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Neuropathologic confirmation of definitional criteria for human immunodeficiency virus–associated neurocognitive disorders

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Research findings have suggested a need for modifications to the original nomenclature for human immunodeficiency virus (HIV)-associated neurocognitive disorders issued in 1991 by the American Academy of Neurology (AAN). The HIV Neurobehavioral Research Center (HNRC) proposed a diagnostic scheme that departs from the AAN 1991 criteria primarily in the inclusion of an asymptomatic neurocognitive impairment (ANI) category that relies on cognitive disturbances as a necessary criterion for diagnosis, without requiring declines in daily functioning, motor, or other behavioral abnormalities. In order to test the predictive validity of these two nomenclatures, the authors compared the correspondence between antemortem neurocognitive diagnoses resulting from AAN and HNRC criteria to a neuropathological diagnosis of HIV encephalitis (HIVE) made at autopsy. Agreement between the two sets of definitional criteria was 79% regarding the classification of cases as either neurocognitively normal or impaired, and 54% with regard to specific neurocognitive diagnoses. When pathological evidence of HIVE was considered as the external indicator of HIV-related brain involvement, 64% of cases were correctly classified by AAN criteria, compared to 72% by HNRC criteria. HNRC criteria had better positive predictive power (95% versus 88%), sensitivity (67% versus 56%), and specificity (92% versus 83%). Three cases with HIVE and were correctly identified by HNRC criteria for ANI but called normal by AAN criteria, supporting inclusion of an asymptomatic neurocognitive condition. The modifications to the AAN 1991 criteria proposed by the HNRC and others in the field have served as a point of departure for a recently revised consensus nomenclature. *Journal of NeuroVirology* (2007) **13,** 23–28.

Keywords: AIDS; cognitive impairment; dementia; diagnostic criteria; HIV; HIV encephalitis; neuropsychological; nomenclature

Background

Research and clinical observations about the neurobehavioral features of human immunodeficiency virus (HIV) disease have suggested the need for a revision of the consensus nomenclature defining HIV-associated neurocognitive disorders published by the American Academy of Neurology (AAN) in 1991 (American Academy of Neurology, 1991).

The 1991 AAN criteria define two levels of neurological manifestations of HIV infection: HIV-associated dementia (HAD) and minor cognitive motor disorder (MCMD). Briefly, AAN criteria for HAD require (1) documented acquired abnormality in at least two cognitive (not motor) areas that causes impairment in work or activities of daily living (ADLs), and (2) an abnormality of motor function or behavior

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(e.g., motivation, emotional control, social behavior). Additionally, the patient has to have sufficient arousal and attention for cognitive abilities to be assessed reliably, and cannot have other conditions that might explain the disorder. This scheme defines three subtypes of HAD: (1) HAD with motor symptoms, (2) HAD with behavioral symptoms, and (3) HAD with both motor and behavioral symptoms. According to the AAN 1991 criteria, the syndrome of HAD can be qualified further according to whether the decline in daily functioning is considered mild, moderate, or severe.

The less severe condition, labeled MCMD, requires (1) a reliable history of impaired functioning in at least two areas encompassing cognitive (attention-concentration, mental slowing, impaired memory) motor (slowed movements, incoordination), or behavioral problems (personality change, irritability, lability); and (2) documented acquired cognitive or motor abnormality verified by clinical or neuropsychological examination. These abnormalities cause mild impairment in work or ADLs, do not meet criteria for HAD or HIV-associated myelopathy, and cannot be attributed to other etiologies.

Some features of the 1991 AAN nomenclature that restrict its applicability for neurocognitive disorders include:

A. HAD cannot be diagnosed, even in the context of severe cognitive impairment, if motor or behavioral abnormalities are absent.
B. It is possible to receive an MCMD diagnosis based on the presence of both motor and behavioral abnormalities, without impairments in cognition.
C. Whereas an HAD diagnosis requires declines in at least two cognitive ability areas, the number of areas of impairment necessary for the MCMD diagnosis is not clearly delineated.
D. The degree of neurocognitive impairment required for HAD versus MCMD is underspecified, such that the same neuropsychological presentation could qualify for either diagnosis.
E. Similarly, there is overlap between the category of HAD with mild functional decline and MCMD.
F. There is no recognition of mild forms of reliably identified cognitive difficulties that have not progressed to the point of interfering substantially with everyday functioning.

To address some of these concerns, investigators at the HIV Neurobehavioral Research Center (HNRC) made modifications to the existing nomenclature to establish working research criteria for HIV-related neurocognitive complications (Grant and Atkinson, 1999). These were based on research and observations made at HNRC, as well as other published sources. The HNRC criteria recognize three conditions (in order of severity): (1) asymptomatic neurocognitive impairment (ANI), (2) HIV-associated mild neurocognitive disorder (MND), and (3) HIV-associated dementia (HAD).

A major difference between AAN and HNRC criteria is addition of the category of asymptomatic neurocognitive impairment (ANI), based on the observation that some patients have documented (usually mild) cognitive impairment, suggesting that HIV is affecting brain function, but no clearly identifiable abnormality in everyday functioning. A fundamental aspect of HNRC definitional criteria is the greater priority given to the cognitive aspects of impairment as compared to motor and emotional difficulties, as the latter may not be present or clearly attributable to HIV (i.e., could result from comorbid psychiatric conditions or medication effects). Furthermore, the HNRC criteria are more fully specified in terms of types and severity of cognitive difficulties, as well as the degree of decline in daily functioning required for each diagnostic category (see Methods for a detailed description). Table 1 summarizes the differences between the two diagnostic schemes.

With the application of the HNRC diagnostic criteria, we previously demonstrated that any degree of neurocognitive impairment within 18 months of death was almost always predictive of substantial HIV encephalitis (HIVE) (Cherner *et al*, 2002). We now utilize the same sample of well-characterized study participants to explore which features of both the AAN 1991 criteria and HNRC criteria are best predictive of postmortem findings of HIVE.

Results

Diagnostic accuracy of AAN 1991 and HNRC diagnoses

In order to compare diagnostic accuracy between the AAN 1991 and the HNRC nomenclatures, we classified all cases with regard to the presence or absence of an HIV-associated neurocognitive disorder (any of HAD, MND, or ANI for the HNRC criteria; HAD or MCMD for the AAN criteria) and determined the correspondence between that antemortem diagnosis and presence of HIVE documented post-mortem.

When pathological evidence of HIV encephalitis was considered as the correct diagnosis, 25 of the 39 patients (64%) were correctly classified by AAN criteria as having brain dysfunction, compared to 28 patients (72%) correctly classified by HNRC criteria. Thus, both sets of definitional criteria were reasonably accurate in predicting postmortem diagnoses of HIVE. However, the HNRC criteria were somewhat better in terms of positive predictive power (95% versus 88%), sensitivity (67% versus 56%), and specificity (92% versus 83%), possibly due to the added emphasis upon cognitive impairment and the inclusion of a third, asymptomatic neurocognitive condition (see Table 2): Two participants with HIVE were classified as normal by AAN criteria and MND by

Table 1 Detailed comparison of 1991 AAN and HNRC diagnostic criteria for HIV-associated neurocognitive disorders

	AAN		*HNRC*		
	HAD	*MCMD*	*HAD*	*MND*	*ANI*
Cognitive/motor/behavioral abnormality by history					
At least 2 of	√	√			
(1) impaired attention/concentration					
(2) mental slowing					
(3) impaired memory					
(4) slowed movements					
(5) incoordination					
(6) personality change, irritability, lability					
Number of self-reported cognitive complaints	(Not specified)		3+	3+	<3
Verified cognitive abnormality	√	√	√	√	√
Number of ability domains impaired	2+	?	2+	2+	2+
Global neuropsychological severity	?	?			
Mild to moderate	(Not specified)			√	√
Moderate to severe			√	√	√
Verified motor or behavioral abnormality	√				
Decline in activities of daily living					
None					√
Mild	?	√		√	
Moderate	√		√		
Severe	√		√		
Sufficient consciousness for testing	√	√	√	√	√
Duration at least 1 month	√	√	√	√	√
No other etiology for observed problems	√	√	√	√	√

? = unspecified; √ = required criterion.

HNRC criteria; also, three HIVE cases were called ANI by HNRC criteria but normal by AAN criteria. This provides empirical support to adding ANI as a third category of HIV-related neurocognitive disorder, specifically because it appears to have prognostic value.

Correspondence between AAN 1991 and HNRC diagnoses

When the two sets of definitional criteria were compared regarding the overall classification of patients as either neurocognitively normal or impaired, the agreement was 79% (31 of 39 patients). Instead, when specific diagnoses were compared, the two sets of criteria gave consistent diagnoses only for 21 patients (54%). Figure 1 compares the neurocognitive diagnosis for the 39 cases that resulted from applying each of the two diagnostic schemes.

Table 2 Sensitivity, specificity, positive and negative predictive power to detect HIV encephalitis (HIVE) obtained by applying the AAN 1991 and HNRC definitions of HIV associated neurocognitive disorder

Criteria	*Sensitivity*	*Specificity*	*PPV*	*NPV*
AAN	15/27 = 56%	10/12 = 83%	14/16 = 88%	10/22 = 45%
HNRC	18/27 = 67%	11/12 = 92%	18/19 = 95%	11/20 = 55%

Sensitivity: Proportion of cases with HIVE who meet criteria for an HIV associated neurocognitive disorder.
Specificity: Proportion of cases without HIVE who are deemed neurocognitively normal.
PPV (Positive Predictive Value): Proportion of neurocognitively impaired cases who have HIVE.
NPV (Negative Predictive Value): Proportion of neurocognitively normal cases without HIVE.

Discrepancies between the two diagnostic schemes fell into three categories:

A. Normal by AAN criteria and impaired by HNRC criteria
   1) Mild cognitive impairment but no ADL decline; meets HNRC criteria for ANI but no AAN category (three cases).
   2) Mild cognitive impairment on testing and mild ADL decline but no self-reported complaints or history of motor, or behavioral decline; meets HNRC criteria for MND but fails to meet AAN MCMD requirement (one case).
B. MCMD by AAN criteria and normal by HNRC criteria
   1) Have normal cognitive functioning but motor or behavioral changes, along with mild ADL decline (three cases).
C. HAD by AAN criteria and MND by HNRC criteria
   1) Mild cognitive impairment (six cases).
   2) Mild-moderate cognitive impairment and mild ADL decline (four cases).

Examination of these classification differences pointed to some of the shortcomings of the AAN 1991 criteria mentioned earlier. First, the degree of neuropsychological (NP) impairment (i.e., mild, moderate, severe) is underspecified in AAN HAD and MCMD criteria, based on the 1991 publication. Second, the number of cognitive areas showing objectively documented decline is also not specified in

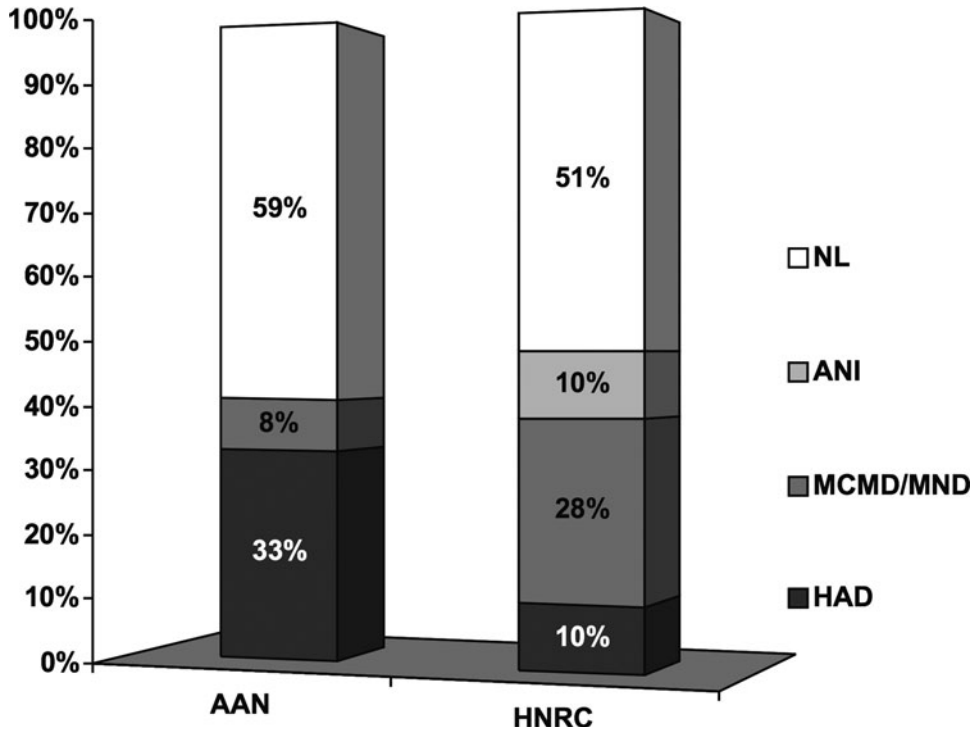

Figure 1 Distribution of neurocognitive diagnoses for the 39 cases according to AAN and HNRC nomenclatures. AAN: American Academy of Neurology; HNRC: HIV Neurobehavioral Research Center; NL: neurocognitively normal; ANI: Asymptomatic neurocognitive impairment; MND: minor neurocognitive disorder; MCMD: minor cognitive motor disorder; HAD: HIV-associated dementia.

the AAN criteria for MCMD criteria. Third, the ability to classify HAD with "mild" ADL decline has some overlap with MCMD diagnosis. Finally, the requirement of abnormality in motor and/or behavioral functioning for AAN HAD and of motor abnormality for AAN MCMD may artificially lower the detection of HIV-associated neurocognitive disorder because it diminishes the importance of cognitive deficits as the primary criterion for HIV-associated neurocognitive disorder.

We next investigated the degree to which each component of the nomenclatures (neuropsychological impairment, motor dysfunction, or behavioral disturbances) predicted a diagnosis of HIVE. In a logistic regression analysis with all components in the model, we found that having cognitive impairment in at least two domains was significantly predictive of HIVE ($\chi^2 = 14.8$; $P < .0001$), whereas motor and behavioral abnormality alone or in combination were not.

Discussion

The aim of our study was to compare the predictive power of the original AAN (1991) nomenclature for HIV-associated neurocognitive disorders to that of modifications suggested by investigators at the HNRC, which have served as a point of departure for a revised nosology that was developed at the NIMH Update on Diagnostic Definitions for HAD and MCMD in the HAART Era consensus meeting in Frascati, Italy, in 2005.

Although the present study is limited by a relatively small sample of cases with antemortem and postmortem characterization, we were able to show relative advantages of using the HNRC diagnostic criteria over the AAN 1991 nomenclature. We found that the original AAN criteria have good sensitivity and specificity for predicting future HIVE diagnosis, but positive predictive power can be enhanced by considering asymptomatic neurocognitive impairment (ANI) as introduced in the HNRC nomenclature. Specifically, we observed that 21% of cases with documented neurocognitive impairment did not have sufficient declines in everyday functioning to meet current AAN criteria, but most such cases (three out of four; see Table 3) had evidence of HIVE. Additionally, we demonstrated statistically that motor and behavioral changes alone do not predict the presence of HIVE. This supports the notion that presence and degree of neurocognitive impairment should constitute the fundamental criterion for establishing diagnosis, and other criteria, e.g., motor disorders, emotional or personality abnormality, should be considered ancillary or corroborative, or used for defining disorder subtypes. The 1996 clinical confirmation of the 1991 AAN criteria (American Academy of Neurology, 1996) showed that it was rare to have both cognitive and functional impairment without associated

Table 3 Detail of the neurocognitive diagnosis for the 39 cases as evaluated by the two nomenclatures

AAN	*HNRC*	*HIVE*	*Number of cases*
HAD	HAD	HIVE+	4
HAD	MND	HIVE+	9
MCMD	*Normal*	*HIVE+*	1
MCMD	**Normal**	**No HIVE**	**2**
Normal	**MND**	**HIVE+**	**2**
Normal	**ANI**	**HIVE+**	**3**
Normal	*ANI*	*No HIVE*	1
Normal	Normal	HIVE+	8
Normal	Normal	No HIVE	9

HAD: HIV-associated dementia; MCMD: mild motor cognitive complex; MND: mild neurocognitive disorder; ANI: asymptomatic neurocognitive impairment.
Regular text denotes cases where the AAN and HNRC neurocognitive diagnoses concur in their ability to predict HIVE.
Italicized text denotes cases where the AAN neurocognitive diagnosis correctly reflected the presence or absence of HIVE at autopsy.
Bold type text denotes to cases where the HNRC neurocognitive diagnosis correctly reflected the presence or absence of HIVE at autopsy.

motor and/or behavioral effects. Our study tends to confirm these findings when HAD is concerned, but not when milder forms of HIV associated neurocognitive disorder are considered. Given the relatively low incidence of HAD but persistence of milder forms of HIV associated neurocognitive disorder observed since the introduction of modern antiretroviral therapies (Deutsch *et al*, 2001; McArthur, 2004), it is particularly important to be able to identify and classify those cases that meet the definitions ANI and MND.

Finally, specifying the degree of neurocognitive impairment along with the degree of functional decline that is required to meet a diagnostic category, as indicated in the HNRC nomenclature, is helpful in avoiding ambiguity and overlap in diagnoses. In order to ascertain the presence and severity of neurocognitive impairment, it is recommended that neuropsychological test results be interpreted with the best available normative data, which should ideally be demographically adjusted and validated for use with the populations to which they are applied. Of course, other factors that might confound interpretation of test results, such as low literacy, active substance dependence, or comorbid medical conditions also need to be considered when attempting to assign a diagnosis of HIV-associated neurocognitive impairment.

Methods

Subjects
Subject characteristics are described in detail in Cherner *et al*, 2002. Briefly, they were 36 HIV+ men and 3 HIV+ women with autopsy information who also had antemortem medical and neuropsychological data collected within 18 months of death as part of their participation in studies at the HNRC in San Diego, and the California NeuroAIDS Tissue Network. The median interval between the last assessment and death was 6.3 months (range 0.3–17.4), and the median postmortem time to autopsy was 19 h (range 2–96). Participants ranged in age between 27 and 51 years (mean = 40, SD = 6.4), with 14 years of education on average (SD = 2.7, range 8–20). Most (82%) were Caucasian (10% Hispanic, and 8% African American). Subjects were excluded if they had a history of central nervous system (CNS) opportunistic infections or non–HIV-related developmental, neurologic, psychiatric, or metabolic conditions that might affect CNS functioning (e.g., loss of consciousness exceeding 30 min, psychosis, substance dependence).

HIV encephalitis
As described in the original publication, HIVE was determined based on evidence of multinucleated giant cells, microgliosis, and myelin pallor in frontotemporal cortex, hippocampus, basal ganglia, midbrain, and cerebellum, using standard histopathologic methods (Budka *et al*, 1987; Masliah *et al*, 1992), as well as substantial presence of HIV in the postmortem tissue. The latter was defined using a semiquatitative method (Wiley and Achim, 1995) that summed the degree of immunocytochemically detected gp41 viral envelope protein (anti-gp41; Genetics Systems, Seattle, WA) in macrophages and microglia across three brain regions (frontal neocortex: Brodmann areas 45 and 46; basal ganglia gray matter: at the anterior commissure; and subcortical white matter: centrum semiovale [Wiley *et al*, 1991]). Cases with a summary score between 0 and 2 (none to occasional gp41-positive cells) were not considered to have significant HIVE; only summary scores of 3 or greater were classified as having substantial presence of HIV in brain tissue. In five subjects, presence of HIV was determined by reverse transcriptase–polymerase chain reaction (RT-PCR) (Amplicor HIV-1 Monitor; Roche Diagnostics, Branchburg, NJ). Substantial HIV was defined as at least 10,000 copies of HIV RNA detected in any of the brain regions examined. Note that this definition of HIVE is more rigorous than some in that it required substantial detection of viral particles rather than *any* presence.

Assignment of neurocognitive diagnosis
The neurobehavioral and neuromedical assessments leading to a diagnosis of HIV-associated neurocognitive disorder have been described in detail elsewhere(Heaton *et al*, 1995; Woods *et al*, 2004). Briefly, study participants completed a comprehensive neuropsychological (NP) battery that tested functioning in the areas of attention/working memory, speeded information processing, learning, delayed recall, verbal functioning, abstraction/problem solving, and motor ability. A neuropsychologist performed clinical ratings of impairment based on

demographically corrected test scores, without being aware of HIV status. These ratings are based on the number of standard deviations above or below the demographically corrected normative mean for the component test scores, and they range from 1 to 9, with 5 denoting definite mild impairment, and higher numbers expressing increasing severity. In order to be considered globally impaired according to HNRC criteria, at least two ability areas[1] must receive ratings of 5 or greater, which corresponds to performances that are at least one standard deviation below the normative mean in a minimum of two ability domains.

Each case was then assigned a neurocognitive diagnosis using the 1991 AAN nosology as well as the HNRC criteria (the requisites for each are summarized in Table 1). This was accomplished by taking into account the participant's medical history, neuromedical examination findings, and review of systems, along with neuropsychological testing as described above. Self-report measures of instrumental activities of daily living (modified Lawton and Brody ADL Questionnaire [Heaton *et al*, 2004]) and cognitive complaints (Patient's Assessment of Own Functioning Inventory—PAOFI; Chelune *et al*, 1986), as well as functional status information gathered during the neuromedical examination, were used to assess functional decline. In order to determine whether motor abnormalities were present as required by the AAN criteria, performance on tests of motor function (i.e., Grooved Pegboard Test, Finger Tapping) was evaluated separately, along with motor findings from the neurological examination (e.g., incoordination, involuntary movement, gait or balance problem). The presence of abnormality in any of these motor items was sufficient for a rating of motor problems. To assess behavioral abnormality, we derived the relevant information from the neuromedical examination assessed by indicators of apathy or lability.

Data analyses

We compared the AAN and HNRC nomenclatures by examining their accuracy in diagnosing HIVE. Diagnostic accuracy was defined as the number of cases that are correctly classified as having or not having the diagnosis in question. For this study, we calculated the sensitivity and specificity, as well as the positive and negative predictive power of the overall diagnosis as impaired or normal in detecting the presence or confirming the absence of HIVE. The ability of individual criteria (cognitive, motor, and behavioral) to predict the presence of HIVE was explored using logistic regression analyses.

References

American Academy of Neurology (1991). Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force. *Neurology* **41:** 778–785.

American Academy of Neurology (1996). Clinical confirmation of the American Academy of Neurology algorithm for HIV-1-associated cognitive/motor disorder. The Dana Consortium on Therapy for HIV Dementia and Related Cognitive Disorders. *Neurology* **47:** 1247–1253.

Budka H, Costanzi G, *et al* (1987). Brain pathology induced by infection with the human immunodeficiency virus (HIV). A histological, immunocytochemical, and electron microscopical study of 100 autopsy cases. *Acta Neuropathol (Berl)* **75:** 185–198.

Chelune GJ, Heaton RK, *et al* (1986). Neuropsychological and personality correlates of patients' complaints if disability. In: *Advances in clinical neuropsychology*. Goldstein RETG (ed). New York: Plenum Press, pp 95–126.

Cherner M, Masliah E, *et al* (2002). Neurocognitive dysfunction predicts postmortem findings of HIV encephalitis. *Neurology* **59:** 1563–1567.

Deutsch R, Ellis RJ, *et al* (2001). AIDS-associated mild neurocognitive impairment is delayed in the era of highly active antiretroviral therapy. *AIDS* **15:** 1898–1899.

Grant I, Atkinson JH (1999). Neuropsychiatric aspects of HIV infection and AIDS. In: Sadock BJ, Sadock VA, eds. Kaplan and Sadock's comprehensive textbook of psychiatry/VII. Baltimore: Williams & Wilkins, pp. 308–335.

Heaton RK, Grant I, *et al* (1995). The HNRC 500—neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. *J Int Neuropsychol Soc* **1:** 231–251.

Heaton RK, Marcotte TD, *et al* (2004). The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc* **10:** 317–331.

Masliah E, Ge N, *et al* (1992). Selective neuronal vulnerability in HIV encephalitis. *J Neuropathol Exp Neurol* **51:** 585–593.

McArthur JC (2004). HIV dementia: an evolving disease. *J Neuroimmunol* **157:** 3–10.

Wiley CA, Achim CL (1995). Human immunodeficiency virus encephalitis and dementia. *Ann Neurol* **38:** 559–560.

Wiley CA, Masliah E, *et al* (1991). Neocortical damage during HIV infection. *Ann Neurol* **29:** 651–657.

Woods SP, Rippeth JD, *et al* (2004). Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. *J Clin Exp Neuropsychol* **26:** 759–778.

[1]These cannot be learning and delayed recall exclusively, as they are highly related; a third ability domain would need to be impaired to meet criteria.