HIV-associated neurocognitive disorders

Five new things

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Summary

HIV-associated neurocognitive disorders (HAND) remain an important cause of cognitive dysfunction. Current nomenclature for HAND includes HIV-associated dementia and milder forms known as asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND). ANI and MND remain highly prevalent despite combined antiretroviral therapy (cART). These mild forms of HAND must be diagnosed through neuropsychological testing. If a patient has HAND, it remains unclear whether using a cART regimen with theoretically superior CNS penetration improves the prognosis. Nevertheless, a CNS penetration effectiveness score for antiretrovirals is available. Other factors to consider when diagnosing and treating HIV infection and HAND include the HIV clade or subtype. Data suggest that HAND occurs more often in association with certain clades, and higher vigilance for cognitive dysfunction may be recommended. Finally, comorbidities, such as diseases associated with advanced age, other infections, and drug abuse, need to be considered as cofactors for cognitive dysfunction and treated accordingly.

Despite the development of effective antiretroviral (ARV) treatment and attempts to develop an effective vaccine, the HIV pandemic continues, with more than 34 million people infected worldwide. HIV-associated neurocognitive disorders (HAND) remain a common complication despite combined ARV therapy (cART), and HAND is the most common cause of cognitive dysfunction in young adults. Although cART has resulted in a decline in the most severe form of HAND, HIV-associated dementia (HAD), milder forms of HAND are common. Overall, HAND occurs in as many as 50% of HIV-infected individuals and even in patients receiving cART.¹

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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The clinical manifestations of HAD were defined early in the AIDS epidemic² and they largely apply today. Initially, bradyphrenia, or slowness of mental functions, is common, and patients can appear apathetic or depressed. These patients need to be distinguished from primarily depressed patients exhibiting memory problems through neuropsychological testing. Components of HAD include memory impairment, impairment of executive functions, and mood abnormalities.² These patients may have trouble reading and comprehending. There may also be gait disturbances with stumbling, tremor, and fine motor impairments. Other signs may include impaired REM, hyperreflexia, and frontal release signs. These signs and memory impairment become more apparent as the disease progresses, eventually culminating in severe neurologic sequelae—a bedridden, mute state. Prior to cART, death usually occurred over several months.²

Changes in nomenclature

There have been several attempts to standardize the nomenclature for HAND, primarily for research purposes. Early on, the Memorial Sloan Kettering Rating Scale was used to stage HAND. In 1991, the American Academy of Neurology (AAN) published criteria, which essentially split HAND into 2 major categories—HAD and minor cognitive motor disorder.³ Briefly, the AAN criteria for HAD were as follows: (1) an acquired abnormality in at least 2 cognitive (nonmotor) areas causing impairment in work or activities of daily living (ADLs), and (2) an abnormality of either motor function or specified neuropsychiatric or psychosocial functions (e.g., motivation, emotional control, social behavior). It should be emphasized that the initiation of cART in 1996 reduced HAD incidence by 50% or more and therefore fundamentally changed the expression of HAND.¹ In the cART era, classic HAD is relatively infrequent, and there has been an apparent increase in milder forms of HAND. In an attempt to better define and recognize the changes caused by cART, the nosology for HAND was revised (table 1).⁴ Mild neurocognitive disorder (MND) can be missed if careful attention is not paid to cognitive symptoms and signs. MND results in mild interference with daily functions, as opposed to HAD, which results in marked interference with ADLs. These impairments include inefficiency at work or at home or problems in social settings. In addition, MND requires neuropsychological testing defining abnormalities in at least 2 cognitive domains. The third category of HAND is asymptomatic neurocognitive impairment (ANI). This also requires formal neuropsychological testing to diagnose. There must be acquired impairments in cognitive functioning in at least 2 test domains assessing language, attention, executive function, speed of memory recall, information processing speed, and sensory and motor skills. It is important to note that forms of HAND may not be stages in a progressive illness. Affected individuals may plateau at any stage of impairment or may even improve with initiation of cART.

Forty percent to 50% of HIV+ individuals on cART still have HAND

The introduction of cART in 1996 led to a rapid decline in the incidence of HAD. Nevertheless, the prevalence of milder forms of HAND appears to have increased because cART has turned HIV infection into a chronic condition. Patients now live longer with their infection and appear to be more likely to develop cognitive dysfunction over their lifetime.

Despite its ability to suppress systemic HIV, cART is not entirely neuroprotective. Nevertheless, cART has decreased the incidence of HAD, probably due to the decreased incidence of systemic immunosuppression. HIV encephalitis has decreased compared to the pre-cART era⁵ but still remains a frequent autopsy finding in cART-treated patients, suggesting that cART is not fully effective at eliminating CNS infection.⁵ Classically, HAD occurred at end stages of HIV infection (i.e., AIDS). Now, milder HAND forms occur at any stage of HIV infection, even in those with well-controlled infection due to cART. Changes in cART regimen may be considered in patients with evidence of any form of HAND (see nomenclature section above and CNS penetration effectiveness [CPE] section below), because switching to a regimen that

Table 1 HIV-associated neurocognitive disorders

Disorder	Criteria
HIV-associated asymptomatic neurocognitive impairment (ANI)	<ol style="list-style-type: none"> 1. Acquired impairment in cognitive functioning involving at least 2 ability domains, documented by performance of at least 1.0 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. 2. The cognitive impairment does not interfere with everyday functioning 3. The cognitive impairment does not meet criteria for delirium or dementia 4. There is no evidence of another preexisting cause for the ANI (e.g., depression)
HIV-associated mild neurocognitive disorder (MND)	<ol style="list-style-type: none"> 1. Acquired impairment in cognitive functioning involving at least 2 ability domains, documented by performance of at least 1.0 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. 2. The cognitive impairment produces at least mild interference in daily functioning (at least 1 of the following): (1) Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning; (2) 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 3. The cognitive impairment does not meet criteria for delirium or dementia 4. There is no evidence of another preexisting cause for the MND (e.g., depression)
HIV-associated dementia (HAD)	<ol style="list-style-type: none"> 1. Marked acquired impairment in cognitive functioning involving at least 2 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 2 domains at least 2 SD below demographically corrected means. (Note that where neuropsychological testing is not available, standard neurologic evaluation and simple bedside testing may be used.) 2. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities) 3. 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 4. 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)

Modified from Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007;69:1789–1799.

has improved CNS penetration may improve neurocognition in HAND. cART remains the only known effective therapy for HAND.

HAD still occurs at a rate of 2%–30% among those with advanced HIV infection, including those with undiagnosed HIV, those with poor compliance or poor access to ARV therapies, and those with multidrug-resistant forms of HIV. In developing nations, where access to cART is limited, the prevalence of HAD among ambulatory HIV-positive patients remains 30% or higher. If this percentage is consistent throughout the developing world, then HAD would be the most common cause of dementia worldwide in patients younger than 40.⁶ Furthermore, people over the age of 50 have double the risk of HAD compared to those under the age of 50.⁷ In fact, the prevalence and effect of the mild forms of HAND on patients living with HIV have made the issue more important to study, because effective treatment is lacking.

There is substantial evidence from basic science studies that viral sequences due to clade differences can influence the neuropathogenesis of HIV infection.

CPE scores could be used to determine better cART

Although it is not neuroprotective and does not prevent HAND, the mainstay of HAND treatment is cART. There has been considerable interest in whether specific cART agents or regimens penetrate the blood-brain barrier (BBB) and suppress CNS HIV better than other agents or regimens. If so, then these penetrating regimens may provide increased prevention or better treatment of HAND.

A CPE ranking system has been proposed (table 2).⁸ ARVs that are considered to be good CNS penetrators are those that achieve CSF concentrations greater than the median 50% inhibitory concentration for HIV replication. These include zidovudine, abacavir, nevirapine, efavirenz, and indinavir. Theoretically, cART regimens with higher CPE scores will be more effective at suppressing CSF HIV viral load and decreasing neurocognitive dysfunction. Therefore, higher CPE regimens could be contemplated, but only if appropriate when considering other factors in the decision-making process, such as effectiveness at controlling plasma viral load and raising CD4 cell count, side effect profile, and drug resistance.

The CPE ranking system is based on measurement of the concentration of the antiviral agent in the CSF, but CSF concentration may or may not be related to parenchymal concentration. Parenchymal concentrations are not easily measured, so CSF concentrations are the best available proxy. Parenchymal level does not depend only on CSF concentration. Other important factors include plasma concentration, ability of the drug to pass the BBB, and, in some cases, transporter proteins that pump the drug out of the brain. Patients with HIV may have disruption of the BBB, which would allow greater concentration of agent in patients than in the healthy volunteers in whom CSF concentration might be measured. Finally, CSF concentrations are often determined based on only a few patients, so they may not be completely reliable or accurate.

Table 2 CNS penetration effectiveness scores for antiretroviral drugs

Drug class	1	2	3	4
Integrase inhibitors			Raltegravir	
Fusion inhibitors	Enfuvirtide		Maraviroc	
Protease inhibitors	Nelfinavir	Atazanavir	Darunivir	Indinavir
	Ritonavir	Fosamprenavir	Lopinavir	
	Saquinavir			
	Tipranavir			
NNRTIs		Etravirine	Delavirdine	Nevirapine
			Efavirenz	
NRTIs	Tenofovir	Didanosine	Abacavir	Zidovudine
	Zalcitabine	Lamivudine	Emtricitabine	
		Stavudine		
Abbreviations: NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.				

While the incidence of HIV infection in the general population has largely stabilized, it has increased significantly since the late 1990s among those ages 50 and older.

The clinical applicability of the CPE score is unknown. One study showed significant cognitive impairment in HIV+ individuals compared to controls despite the use of cART, and CNS-penetrating regimens were no more effective than nonpenetrating regimens.⁹ Patients with neurocognitive impairment despite good plasma HIV control are frequently checked for CSF HIV viral load, with high CSF viral load possibly dictating a change to a more penetrating regimen. Patients with improvement in neurocognitive testing after initiation of cART correlate with CSF viral load decline, while patients with no CSF viral load decline also have no neurocognitive testing improvement.¹⁰ In another study, patients who received a greater number of CSF-penetrating drugs had a significantly greater reduction in CSF viral load, and those who achieved an undetectable CSF viral load had greater improvements on cognitive test batteries than those who did not.¹¹

Does HAND prevalence differ among HIV clades?

The effect of HIV clade or subtype on the development or course of HAND is an aspect of HAND pathogenesis that has received recent attention.¹² HIV infections are predominantly caused by group M. Within this group there are 9 clades or subtypes. In North America and Europe, the predominant clade is B. Worldwide it is C, which is particularly prevalent in sub-Saharan Africa and India. A, D, and F are also common clades in Africa. Clades A and D have also been reported to have potential effects on HAND pathogenesis.

There is substantial evidence from basic science studies that viral sequences due to clade differences can influence the neuropathogenesis of HIV infection. These studies have focused on the *tat* gene.¹³ They indicate that the genetic differences in *tat* that in most cases differentiate clade B from C may cause clade B to be more strongly associated with higher prevalence, faster progression, or earlier onset of HAND than clade C. The studies further indicate that Tat protein has at least 2 properties that could influence the onset or severity of HAND.¹³ These in vitro studies show that Tat acts as a chemokine to attract mononuclear phagocytes, which are strongly implicated in HAND pathogenesis.¹⁴ Tat also appears to have a direct toxic effect on neurons that is mediated through the NMDA receptor.¹⁵

Despite in vitro and animal model studies indicating that HIV clade differences are important in neurovirulence, clinical studies have produced conflicting results.¹⁵ Some studies have suggested that clade D results in a higher prevalence of HAND, followed by clades B, C, and A, in that order. However, other clinical investigations suggest that clade status does not influence HAND prevalence. It is important to note that all of these studies have limitations, such as relatively small numbers of patients, limited area of sampling, potential referral bias, unknown clade status, inconsistencies with receiving ARVs, lack of detailed neuropsychological testing and defining HAND subtypes, lack of neuroimaging, and lack of proper control populations. One critical possibility is that clade status affects the severity of HAND and not necessarily the total number of HIV+ individuals with HAND. Many of the studies outlined above may have missed this important aspect of clinical epidemiology.

The overriding problem is that these studies were not designed to detect the relative severity of HAND or changes over time. Larger longitudinal and more detailed clinical studies must be performed to adequately address the clade status influences suggested by the basic investigations outlined above. Clade differences probably provide important clues about HAND pathogenesis, which could lead to more-effective therapies.

Comorbidities, including hepatitis C, aging, and drug abuse

HIV infection causes neuronal dysfunction through a variety of complex and interacting mechanisms. The addition of various comorbidities only adds to the complexity of these mechanisms.

Factors associated with aging and cognitive dysfunction significantly affect the development of HAND.¹⁶ While the incidence of HIV infection in the general population has largely stabilized, it has increased significantly since the late 1990s among those ages 50 and older. There is also a separate increasing cohort of HIV-positive individuals over the age of 50 as a result of the success of cART at transforming HIV into a chronic disease. Studies in both the pre- and post-cART era have shown that the risk of HAD is higher in older compared to younger populations. Older age has also been associated with an increased frequency of symptoms of more mild forms of HAND. A variety of mechanisms for the interaction between aging and HIV infection have been proposed, including increases in oxidative stress and increases in proinflammatory mediators. There is also an increased likelihood of comorbid diagnoses that may contribute to neurocognitive impairment, such as HIV infection, cerebrovascular disease, and Alzheimer pathology. Neurocognitive testing can assist in distinguishing between Alzheimer disease and HAND. Patients with Alzheimer disease will show more “cortical” features on neurocognitive testing, whereas HAND typically results in a subcortical dementia. At least some regimens of cART cause dyslipidemia, which in turn could increase the risk of cerebrovascular disease, and of course cerebrovascular disease can also lead to cognitive impairment.

Hepatitis C virus (HCV) is a rare cause of clinical viral encephalitis, but it is frequently detected in the brains of HIV- and HCV-positive individuals.¹⁷ HIV-HCV coinfection is common, as the 2 viruses share similar modes of transmission. The effect of HCV positivity on neurocognitive function in HIV-positive individuals remains unclear. Study of this issue is confounded by other comorbidities, including liver disease and drugs of abuse. One recent study suggested that HIV and HCV coinfecting individuals have more severe HAND than patients with only HIV infection.¹⁸ The authors tried to control for the confounding variables by excluding active drug abusers from the study, but coinfecting individuals were significantly more likely than HIV-monoinfected individuals to have a history of drug abuse. Clinically, the recommendation is to optimally treat both infections, reducing both viral loads, especially in patients with cognitive impairment.

It is difficult to separate the direct consequences of drugs of abuse on neurocognitive function from indirect consequences through repeated exposures to HIV and associated behaviors, including noncompliance with cART with resultant increased HIV replication. Drugs of abuse also have complex and often immunosuppressive effects on the immune system, possibly increasing the risk of CNS opportunistic infections. However, several lines of evidence indicate that alcohol, cocaine, morphine, and methamphetamine directly, and even synergistically, worsen HIV-associated neurotoxicity.^{19,20} Cocaine, methamphetamine, and morphine all synergize with HIV Tat protein and HIV gp120 protein to worsen neurotoxicity. Possible mechanisms for this synergism include increases in oxidative stress, upregulation of host

HIV-associated neurocognitive disorders: Five new things

- Recently the classification of HIV cognitive disorders was changed to the overall term HIV-associated neurocognitive disorders (HAND), which includes the common, relatively mild disorders of asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) along with the traditional severe form, HIV-associated dementia (HAD).
- It is important to note that ANI and MND are defined by abnormal neuropsychological testing and can be easily missed clinically if this testing is not performed.
- Fifty percent or more of HIV-positive patients develop HAND regardless of ARV treatment, so consideration could be given to the CNS penetration ranking score of ARV agents if the patient has HAND.
- Since ARV agents do not eradicate HIV from the CNS and HAND persists, ongoing studies looking into issues such as the effects of HIV clade or subtype on HAND pathogenesis are important in order to devise better treatment strategies.
- It is important to identify and treat comorbidities such as drug abuse and hepatitis C since they may exacerbate HAND.

inflammatory mediators, and disruption of the BBB. The addictive properties of many drugs of abuse are mediated through the dopaminergic system, which is also prominently affected by HIV. These factors make it even more important for HIV-infected patients who abuse drugs to have the opportunity to participate in drug rehabilitation programs. Also, there may be an overemphasis on drug abuse and an underemphasis on other obstacles to cART adherence, which may lead to unequal access of drug abusers to cART compared to other HIV-positive populations.

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STUDY FUNDING

No targeted funding reported.

DISCLOSURES

J.A. Rumbaugh receives research support from Diogenix, Hoffman-La Roche LTD, Biogen Idec, Emory Center for AIDS Research, Emory University, and Atlanta VA Medical Center. W. Tyor receives research support from the Veterans Administration and the NIH. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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