomatic neurologic impairment to severe, HIV-associated dementia (HAD).² Symptoms of HAND include behavioral changes; difficulties with decision-making, problem solving, concentration, learning, language, and memory; loss of coordination; weakness; and tremors.^{3,4}

Combination antiretroviral therapy (cART) use has changed the pattern—but not the overall prevalence—of neurocognitive impairment among people living with HIV (PLWH). In the pre-cART era, moderate-to-severe impairment was more common among people with AIDS than those with less advanced HIV disease (ranging from 4% in asymptomatic persons to 17% in people with AIDS).⁵ “We are simply not seeing new cases of AIDS dementia in treated patients, but mild cognitive impairment remains a challenge,” says Dr. David B. Clifford, Professor of Clinical Neuropharmacology in Neurology and Professor of Medicine at Washington University School of Medicine.

In the cART era, both the rate and severity of cognitive impairment have doubled among people with asymptomatic HIV, possibly due to prolonged immunosuppression and lower CD4 cell counts prior to commencement of cART.⁶ According to Dr. Victor Valcour, Associate Professor of Geriatric Medicine and Neurology at the University of

DID YOU KNOW?

- It is estimated that 50% of HIV-positive people have some degree of neurocognitive impairment.
- Since 1998, the National Institutes of Health has funded a national HIV brain bank with four sites: New York, N.Y.; Galveston, Texas; Los Angeles, Calif.; and San Diego, Calif. Together, these are referred to as the National NeuroAIDS Tissue Consortium. The Consortium represents a partnership between people living with HIV (PLWH) and researchers. Study volunteers provide body fluid samples, undergo regular evaluations, and have agreed to become organ donors to advance knowledge about HIV's effects on the brain and nervous system. More information is available at: www.hivbrainbanks.org.

Sources: Valcour VG. HIV, aging, and cognition: emerging issues. *Top Antivir Med.* Jul–Aug 2013;21(3):119–23.

Icahn School of Medicine at Mount Sinai. Manhattan HIV Brain Bank. Overview. 2013. Available at: <http://icahn.mssm.edu/research/programs/manhattan-hiv-brain-bank/about-us>. Accessed October 31, 2013.



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➔ DIRECTOR'S NOTES

Highly active antiretroviral therapy (HAART) has dramatically decreased incidence of HIV-associated dementia (HAD), the most severe form of HIV-associated neurocognitive disorder (HAND). As people living with HIV (PLWH) age, they become more vulnerable to HAND, although it can also occur in younger people too. HAART can stop progression of HAND, but does not prevent it; 50% of PLWH are affected, although most cases are mild to moderate.

Screening for HAND is an important part of total HIV care, especially for patients with a low CD4 cell nadir, and poor immunologic or virologic response to treatment. We are dedicated to assisting PLWH meet their needs and arming providers with resources to do so. As such, we have included links to simple screening tools to assess patients for HAND, as well as a review of management strategies for HAND in this issue of *HRSA CAREAction*.

Clinicians can help PLWH to prevent, delay, or mitigate HAND by encouraging adherence to HAART, a healthy diet, exercise, smoking cessation, and by managing comorbidities known to promote or worsen HAND (e.g., type 2 diabetes, cardiovascular disease, substance abuse, psychiatric disorders, and hepatitis C coinfection). Cognitive rehabilitation—using alarms and reminders to support adherence and computerized training programs to improve attention, memory, logic, visual and motor skills—has demonstrated some success against HAND.

While there is currently no cure for HAND, there have been strides in this field. We remain dedicated to addressing the mental health needs of Ryan White HIV/AIDS Program patients, and increasing awareness of HAND is just one more way we continue to do so.

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HRSA CAREAction

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California, San Francisco, "Cognitive impairment is quite frequent in HIV. If you test 100 people, about 50% of them will test below what we expect, yet only a quarter or a third of them will have symptoms."

In the pre-cART era, patients with the more serious form of HAND—HIV-associated dementia, or HAD—progressed rapidly and their prognosis was poor. Fortunately, cART use has decreased the incidence of HAD (from 15% to 2%), and dramatically extended median survival among people with this condition, from five months to four years.⁷⁻¹⁰ Impairment in motor skills, verbal fluency, and cognitive speed were common in the pre-cART era; nowadays, HAND appears more similar to Alzheimer's disease.¹¹ "Save for very rare viral escape in the central nervous system, HIV-driven brain disease, like HIV-associated dementia, is hardly ever seen on effective ARV," says Dr. Clifford, "It has essentially been cured by cART."

Nonetheless, even in the cART era, PLWH are still vulnerable to neurological complications, even when HIV is undetectable.¹²⁻¹⁴ Researchers have reported that the presence of inflammatory markers—rather than the HIV RNA or CD4 cell count—are associated with HAND in people on cART.¹⁵ In fact, immunologic recovery and virologic suppression have been associated with increased abnormalities in white and gray matter, which supports the role of neuroinflammation as a cause of HAND.¹⁶

PREVALENCE OF HAND

It is estimated that at least 50% of HIV-positive people have some degree of neurocognitive impairment.¹⁷⁻¹⁹ An estimated 33% of HIV-positive people experience mild neurocognitive impairment.²⁰ The most common presentations of HAND are impaired memory and executive function (the ability to remember details, make plans, organize, focus, manage time, and control behavior). But even in mild cases, HAND may cause real-life consequences, such as poor adherence to HIV treatment and difficulty with everyday functioning (e.g., shopping, cooking, driving, multitasking and financial management).²¹⁻²⁷

➔ **TABLE 1. HAND: TYPES AND DESCRIPTION**

Criteria for HIV-Associated Neurological Disorders (HAND)

TYPE	DESCRIPTION
HIV-Associated Dementia (HAD)	Marked cognitive impairment with marked functional impairment
Mild Neurocognitive Disorder (MND)	Cognitive impairment with mild functional impairment
Asymptomatic Neuropsychological Impairment (ANI)	Impairment in two or more cognitive abilities

Source: Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. Oct 30, 2007, 69(18):1789–99.

Fortunately, progression from the milder forms of HAND to severe impairment is rare; in fact, most people with mild HAND remain stable or improve after starting cART.

28–31

As Dr. Valcour explains,

Most of the patients that I see over time have mild to moderate impairment. My patients are often very worried about what will come of this; they worry that they will have the kind of progression that people with Alzheimer’s have. In general, most don’t tend to progress; instead, I often see that people fluctuate within a steady state. Patients who have had symptoms for 5 or 10 years have good days and bad days, good months and bad months. I don’t think we can entirely cure this now, but it doesn’t tend to be relentlessly progressive in most of the patients I’ve seen.

Dr. Clifford agrees, “The majority of our patients are not getting progressively worse. When they are taking care of their HIV, our patients are doing quite well; they don’t seem to be progressing faster than HIV-negative people.”

Although HAND is associated with aging, it has also been reported in children, adolescents, and young adults. In the United States, where more than a third of new HIV infections occur among young people, a recent survey reported HAND in 67% of treatment-naïve youth (18 to 24 years of age).³² Neurocognitive impairment has been found in treatment-naïve HIV-positive children aged 6 to 12, despite high CD4 cell counts (>350 cells/mm³).³³ Neurocognitive impairment and white matter abnormalities are common among HIV-infected children, regardless of cART use, although neurocognitive benefits

of cART have been demonstrated in perinatally infected children.^{34,35}

What Causes HAND?

Many factors can cause or worsen HAND, including HIV itself. Shortly after infection, HIV enters the brain and the central nervous system; this is called neuroinvasion.^{36–38} Certain types of white blood cells (macrophages and monocytes) carry the virus throughout the body, including into the central nervous system and the brain, causing inflammation and persistent infection.^{39, 40} Infected macrophages and monocytes pass HIV into microglia (immune cells found only in the brain) and astrocytes (star-shaped cells found in the brain and spinal cord); when these cells are activated in response to HIV, they release neurotoxins that are harmful to brain tissue.^{41,42}

Although HAND is seen more frequently in people with AIDS, it also occurs in people with asymptomatic HIV and has been reported in people with recent HIV infection.^{43,44} But the risk of neurologic complication is higher among people with a low CD4 cell nadir (<200 cells/mm³), even after initiation of and response to cART.^{45,46}

HIV is not the only cause of cognitive impairment. Opportunistic infections, inflammatory immune reconstitution syndrome, and other comorbidities that are more prevalent among PLWH than their HIV-negative counterparts (hepatitis C virus [HCV] coinfection, cardiovascular disease, type 2 diabetes, certain cancers, and syphilis) have been implicated in HAND. In addition, aging, antiretroviral drug toxicity, and long-term, heavy illicit drug and alcohol use are potential contributing factors in HAND.^{47–58}

**TABLE 2. CAUSES OF, AND POTENTIAL CONTRIBUTORS TO, NEUROLOGICAL IMPAIRMENT IN HIV PATIENTS ***

HIV-RELATED	VIRAL	METABOLIC	LIFESTYLE	AGING
I N F L A M M A T I O N				
↓	↓	↓	↓	↓
Low CD4 cell nadir	Hepatitis C virus coinfection	History of, or risk for cardiovascular disease	Heavy, long-term use of drugs and/or alcohol	Neurodegenerative disease
Inflammatory Immune Reconstitution Syndrome	Polyomavirus JC (JC virus)	Insulin resistance/type 2 diabetes	Injection drug use (IDU)	Polypharmacy/drug toxicity
Poor cART adherence	Cytomegalovirus	Dyslipidemia	Sedentary lifestyle	
Opportunistic infections; certain cancers, past syphilis			High BMI/unhealthy diet	
ART-associated toxicities (central nervous system toxicity, dyslipidemia, insulin resistance)			Smoking	
*Many of these factors foster neuroinflammation and can cause or worsen neurocognitive impairment.				

HIV and Aging: HAND in HAND?

The risk for neurodegenerative diseases increases with age.⁵⁹ By 2020, 50% of PLWH in the United States will be over 50 years old. Older HIV-positive people may be long-term survivors or newly infected; in 2010, the Centers for Disease Control and Prevention (CDC) reported that 5% of all new HIV infections occurred in people aged 55 and over.⁶⁰ Older adults are often diagnosed later, since they are often not perceived to be at high risk; delayed initiation of cART, lower CD4 nadir, and blunted immune response increase the risk for HAND.

The risk factors for Alzheimer’s disease in elderly people—immune dysfunction, inflammation, and hyperlipidemia—are also associated with HIV. Comorbidities that become more common as people age—metabolic disorders, and cardiovascular and cerebrovascular disease—are also associated with neurocognitive impairment. Cumulative toxicity from certain antiretroviral agents may contribute to, or increase the risk of HAND among long-term survivors as they age.⁶¹ In fact, HAND is almost

twice as prevalent among HIV-positive people over 50 years of age than their younger counterparts, and they are three times more likely to experience HIV-associated dementia.⁶²

Although age-related comorbidities may complicate adherence to cART, older patients are usually more adherent than those under 50 years of age—unless they are experiencing neurocognitive impairment.^{63–66} HAND-associated poor adherence could result in a vicious cycle that may limit the benefits of cART among older people by worsening neurocognitive impairment.

The complexity of cART regimens varies, according to the number of medications, actual pill count, dosing schedule, and special instructions (such as food requirements). Treatment simplification may improve cART adherence, especially for older people who are likely to be taking other medications.

Use of five or more drugs for various comorbid conditions—known as polypharmacy—is common among

HIV-positive people as they age; 55% of people over 50 years of age are on at least five medications.⁶⁷ Polypharmacy can have a negative impact on adherence, and increases the risk of drug-drug interactions that may lower the effectiveness of cART or worsen drug toxicity.⁶⁸

Late diagnosis and untreated HIV increase the risk for opportunistic infections, particularly in people with advanced immunosuppression. Fortunately, cART has decreased the incidence of and mortality from several of the opportunistic infections known to cause HAND: progressive multifocal leucoencephalopathy, HIV encephalopathy, cytomegalovirus, and primary central nervous system lymphoma.^{69–72}

Delaying cART initiation also increases the risk for inflammatory immune reconstitution syndrome. Usually, this syndrome occurs in people with advanced immunosuppression (CD4 cell count of <50 cells/mm³), most frequently within months of starting, re-starting, or switching cART. After the immune system begins to recover, it may mount a fierce response to pathogens.⁷³ Sometimes, inflammatory immune reconstitution syndrome manifests in the nervous system. Although this can occur in the absence of any pathogen, it is usually a response to tuberculosis; progressive multifocal leucoencephalopathy; toxoplasmic encephalitis; cryptococcal meningitis; or cytomegalovirus.^{74–77} Inflammatory immune reconstitution syndrome is usually manageable, but it can be life threatening, depending on cause and severity.

DIAGNOSING HAND

“Unfortunately,” says Dr. Scott Letendre, Professor of Medicine at University of California, San Diego, “there does not seem to be any single test that performs well in all clinical settings. If you find a test that has been reported to work well in your setting, try it; if it isn’t working, change it. The European AIDS Clinical Society Guidelines include three questions that seem to work well.”

Clinicians must rule out—or identify—other factors that may be causing or worsening HAND, such as opportunistic infections and neurodegenerative disease. Milder forms of HAND can be tricky for clinicians to diagnose because patients do not always notice subtle changes in their own mental status or are unable to monitor or recognize problems with cognition.⁷⁸

QUESTIONS FROM THE EUROPEAN AIDS CLINICAL SOCIETY

- ▶ Do you experience frequent memory loss (e.g., do you forget the occurrence of special events, even the more recent ones, appointments, etc.)?
- ▶ Do you feel that you are slower when reasoning, planning activities, or solving problems?
- ▶ Do you have difficulties paying attention (e.g., to a conversation, book, or movie)?

For each question, answers could be: a) never, b) hardly ever, or c) yes, definitely. HIV-positive persons are considered to have an “abnormal” result when answering “yes, definitely” on at least one question.

Source: European AIDS Clinical Society, Guidelines Version 7.0. October 2013. Available at: www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf. Accessed February 2, 2014.

At present, only clinical criteria and neuropsychiatric testing are used to diagnose HAND; no single laboratory test or biomarker has been established.^{79,80} Experts in the field have practical ideas about screening for HAND.

“There’s really not a great test right now that can be done in a reasonable amount of time in a clinical setting; the dementia scales are good, but not for milder impairment—95% of what we see are milder cases,” says Dr. Victor Valcour, who recommends asking patients if they are having symptoms, but cautions that this can be tricky, since “most people with mild impairment don’t have symptoms.”

Testing for asymptomatic neuropsychological impairment and mild neurocognitive impairment is usually available in research settings. A 1990 workshop held by the National Institute of Mental Health recommended an extensive (7- to 9-hour) or brief (1- to 2-hour) battery of tests to assess neurocognitive impairment in HIV-positive, asymptomatic persons.⁸¹ Since then, researchers have worked to find brief screening instruments—tests that are easy to administer and interpret, and yield results comparable to a comprehensive battery of neuropsychological tests.

The Health Resources and Services Administration (HRSA) has worked hard over the years to address HAND so that providers may be armed with the tools they need. Through newsletters like this one, along with the *Guide for HIV/AIDS Clinical Care*, which includes chapters on neurocognitive disorders (<http://hab.hrsa.gov/deliverhivaidscares/clinicalguide11>), grantees and providers alike have the information they need to best diagnose—and treat—their patients. Mental health screenings are part of HRSA's HIV/AIDS Bureau (HAB) performance measures and an associated mental health newsletter to complement this piece is forthcoming.

Dr. Clifford believes in taking a medical history from his patients "... more than anything else. The simple screening exams are not very sensitive, and don't always pick up a small amount of cognitive impairment. If patients have persistent viral load control and a high CD4 count, I ask people directly about their memory, if they are having trouble remembering appointments and taking care of their finances."

A combination of simple, paper-based tests has been used to screen for mild neurocognitive impairment, although the tests are not always reliable. In clinical settings, simple tests are used for screening and to diagnose mild-to-moderate neurologic impairment and severe neurologic impairment.

Who, When, and How Often to Screen

Although screening for HAND is an important part of HIV care, it is not always clear who should be screened and how often to perform screening. The Mind Exchange Working Group has developed guidance for assessing, diagnosing, and treating HAND; screening for HAND is recommended every 6–12 months in higher risk patients, and every 12–24 months in lower risk patients; immediate screening is recommended at initiation of cART, upon diagnosis with a psychiatric disorder, or if a patient's health has deteriorated.⁸²

"Screen right away," advises Dr. Letendre. "Everyone should be screened when they come to the clinic, especially if they are not on therapy. We want to know if someone has HAND before they begin HIV treatment. It is worthwhile knowing who has problems, since they may resolve with treatment, or inform the choice of

treatment. Be willing to refer patients to a neurologist or psychiatrist for an expert opinion," Letendre says, adding that screening for neurocognitive impairment should be performed every 1 to 2 years, and "at critical time points [such as] if immune suppression is progressing, or if patients develop an opportunistic infection."

Dr. Clifford suggests, "The people to watch closely are those who have a low CD4 cell nadir; a persistently low CD4 cell count; who don't get a good CD4 response from treatment; people who have inconsistent viral load control—and are blipping—they may be at greater risk for HAND," advised Dr. Clifford. "If there is symptomatic new brain disease, do a workup that includes an MRI brain scan and lumbar puncture."

WHAT TO DO ABOUT HAND

"Optimal HIV control is critical for the best brain performance." — Dr. David Clifford

cART

Although several approaches are being studied, initiation of and adherence to cART are the most successful interventions to prevent, delay, or improve HAND.^{83,84} The brain is known to be a reservoir for HIV, even in the context of effective cART.^{85,86} Researchers have found HIV DNA in peripheral blood (despite undetectable HIV RNA after more than a year of cART) and linked it with decreases in brain gray matter.⁸⁷ Antiretroviral agents with activity against HIV-infected macrophages may prevent or improve HAND, since these cells deliver HIV to the brain.⁸⁸

➔ TABLE 3. CRITERIA FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDER

HIV-ASSOCIATED ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT (ANI)

- Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1 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.
- The cognitive impairment does not interfere with everyday functioning.
- The cognitive impairment does not meet criteria for delirium or dementia.
- There is no evidence of another preexisting cause for the ANI.

MILD NEUROCOGNITIVE DISORDER (MND)

- Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1 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 and recall), speed of information processing, sensory-perceptual and motor skills.
- 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 pre-existing cause for the mild neurocognitive disorder. If the individual with suspected mild neurocognitive disorder also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of mild neurocognitive disorder 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.

HIV-ASSOCIATED DEMENTIA (HAD)

- Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in the 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 being 2 standard deviations or greater below that of demographically corrected means.
- The cognitive impairment produces marked interference with day-to-day functioning (work, home life and social activities).
- The pattern of cognitive impairment does not meet criteria for delirium.
- There is no evidence of another, pre-existing cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, pre-existing neurologic disease or severe substance abuse compatible with CNS disorder).

Sources: U.S. Department of Health and Human Services, Health Resources and Services Administration, *Guide for HIV/AIDS Clinical Care* – 2014 Edition. Rockville, MD: U.S. Department of Health and Human Services, 2014.

Adapted from Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007 Oct 30;69(18):1789-99.

Sometimes, high levels of HIV RNA can be detected in the central nervous system even when cART has suppressed HIV to very low or undetectable levels in the blood stream; this is known as “central nervous system (or CNS) escape.” Researchers are studying the relationship between the degree of central nervous system penetration in cART and improvement of neurocognitive function. They devised a central nervous

system penetration-effectiveness (CPE) index to classify antiretroviral agents according to their ability to cross the blood-brain barrier. The scoring is based on the properties of individual drugs, their concentration in cerebrospinal fluid, and/or their effectiveness in clinical studies. Regimens with higher CPE scores are more likely to fully suppress HIV in the central nervous system.^{89,90}

➔ **TABLE 4. INITIAL ASSESSMENT FOR HAND: WHAT GUIDELINES RECOMMEND**

SOURCE	INITIAL ASSESSMENT
<p><i>Guide for HIV/AIDS Clinical Care</i> (HRSA)</p>	<ul style="list-style-type: none"> • Mental status, including orientation, registration, recent and remote memory, and ability to calculate (serial subtraction) • Cranial nerves • Peripheral sensory examination, including pinprick, temperature, and vibratory stimuli • Extremity strength and gait to discern myopathy, neuropathy, and cerebellar disease • Fine motor skills such as rapid alternating movements (often abnormal in dementia) • Deep tendon and plantar reflexes.
<p>Primary Care Guidelines for the Management of Persons Infected With HIV (HIV Medicine Association of the Infectious Diseases Society of America)</p>	<p>Review neurologic and psychiatric symptoms: “. . . persistent and severe headaches, memory loss, loss of concentration, depression, apathy, anxiety, mania, mood swings, lower extremity paresthesia, pain or numbness, paralysis or weakness, cognitive difficulties, dizziness, seizures, sleep disorders. Neurology and/or neuropsychology referral for assessment of neurocognitive disorders, dementia, and focal neuropathies may be indicated.”</p>
<p>Mind Exchange Working Group</p>	<p>“... all HIV patients should be screened for HAND early in disease using standardized tools. Follow-up frequency depends on whether HAND is already present or whether clinical data suggest risk for developing HAND.</p> <p>Since neuropsychological resources are limited in many clinical settings, a presumptive clinical diagnosis of HAND could be based on symptom questionnaires, screening tools, functional assessments, and limited neuropsychological testing. Patients with particular characteristics could then be targeted for full assessments (thorough medical and developmental history, assessment of current and past alcohol and substance abuse or dependence, assessment of depression, anxiety, and post-traumatic stress disorder); a neurological exam, laboratory studies, analysis of cerebral spinal fluid, MRI, and assessment of functional impairment.</p>
<p>Sources: U.S. Department of Health and Human Services, Health Resources and Services Administration, <i>Guide for HIV/AIDS Clinical Care</i> – 2014 Edition. Rockville, MD: U.S. Department of Health and Human Services, 2014.</p> <p>Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. <i>Clin Infect Dis</i>. 2014 Jan;58(1):1–10. doi: 10.1093/cid/cit757. Available at: http://cid.oxfordjournals.org/content/early/2013/11/12/cid.cit665.full?sid=b0ca64ea-960e-45ca-aa17-158c48cca6c9 Accessed January 31, 2014.</p> <p>Mind Exchange Working Group. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. <i>Clin Infect Dis</i>. 2013 Apr;56(7):1004–17. Available at: www.ncbi.nlm.nih.gov/pubmed/23175555. Accessed October 31, 2013.</p>	

Although regimens with a high CPE score (see Table 5) may improve neurocognitive function, this remains controversial; the usual selection criteria for cART is often related to more practical concerns, such as pill burden, dosing schedule, and side effect profile. Antiretroviral agents themselves can have side effects, despite their lifesaving benefits: Efavirenz, for example, is associated with central nervous system side effects.^{91,92} “Data support the underlying principle that some ARVs are better than others for the nervous system, even if the CPE is not the best way to describe the effect,” explains Dr.

Letendre, adding “Of course toxicity must be considered: No one believed that efavirenz could have long-term toxicity, but it is increasingly clear that long-term toxicity from efavirenz does occur.”

Dr. Clifford cautions, “At this point we’re not in a position to say more than CPE was a hypothesis for people to consider in revision of therapies. Having people on effective therapy that they can tolerate and take is very important—it overrides any other characteristics of their regimen, in my opinion.”

Addressing Comorbidities Associated with HAND

HIV care offers an ideal opportunity to deliver a range of interventions that can stave off or lessen HAND. Clinicians can help delay, prevent, or mitigate HAND with cART, and by diagnosing and managing comorbidities. Of course, adherence support remains central to successful HIV treatment, especially in persons with neurocognitive impairment.

Substance Use and Psychiatric Disorders

In order to properly diagnose HAND, other causes of dementia should be ruled out, and effects of substance use and psychiatric illness should be considered. Substance use and psychiatric disorders are more prevalent among PLWH than the general population.⁹³ Heavy, long-term use of illicit drugs and/or alcohol directly—and indirectly—contribute to neurocognitive impairment. If untreated, these comorbidities can complicate entry and engagement in HIV care, as well as worsen adherence and response to cART.^{94,95}

Methamphetamine dependence is known to cause neurocognitive impairment among HIV-positive persons, especially long-term users with low CD4 cell counts (<200 cells/mm³).⁹⁶⁻⁹⁸ Long-term heavy use of cocaine and opioids causes neuroinflammation and neurotoxicity and also promotes HIV entry into the central nervous system.^{99,100}

On its own, long-term alcohol use is known to cause neurocognitive impairment.¹⁰¹ Heavy alcohol intake may worsen HIV-associated cognitive dysfunction, since alcohol also induces neuroinflammation, and is associated with poor adherence to cART.¹⁰²⁻¹⁰⁶

In PLWH, substance use and psychiatric disorders often co-occur. Depression is more prevalent among PLWH—especially those with substance use disorders—than the general population, due to psychosocial, viral, and biological factors and it is linked with poor adherence to ART.¹⁰⁷⁻¹¹⁰ Depression often accompanies HAND; symptoms can overlap, making it important to screen for, and treat depression in PLWH.¹¹¹⁻¹¹³ In fact, depression rates are significantly lower among HIV-positive people who do not exhibit neurocognitive impairment.¹¹⁴ Fortunately, pharmacotherapy for depression in PLWH improves adherence to cART and may even have a beneficial effect on neurocognitive impairment.¹¹⁵⁻¹¹⁷

A range of interventions familiar to Ryan White HIV/AIDS Program grantees (integrating or linking mental



A HELPING HAND

The Mind Exchange Working Group, which includes more than 60 experts from 30 countries, has produced Guidelines for Assessment, Diagnosis and Treatment of Human Immunodeficiency Virus (HIV)-Associated Neurocognitive Disorders (HAND).

Source: Mind Exchange Working Group. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. *Clin Infect Dis*. 2013 Apr; 56(7):1004–17

health care and treatment for substance use disorders, directly observed therapy, medication assisted treatment, pharmacotherapy, smoking cessation to reduce neuroinflammation, assistance with housing and medical coverage, and provision of incentives) are associated with improved engagement in HIV care and adherence to ART among people with substance use and psychiatric disorders.¹¹⁸⁻¹²²

Hepatitis C Virus Coinfection

Coinfection with hepatitis C virus (HCV) is common among HIV-positive people, due to overlapping transmission routes. HCV is also neuroinvasive—in fact, HCV infects the same brain cells as HIV, and it is an independent cause of neurocognitive impairment.¹²³⁻¹²⁸ HCV coinfection may increase the risk of insulin resistance and type 2 diabetes among PLWH; these conditions are also associated with neurocognitive impairment.¹²⁹⁻¹³⁰

Unlike HIV, HCV is curable (an outcome known as sustained virologic response, or SVR). Treating—and curing—HCV coinfection treatment offers an opportunity to address HAND, since SVR is associated with improved neurocognitive function.¹³¹ HCV treatment has become highly effective, safer, and more tolerable with the advent of oral, direct-acting antivirals. HIV coinfection is no longer considered a poor prognostic factor; clinical trials of direct-acting antiviral-based regimens report similar SVR rates, regardless of HIV status.¹³²⁻¹³⁶

Cardiometabolic Comorbidities

Side effects come with the lifesaving benefits of cART. Certain antiretroviral agents are known to cause or worsen other cardiometabolic conditions that have been linked with cognitive impairment.

➔ **TABLE 5. CENTRAL NERVOUS SYSTEM PENETRATION-EFFECTIVENESS RANKING**

CPE SCORE	4 (MUCH ABOVE AVERAGE)	3 (ABOVE AVERAGE)	2 (AVERAGE)	1 (BELOW AVERAGE)
Nucleoside Reverse Transcription Inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease Inhibitors	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r Enfuvirtide
Entry/Fusion Inhibitors		Maraviroc		
Integrase Strand Transfer Inhibitors		Raltegravir		

Source: Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. *Top Antivir Med.* 2011;19(4):137–142 ©2011, IAS–USA. Available at: www.iasusa.org/sites/default/files/tam/19-4-137.pdf. Accessed February 14, 2014.

In PLWH, the traditional risk factors associated with cardiovascular disease are potentially augmented by cART-associated insulin resistance, steatosis (fatty liver) hypertriglyceridemia, and hyperlipidemia, as well as HIV-associated inflammation.¹³⁷⁻¹⁴³ Management of type 2 diabetes is an important aspect of HAND prevention; both hypoglycemia and hyperglycemia have been linked to neurocognitive impairment.^{144,145}

Insomnia is common among PLWH; up to 70% experience insomnia or obstructive sleep apnea syndrome.¹⁴⁶ In PLWH, insomnia often becomes chronic and can cause neurocognitive impairment.¹⁴⁷ In particular, sleep apnea is associated with neurocognitive dysfunction and other conditions that foster it: type 2 diabetes and cardiovascular disease.¹⁴⁸ Treatment for insomnia may involve behavioral strategies and/or pharmacotherapy.

Both history of and risk for cardiovascular disease and current risk are associated with inflammation of, and damage to, neurons in people on long-term cART.¹⁴⁹ Switching to cART regimens with a favorable lipid profile, use of a

statin that does not interact with HIV medication, exercise, and a healthy diet may lower risk of cardiovascular disease among PLWH.

Healthy Living

“Some caregivers just want to prescribe a pill, and some patients prefer to take a pill” says Dr. Letendre, “but people may have to change their behavior: quit smoking cigarettes and using illicit drugs, eat a healthy Mediterranean diet, and exercise, which may be more important than anything else.”

The risk for multiple morbidities increases with higher body mass index (BMI). In the United States, obesity has become more common than wasting among PLWH.¹⁵⁰ A recent study of 681 HIV-positive treatment-naïve adults in Alabama found an obesity rate of 20%, signaling that clinicians have an opportunity to discuss healthy lifestyles with HIV patients.¹⁵¹ Obesity, HIV, and the use of certain antiretroviral agents are risk factors for type 2 diabetes and cardiovascular disease, which are also associated with HAND.^{152,153}

➔ TAXI DRIVERS AND NEUROPLASTICITY

After establishing a relationship between the amount of stimulation and number neural connections in the brain in rats, researchers turned to humans. The London Taxi Driver Study compared brain MRI scans from bus and taxi drivers. Since 1865, taxi drivers in London are required to pass The Knowledge, a test demonstrating their capacity to navigate 25,000 city streets and locate numerous points of interest. London's bus drivers do not receive the same level of training, and drive repetitive routes. The study participants had MRIs; when researchers examined them, they found that the part of the brain related to spatial knowledge was larger in taxi drivers than bus drivers, and the size increased with years of experience.

Cognitive reserve can be increased by doing new things, such as taking a class, learning a new skill, traveling by a different route, or even writing with the hand you don't usually use.

Sources: Maguire EA, Woollett K, Spiers HJ. London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. *Hippocampus*. 2006;16(12):1091–101.

Petrosini L, De Bartolo P, Foti F, et al. On whether the environmental enrichment may provide cognitive and brain reserves. *Brain Res Rev*. 2009 Oct;61(2):221–39.

Clearly, diet has an important role in the overall health of PLWH. In particular, diet can promote cognitive function. Antioxidant-laden foods (e.g., dark chocolate, dark berries, and many other fruits, as well as vegetables and legumes) and beverages (e.g., coffee, green and black tea) reduce inflammation and may preserve or improve cognitive functioning in older HIV-negative adults.^{154,155}

Physical exercise is known to improve neurological impairment in HIV-negative adults, and is likely to offer the same benefit for HIV-positive adults; a recent study reported lower rates of impairment among HIV-positive people who exercise than those who are sedentary.¹⁵⁶

Pharmacotherapy

The stimulants methylphenidate (ritalin) and modafinil (provigil) are often used to treat fatigue in PLWH. These drugs improve cognition in adults with attention deficit disorder and multiple sclerosis, and have been effective in small studies of HIV-positive patients.¹⁵⁷⁻¹⁶¹ Certain psychiatric medications (lithium, citalopram, sertraline, and trazodone) have also improved neurocognitive functioning in PLWH.^{162,163} However, the benefits of pharmacotherapy in people with neurocognitive impairment may be limited by poor adherence; it is crucial that adherence support be provided.

Enhancing Cognitive Reserve

Cognitive reserve describes the mind's capacity to function despite brain damage. The term was coined after researchers noticed that some elderly Alzheimer's patients did not show signs of functional impairment, even though they had brain abnormalities.¹⁶⁴ Cognitive reserve has been studied in the elderly, people with traumatic brain injury, and people living with Parkinson's Disease or HCV.¹⁶⁵⁻¹⁶⁸

Cognitive reserve is related to *positive neuroplasticity*, which is the brain's ability to compensate for damage and disease by actually forming new connections between neurons (nerve cells) in response to stimuli. These new neuronal connections allow people to adjust to new situations and environments. The more connections between neurons, the greater a person's cognitive reserve—and the more neurological damage they can withstand.¹⁶⁹

In contrast, *negative neuroplasticity* diminishes cognitive reserve; it occurs when the brain atrophies and neuronal connections weaken. Depression, substance abuse, poor nutrition, lack of sleep, and illness are known to promote negative neuroplasticity.¹⁷⁰

PLWH are vulnerable to negative neuroplasticity for several reasons. Poverty and unemployment are prevalent among HIV-positive people, making it difficult for them

to enhance neuroplasticity either through taking classes, or by traveling.^{171,172} The stigma associated with HIV may prompt people to avoid social circumstances, furthering negative neuroplasticity.

Researchers have identified lower cognitive reserve as a risk factor for HAND.¹⁷³ Cognitive reserve can be enhanced through “cognitive prescriptions,” an approach that combines individualized health education and modification in sleeping habits, as well as physical and mental exercise.¹⁷⁴

Cognitive Rehabilitation

Cognitive reserve can be enhanced by rehabilitative therapy. Clinicians can address non-adherence by working to restore or improve cognitive functioning and compensating for deficits in cognition.^{175,176}

The restorative approach to cognitive rehabilitation enhances neuroplasticity with computerized training programs. These game-like modules focus on improving attention, memory, logic, and visual and motor skills; they become more difficult as people progress, and offer positive and negative feedback (as an example, in “Bird Safari” participants are shown a bird with certain distinctive characteristics [such as colored wing tips], which they must then pick out after briefly viewing an entire flock of similar birds). Studies of these computerized training programs have reported neurocognitive improvements in different areas among HIV-positive children and adults.¹⁷⁷

In contrast, compensatory cognitive therapy, an approach used in people with schizophrenia and anorexia, focuses on overriding the effects of impairment with the use of tools, such as alarms and calendars to prompt and support adherence to medication, and “chunking”—breaking down large tasks into smaller steps.¹⁷⁸

Research

cART has dramatically prolonged survival among HIV-positive people, but it does not effectively prevent or eliminate HAND. While progress has been made in identifying potential causes of HAND, more research into the pathogenesis of, and diagnostics and treatment for, HAND is a priority. Clinicians need simple, accurate tools to screen for HAND, and therapies to avert or improve HIV-associated cognitive impairment. Research on a range of

approaches—pharmacologic, cognitive, and behavioral—is needed to tackle HAND.

CONCLUSION

Although the incidence of severe, AIDS-associated dementia has decreased dramatically with the advent of cART, milder neurocognitive impairment remains highly prevalent among people living with HIV/AIDS. Screening for HAND is an important part of an initial assessment. PLWH should be screened upon entry to care, and when clinically significant changes occur (such as initiation of cART, worsening health, or diagnosis with a psychiatric disorder). Patients who have a low CD4 nadir, poor immunologic recovery, or suboptimal virologic response to cART should be screened more frequently.

Although there is no single, validated screening instrument for HAND, clinicians can use simple tests, and ask their patient about forgetfulness, difficulty managing finances and concentrating, and mental “slowing down” to assess neurocognitive function.

Diagnosing, engaging, and retaining in HIV primary care—and cART—are crucial interventions against HAND. People who have high baseline HIV RNA and low CD4 cell nadir are most vulnerable to HAND, especially as they age; this underscores the importance of cART for untreated patients with advanced HIV. But many people are not reaping the full benefits of cART: In the United States, an estimated 20% of PLWH remain undiagnosed, and only 28% are virologically suppressed.^{179,180} “Lack of treatment is the biggest risk factor for cognitive problems,” says Dr. Letendre.

Comorbidities that become increasingly common with age, such as type 2 diabetes, lipid abnormalities, and cardiovascular disease—as well as aging itself—are known to be associated with HAND. While more research into, and better treatment for HAND are needed, it is reassuring to note that the recommendations that clinicians commonly give—weight loss, exercise, healthy diet, healthy lifestyle choices (e.g. elimination of substance abuse and smoking), dyslipidemia management, and cART adherence—offer significant benefits to their HIV patients. “It is our hope and belief that a healthy lifestyle is also beneficial for the brain,” says Dr. Clifford.

➔ ONLINE RESOURCES

Guidance on assessment, laboratory and diagnostic evaluation and treatment of HIV-associated dementia and other neurocognitive disorders: www.hivguidelines.org/clinical-guidelines/hiv-and-mental-health/cognitive-disorders-and-hiv-aids/

HIV Dementia Scale: www.hivguidelines.org/clinical-guidelines/hiv-and-mental-health/cognitive-disorders-and-hiv-aids/#APPENDIX%20A:%20HIV%20DEMENTIA%20SCALE.

Information on prevention, diagnosis and management of immune reconstitution inflammatory syndrome and opportunistic infections: www.hivguidelines.org/clinical-guidelines/adults/immune-reconstitution-inflammatory-syndrome-iris-in-hiv-infected-patients/; http://aidsinfo.nih.gov/contentfiles/adult_oi.pdf.

Memorial Sloan Kettering Test for AIDS Dementia: <http://www.hivguidelines.org/clinical-guidelines/hiv-and-mental-health/cognitive-disorders-and-hiv-aids/#APPENDIX D: THE MEMORIAL SLOAN-KETTERING SCALE FOR AIDS DEMENTIA COMPLEX>

Mental Alteration Test: www.hivguidelines.org/clinical-guidelines/hiv-and-mental-health/cognitive-disorders-and-hiv-aids/#APPENDIX%20C:%20MENTAL%20ALTERNATION%20TEST.

Mini Mental Status Exam: www.health.gov.bc.ca/pharmacare/adi/clinician/pdf/ADTI%20SMMSE-GDS%20Reference%20Card.pdf.

Modified HIV Dementia Scale: www.hivguidelines.org/clinical-guidelines/hiv-and-mental-health/cognitive-disorders-and-hiv-aids/#APPENDIX%20B:%20MODIFIED%20HIV%20DEMENTIA%20SCALE.

Montreal Cognitive Assessment: www.mocatest.org/pdf_files/test/MoCA-Test-English_7_1.pdf.

The Controlled Oral Word Association Test (COWAT) is a type of verbal fluency testing used to assess cognitive function. Participants have 60 seconds to say as many words as they can that begin with a certain letter. Usually, the test is performed three times with different letters (usually F, A and S, or C, F and L).

The Wisconsin Card Sorting Test: www.bowdoin.edu/faculty/e/enyhus/pdf/nyhus,barcelo,2009.pdf.

Trail Making Test Part A and B: http://doa.alaska.gov/dmv/akol/pdfs/uiowa_trailmaking.pdf.

Many PLWH face additional, overlapping challenges: substance use and psychiatric disorders, and coinfection with HCV virus. Each can contribute to, or exacerbate neurocognitive impairment. Addressing substance use and psychiatric disorders has long been a cornerstone of HIV care and treatment among Ryan White HIV/AIDS Program grantees. Provision of medication-assisted treatment, and mental health care facilitate engagement in care, and improve adherence to and outcomes of treatment for HIV and HCV.

Clinicians can use different approaches to improve or compensate for neurocognitive impairment, and to build up and maintain cognitive reserve, including prompts to support adherence, breaking down large tasks into

smaller steps, and computerized training programs developed to improve attention, memory, logic, visual, and motor skills. Pharmacotherapy may be helpful when accompanied by adherence support. “Being engaged in their own care, physically and mentally active, and socially engaged can help maintain cognitive reserve and protect PLWH from neurocognitive impairment,” says Dr. Valcour.

Finally, the brain can—and does—change, in response to stimuli, such as physical activity, socializing, and learning. “Encourage patients to remain engaged, exercise their brain, do things that are challenging to maintain optimal neurological function,” says Dr. Clifford. Doing so could mean a healthier—and fuller—future for people living with HIV.

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