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Emerging Issues in the Neuropsychology of HIV Infection

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Abstract

Neurocognitive compromise, a common sequela of HIV infection, ranges in severity from minor motor and information-processing speed decrements to severely incapacitating symptoms that affect functional independence. However, with the emergence of highly active antiretroviral therapy (HAART), neurocognitive phenotypes have become highly heterogeneous and increasingly fail to resemble pre-HAART presentations. This article provides an overview of our current knowledge of HIV-associated neuropsychological abnormalities, with an emphasis on the most recent attempts to classify cognitive impairment within Western and developing societies, the emergence of diverse cognitive presentations in the post-HAART era, factors that moderate the development or impact of HIV-related neurocognitive and functional deficits, and the neurophysiologic consequences of infection.

Introduction

HIV type 1 (HIV-1) infection is the most common preventable cause of neurologic decline in individuals under the age of 50 years [1•]. Between 30% and 50% of HIV-positive (HIV +) individuals will experience some form of neurocognitive decline [2], ranging from mild motor and information-processing decrements to severe dysfunction that affects activities of daily living (ADLs) [3–5]. Despite advances in the diagnosis and treatment of HIV infection, cognitive impairment remains common and tends to correlate with disease severity. HIV infection most prominently affects the domains of motor functioning, attention, processing speed, executive functioning, and memory [2,6].

Language, visuospatial, and global cognitive functioning are typically intact in the earlier stages of illness, with substantial deficits observed only in late-stage illness or in those with dementia. Symptoms of cortical dementias such as apraxia, agnosia, and aphasia are absent unless patients develop a central nervous system (CNS) opportunistic infection or neoplasm.

This profile of neurocognitive impairment has most commonly been interpreted as reflecting a primarily frontal–subcortical pathogenesis [2], but some neurocognitive (eg, memory) abnormalities may be secondary to mesial temporal disruption [6,7]. A variety of clinical brain markers from MRI [2], magnetic resonance spectroscopy (MRS) [8], diffusion tensor imaging (DTI) [9,10], positron emission tomography (PET) [11], and postmortem histopathologic examination [6] have been linked to the severity of these behaviorally measured neurocognitive deficits. HIV-related cognitive impairment is associated with several immunologic markers, such as reduced plasma CD4 count, increased plasma viral load [12], and elevated cerebrospinal fluid β_2 -microglobulin [2]. HIV-associated cognitive

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deficits may lead to difficulties performing instrumental ADLs [3], resulting in poor adherence to highly active antiretroviral therapy (HAART) [4] and risky decision making [13].

Classification of HIV-Associated Cognitive Impairment

To promote accurate diagnosis of HIV neurocognitive manifestations, the AIDS Task Force of the American Academy of Neurology (AAN) published the first research case definitions for HIV-related neurocognitive disorders in 1991 [14]. Two variants of HIV-associated neurocognitive disorder were recognized: a more severe variant—HIV-1-associated dementia (HAD) complex—and a less-pronounced presentation—HIV-associated minor cognitive motor disorder (MCMD). A revision of this nosology emerged from a 2007 consensus conference that advanced a modified classification scheme for HIV-associated neurocognitive disorders (Table 1) [15•]. These new diagnostic criteria differ from the AAN criteria in that they give greater weight to the cognitive aspects of impairment (rather than emotional or motor difficulties) and offer increased recognition of the functional aftermath of neurocognitive decline. Diagnostic criteria are offered for three conditions: HAD, HIV-associated mild neurocognitive disorder (analogous to MCMD), and asymptomatic neurocognitive impairment. Inclusion of the last category is an acknowledgment that patients may demonstrate detectable declines on neuropsychological testing without overt functional declines or patient complaints.

Neurocognitive Effects of HIV in Non-Westernized Societies

The vast majority of HIV infection cases are in sub-Saharan Africa, yet little research to date has investigated the cognitive consequences of HIV infection in this and other resource-limited environments. Many factors, including nutritional differences, alternative HIV strains, and concomitant illnesses, make comparison with Western HIV cases difficult. One recent study in Uganda showed reduced processing speed, attention, executive functioning, and verbal learning/memory among HIV+ individuals relative to controls, thus highlighting neurocognitive similarities between sub-Saharan Africa and the developed world [16]. However, other research has shown that varying viral subtypes (specifically clades A and D) may confer immunologic progression and death at different rates [17]; therefore, it is possible that regionally specific clades are associated with differing neuropathogenic properties and symptom presentations. For example, HIV dementia is far more prevalent (31%) among Ugandans with advanced infection than in North Americans (10%–15%) [18], although, notably, Ugandan prevalence rates for HIV dementia are similar to epidemiologic data from the United States before the HAART era [19]. Various viral subtypes may therefore have differing biological properties and lead to unpredictable patterns of systemic disease progression, neurologic changes, and cognitive compromise, thus signaling the need for more comprehensive research to define the frequency and patterns of cognitive impairment within resource-limited, developing societies.

HIV in the Post-HAART Era

Since the introduction of HAART, the incidence of HAD has declined; however, with increasing longevity, prevalence rates are rising. There also has been a concomitant reduction in the severity of neurocognitive compromise and an alteration in the natural history and trajectory of neurocognitive decompensation. For example, gradual, stabilizing, and fluctuating cognitive courses have been observed among HAART-treated patients [15•]. Others have identified three distinct dementia subtypes, including a subacute progressive dementia among untreated patients (consistent with pre-HAART deterioration), a chronic active dementia in poorly adhering or viral-resistant patients at risk for neurologic progression, and a chronic inactive dementia (“burnt-out” dementia) in medication-adherent

patients with effective virologic suppression and resulting neurologic recovery [20]. These varying clinical manifestations have led researchers to promulgate a more global, cortically driven pathogenesis for subsets of HIV-infected individuals, thus straying from historically espoused dysfunction of more restricted subcortical regions [20]. Before the introduction of HAART, the degree of immunosuppression, as indexed by current CD4 count, was loosely associated with the degree of neuropsychological compromise. With the advent of HAART and the resultant immune reconstitution experienced by many patients, this relationship has lessened. Rather, nadir CD4 level and disease duration may now be more predictive of neuropsychological status [7].

Factors That Moderate the Effects of HIV on Cognitive Functioning

The cognitive heterogeneity that has surfaced during the post-HAART era has led investigators to examine several risk factors for the development of HIV impairment and dementia. Areas receiving heightened attention include the effects of aging, coinfection with hepatitis C virus (HCV), substance abuse, and genetic factors; these are discussed in detail in the following paragraphs.

Aging

With the introduction of more effective treatment, mortality rates have plummeted, resulting in the HIV epidemic evolving into a disease increasingly affecting older adults. The number of AIDS cases in individuals over the age of 50 has more than tripled over the last several years; approximately 15% of AIDS patients are now older than 50 years [21]. In some settings, the ranks of older HIV-infected patients are even larger. For example, 42% of HIV-infected patients receiving care through the Veterans Affairs Health Care System are 50 years or older [22]. Compelling evidence suggests that the clinical manifestations and natural history of infection among older HIV+ individuals differ considerably from those observed in younger cohorts, as older adults are at a substantially increased (roughly threefold) risk for developing cognitive decline/dementia. In a recent study, 25.2% of older infected adults received a diagnosis of dementia, whereas only 13.7% of the younger group received this diagnosis [23]. Risk factors for the development of dementia among older infected adults may include low CD4 lymphocyte counts and depressive symptomatology. Besides the higher prevalence of dementia in older versus younger adults, differences also have been found in milder cognitive diagnoses, with 44.7% of the older group and 26.3% of the younger group meeting formal criteria for MCMD.

HIV/HCV comorbidity

Coinfection with HIV and HCV is a burgeoning phenomenon, with approximately one third of HIV-infected individuals in the United States also infected with HCV [24]. Mounting evidence suggests that these viruses exert additive and perhaps synergistic deleterious effects, as both viruses have been observed in the same cell lines (ie, monocytes/macrophages and T and B lymphocytes), HIV infection facilitates HCV replication in monocytes and macrophages, and there is a loss of immunologic control and more rapid progression of HCV in coinfecting individuals. Coinfected patients tend to have higher rates of AIDS, lower CD4 counts, and higher plasma viremia than do HIV-monoinfected individuals [25]. They also evidence a greater degree of neurocognitive compromise than do HIV- or HCV-monoinfected persons, with slower reaction times and higher rates of HAD [26•]. The neurophysiologic mechanisms underlying such abnormalities remain unclear.

Although it is possible that some patients have a subclinical hepatic encephalopathy that escapes medical attention, the preponderance of evidence indicates that HCV is a neurotropic virus. HCV is a member of the Flaviviridae family of viruses, which includes

many viruses that cause neurologic disease. Increasing evidence suggests that HCV can develop tissue-specific variants and can replicate (albeit at low levels) outside the liver—for example, in peripheral blood mononuclear cells [27].

Because HCV can replicate in cell types (eg, monocytes, macrophages) that can cross the blood–brain barrier and enter the brain, HCV may be capable of penetrating the CNS in a manner similar to that ascribed to HIV, the so-called Trojan horse mechanism [28]. Other possible causes for neuropsychiatric syndromes in HIV+/HCV+ patients without overt hepatic disease include changes in the endocrine system associated with HCV-induced thyroiditis and diabetes [29], HCV-induced rheumatologic disease [29], and/or secondary cytokines.

Studies using neuroimaging techniques in tandem with neuropsychological measures may shed light on the brain regions most affected and the corresponding functional repercussions.

Substance abuse and HIV-associated cognitive impairment

HIV-associated cognitive decline has been linked to disruptions of frontostriatal circuitry [2]. Although drugs of abuse have differing mechanisms of action, it is believed that many increase dopamine levels, thereby creating a frontostriatal nexus where HIV disease and substances of abuse might interact to compound neurocognitive deficits. The impact of drug abuse on other neurotransmitter systems and blood–brain barrier integrity may also play a role in neurocognitive deficits. Given the high prevalence of substance abuse in the HIV-infected population, understanding the possible CNS interaction between drugs of abuse and HIV is of clinical significance. Surprisingly, much of the work investigating this possible interaction has suggested subtle or no interactive effects. However, many of these studies used mixed samples of drug abusers, examined possible HIV–drug interactions weeks or months post substance use, and/or lacked appropriate control for HIV and/or substance use.

Studies with less variance in sample characteristics, shorter latencies between substance abuse and neuropsychological examination, and/or appropriate control conditions tend to support an interaction between drugs of abuse and HIV in reducing neurocognition. Taylor et al. [30] found compelling evidence for an HIV–drug interaction effect on frontostriatal circuitry and cognition in a fairly small sample of HIV-negative and HIV+ stimulant-dependent participants. Among the HIV+ stimulant-dependent group, results showed lower *N*-acetylaspartate (NAA) values in the anterior cingulate gyrus, which correlated with deficits in attention/information processing, psychomotor abilities, memory, and executive functioning. Our group has shown that recent stimulant use impairs psychomotor speed [31] and sustained visual attention [32]. Finally, Martin et al. [33] demonstrated that stimulant use is associated with executive deficits in increased risk-taking behavior among HIV+ individuals.

In conclusion, although previous work investigating the possible effects of an HIV–drug abuse interaction on cognition have yielded mixed results, recent data strongly suggest that stimulant abuse tends to further affect frontostriatal circuitry in HIV+ individuals, leading to greater declines in attention, psychomotor function, and executive abilities. The greater deficits in HIV+ stimulant-abusing groups may also be the result of a third variable, such as a genetic predisposition to cognitive and affective deficits (discussed in the next section) that might make individuals more likely to abuse drugs and to contract HIV disease.

Genetic factors

Research has suggested a number of genetic factors that may protect against or potentiate the cognitive effects of HIV infection [34•]. Many of these genetic factors appear to modulate activation of chemokine receptors that may result from exposure to the HIV

glycoprotein gp120, which is associated with HIV-related neuronal damage. For example, a relatively common genetic polymorphism of the chemokine receptor CCR5 (CCR5-delta 32) is believed to confer a protective effect against neurocognitive deterioration, as studies have found reduced CCR5-delta 32 in cases of HIV dementia [35] and a single nucleotide polymorphism of the chemokine receptor CCR2 (ie, CCR2-V64I) has been associated with slowed progression to cognitive impairment [36]. In contrast to these cognitively beneficial mutations, genetic polymorphisms for CXCR4 (ie, SDF-1) may promote neuronal toxicity [37]. Finally, possession of the apolipoprotein E4 polymorphism may increase susceptibility to HIV dementia among older infected individuals [38]. Several other, albeit unexplored, genetic mechanisms have been proposed, including genetic mutations affecting dopamine metabolism and brain-derived neurotrophic factor [34•].

Cognitive Impairment and Everyday Functional Abilities

With advanced disease, HIV-infected individuals may experience reduced ability to complete basic ADLs (eg, grooming), and neuropsychological status has been shown to predict such declines [3]. In the following paragraphs, we present a review of the neuropsychological findings associated with three common ADLs: medication management, driving ability, and vocational status.

Medication adherence

Medical advances in treating HIV infection, including the advent of HAART, may dramatically improve mortality, functional level, and quality of life among HIV+ individuals [21] by bolstering immune function as well as cognitive abilities affected by the disease process [39]. However, consistently high levels of adherence are required to modulate aspects of immune functioning (eg, antigen-specific responses and cytokine production) and successfully reconstitute or maintain desirable levels of immune functioning [40]. Unfortunately, objective measures show that only 50% to 60% of HIV-infected patients achieve adequate adherence to their medications [40].

One study conducted by our group [4] revealed that cognitively compromised participants were twice as likely to fail to adequately adhere to their medication regimen, with deficits in executive functioning, attention, and verbal memory specifically associated with poorer HAART adherence. We also found that regimen complexity adversely affected medication adherence for cognitively impaired subjects, whereas regimen complexity was relatively unproblematic for cognitively normal participants (Fig. 1). Follow-up analyses revealed that cognitive compromise in executive abilities and working memory interacted with regimen complexity to produce these marked declines in adherence.

Although cognitive dysfunction may indeed cause poor adherence, it is also plausible that suboptimal adherence results in untoward clinical outcomes. In fact, a bidirectional relationship may exist between adherence and cognition, with cognitive impairment adversely affecting adherence, in turn resulting in disease progression and worsening of cognitive function.

Recognizing the high prevalence of substance abuse among those with HIV, our group also conducted a longitudinal study of 150 HIV-infected individuals, 102 of whom had recently used illicit drugs [41•]. The results indicated significantly poorer medication adherence among drug-positive subjects when compared with drug-negative subjects. Drug use was associated with a more than fourfold greater risk of poor adherence, with stimulant use, in particular, associated with a sevenfold greater risk. These findings clearly underscore the deleterious effects of substance abuse (particularly of stimulants) on adherence and further suggest that medication adherence is especially affected by the acute effects of intoxication.

Driving ability

Neuropsychological deficits have been associated with declines in driving ability across a number of research paradigms. Marcotte et al. [5] found that mild cognitively impaired subjects failed driving simulations at a rate five to six times greater than that of cognitively intact participants, with attention/working memory, fine motor abilities, visuoconstructive abilities, and nonverbal memory especially predictive of driving ability. Marcotte et al. [42] later showed that neuropsychologically impaired HIV+ participants had more simulator accidents and reduced simulator driving efficiency, failed on-road driving tests at a higher rate, and demonstrated decreased visual processing and divided attention. Moreover, global neuropsychological functioning, simulator accidents, and simulator driving efficiency accounted for 47.6% of the variance in on-road driving performance. In a more recent study, HIV+ participants demonstrated poorer divided attention than controls, with an 11-fold greater risk of problems with divided attention compared with control participants. Attentional performances were used to classify risk level; when high-risk status and general neuropsychological impairment were considered simultaneously, 93% of the HIV+ participants who acknowledged prior automobile accidents were correctly classified [43]. These studies suggest relationships between reduced driving performance and neurocognitive decrements across a variety of domains in infected subjects.

Employment

Unemployment (or underemployment) is common among the HIV-infected population, and research has suggested that neurocognitive functioning may play a significant role in occupational success and maintenance. Heaton et al. [44] found that medically asymptomatic HIV-infected neuropsychologically impaired patients were more than two times more likely to be unemployed and perceived greater vocational difficulties than their unimpaired counterparts, despite their earlier disease stage. Regardless of employment status, HIV+ patients who evidenced neuropsychological impairment perceived themselves to have greater difficulties in vocational functioning than their unimpaired cohorts. The relationship between neuropsychological impairment and employment difficulties could not be explained by depression. Work conducted by van Gorp et al. [45] also suggested that cognitive functioning is associated with vocational success, as effortful learning and memory and motor speed predicted return to employment in HIV+ persons who had terminated employment following diagnosis. These findings argue for a relationship between intact neuropsychological functioning and occupational stability and success.

Neuroimaging and Neuroanatomy of HIV-Associated Neuropsychological Dysfunction

White matter degeneration

It is well established that HIV infection is associated with myelin sheath damage (readily detectable by reduced white matter [WM] volume, WM gliosis and pallor, and high signal intensity), strongly suggesting that infection exercises a predilection for subcortical WM pathways. With the advent of DTI, an advanced MRI method for investigating WM integrity, in vivo analysis of the ways in which WM microstructure contributes to neuropsychological functioning has become possible. Research has shown that DTI possesses the requisite sensitivity to detect HIV-associated WM abnormalities in cases in which tissue appears normal on conventional MRI [46]. The earliest work examining HIV-related microstructural injury using these methods showed that despite having normal-appearing WM on conventional MRI, HIV subjects with detectable viral loads showed DTI findings of decreased fractional anisotropy within the genu and splenium of the corpus callosum and increased diffusion within the frontal and parieto-occipital WM [46].

DTI investigations exploring relationships between WM regions and cognitive functioning in HIV have demonstrated that splenium abnormalities are associated with dementia severity and psychomotor slowing and genu abnormalities are associated with visual memory dysfunction [10]. Reduced integrity of the centrum semiovale was correlated with visuoconstruction and verbal memory impairments [9,10]. The pattern of diffuse WM pathology repeatedly demonstrated in the HIV literature suggests that this may be an important neuropathologic disease manifestation and a possible cause of many observed cognitive deficits. Studies using MRS methods to document metabolite concentrations within frontal WM have found relationships between reduced NAA (a marker of neuronal integrity) and poorer cognition among HIV+ subjects [8].

Basal ganglia degeneration

Arguably the most consistent structural MRI finding to date is HIV-related atrophy of the caudate and the association between caudate volume loss and neuropsychological decrements. Relationships have been reported between caudate atrophy and reduced fine motor dexterity, psychomotor speed, verbal fluency, and auditory attention [47]. DTI methods also have been used to investigate relationships between the basal ganglia and neurocognitive functioning in HIV. Ragin et al. [9] found associations between integrity of the putamen and verbal/visual memory, working memory, and general cognitive status; between the caudate and visual memory; and between the centrum semiovale and visual memory and visuoconstruction. Studies using PET with fluorodeoxyglucose have revealed a two-stage process, with basal ganglia hypermetabolism present initially, followed by global hypometabolism in later stages [11].

Studies exploring relationships between basal ganglia abnormalities detected on MRS imaging and cognitive dysfunction have suggested that higher myoinositol and reduced NAA are associated with poorer cognitive functioning [8]. Other studies examining abnormalities among patients with HIV dementia have suggested glial proliferation and cell membrane injury (with elevated myoinositol and choline levels), as well as significant neuronal injury (lower NAA concentrations) [48]. Histopathologic studies have found associations between antemortem neuropsychological impairment and a reduction in combined microtubule-associated protein (MAP2; a marker of cell bodies and dendrites) and synaptophysin (SYN; a marker of synapses) in the putamen [6].

Cortical degeneration

Although cortical neurodegeneration occurs in HIV/AIDS [49], its relationship to neurocognitive function has been equivocal. Recent neuroimaging research has revealed preferential thinning of primary sensory, motor, and premotor cortices among AIDS patients [50••]. Immunosuppression has been linked to thinning of the language areas and frontal poles bilaterally, and neuropsychological decrements were predicted by cerebral tissue loss within the parietal and prefrontal cortices. Studies examining pathologic involvement within mesial temporal structures have yielded conflicting findings. Although neuroimaging findings have been unclear, a recent immunohistochemical study showed that postmortem neurodegeneration of cell bodies and dendrites (MAP2) and synapses (SYN) in the hippocampus was a strong predictor of antemortem HIV-associated cognitive impairment [6].

Conclusions

Our understanding of the neuropsychological sequelae of HIV infection has grown considerably over the past 20 years. The neurocognitive symptoms that characterize HIV-associated neurocognitive disorder—learning and memory dysfunction, psychomotor

slowing, executive dysfunction, and higher-order attentional problems—are well established. Consensus has also been reached regarding the neuropsychiatric effects of the virus, such as increased apathy and irritability, depressive symptoms, and increased levels of anxiety. Studies examining the “real-world” functional impact of HIV-associated neurocognitive impairment on behaviors such as medication adherence and driving ability are under way. Refinements in diagnostic nosology have been advanced. Increasingly, the neuroanatomic and neurophysiologic mechanisms underlying neuropsychological dysfunction are being identified.

However, much work remains to be done. Fundamental questions regarding the precise cause(s) of neurocognitive dysfunction remain. We are only beginning to address the additive and interactive effects of common comorbid conditions, such as illicit drug use and HCV infection, on the trajectory of neurocognitive decline. With improvements in HIV-associated morbidity, patients are living for many decades. In a manner reminiscent of the natural history of prostate cancer, the prospects of dying *with* HIV rather than dying *from* HIV must now be recognized. Whether HIV infection will act to lower the threshold for age-related cognitive decline has yet to be determined. Other critical gaps include studies linking structural and functional neural systems known to be affected by HIV disease with their real-world functional correlates. Such data not only may improve our scientific understanding regarding the neuropathology of HIV functional decline, but also might suggest neuroanatomic targets for novel pharmacologic and neurocognitive therapies. Finally, we have had only modest success in developing pharmacologic treatments for HIV-associated neurocognitive dysfunction; therefore, this area remains one of the more formidable yet important challenges we must address.

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Figure 1. Relationship between cognitive status, regimen complexity, and medication adherence among HIV-infected adults. (*Adapted from Hinkin et al. [4]; with permission.*)

Table 1

Revised research criteria for HIV-associated neurocognitive disorders

Disorder	Criteria
HIV-associated ANI [*]	<p>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 and motor skills.</p> <p>The cognitive impairment does not interfere with everyday functioning</p> <p>The cognitive impairment does not meet criteria for delirium or dementia</p> <p>There is no evidence of another preexisting cause for the ANI[†]</p>
HIV-associated MND [‡]	<p>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 and motor skills. Typically, this would correspond to an MSK scale stage of 0.5–1.0.</p> <p>The cognitive impairment produces at least mild interference in daily functioning (at least 1 of the following):</p> <ul style="list-style-type: none"> Self-report of reduced mental acuity or 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 <p>The cognitive impairment does not meet criteria for delirium or dementia</p> <p>There is no evidence of another preexisting cause for the MND[§]</p>
HAD [¶]	<p>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 2.0 SD or greater than demographically corrected means. (Note that where neuropsychological testing is not available, standard neurologic 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.</p> <p>The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities)</p> <p>The pattern of cognitive impairment does not meet criteria for delirium (eg, 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 at which delirium was not present</p> <p>There is no evidence of another, preexisting cause of the dementia (eg, other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse compatible with CNS disorder)^{**}</p>

^{*} If there is a prior diagnosis of ANI, but currently the individual does not meet criteria, the diagnosis of ANI in remission may be made.

[†] If the individual with suspected ANI also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of ANI 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.

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

[§] If the individual with suspected MND also satisfies criteria for 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.

[¶] If there is a prior diagnosis of HAD, but currently the individual does not meet criteria, the diagnosis of HAD in remission may be made.

^{**} 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 1 month after 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.

ANI—asymptomatic neurocognitive impairment; CNS—central nervous system; HAD—HIV-1–associated dementia; MND—mild neurocognitive disorder; MSK—Memorial Sloan-Kettering.

(From Antinori et al. [15••]; with permission.)