



NOMENCLATURE AND RESEARCH CASE DEFINITIONS FOR NEUROLOGICAL MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS TYPE-1 (HIV-1) INFECTION

Report of a Working Group of the American Academy of Neurology AIDS Task Force*

Infection with human immunodeficiency virus type-1 (HIV-1) has been associated with a variety of neurological disorders thought to be caused, directly or indirectly, by HIV-1.⁽¹⁻⁶⁾ Although these disorders have been described clinically, there are no consensus terminology or criteria for diagnosis. To develop consensus nomenclature and case definitions for HIV-1-associated neurological conditions for *research* purposes, the American Academy of Neurology AIDS Task Force convened a working group of neurologists, neuropsychologists, psychiatrists, and sociologists, including representatives of the American Neurological Association, the World Federation of Neurology, the International Neuropsychological Society, the National Academy of Neuropsychology, the American Psychological Association, the American Psychiatric Association, the World Health Organization, and the Centers for Disease Control (CDC). The definitions have been developed in conjunction with the International Classification of Diseases-10 (ICD-10, unpublished draft of the World Health Organization) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, unpublished draft of the American Psychiatric Association). Although consistent with the ICD-10, the definitions are not identical. Although HIV-2 may cause similar disorders, the neurological manifestations of HIV-2 are unknown and are not addressed in this article.

NOMENCLATURE AND CRITERIA FOR CENTRAL NERVOUS SYSTEM DISORDERS.

Central nervous system (CNS) illness associated with HIV infection encompasses neurological, neuropsychological, and psychiatric aspects. Proposed nomenclature for these CNS disorders is listed in Table 1 with the terms currently used for the same disorders; clinical criteria for diagnosis in adolescents and adults are outlined in Table 2. Although *HIV-1-associated cognitive/motor complex* is consistent with, but not identical to, the AIDS dementia complex,⁽⁷⁾ it may be a single entity with a broad spectrum of clinical presentations and severity. Using current knowledge, working group participants separated the complex into two categories: 1) a more severe form (*HIV-1-associated dementia complex* and *HIV-1-associated myelopathy* [consistent with *HIV encephalopathy*]⁽⁸⁾ and 2) a less severe form (*HIV-1-associated minor cognitive/motor disorder* [consistent with *HIV-1-associated neurocognitive disorder*]⁽⁹⁾). The manifestations of the severe form are sufficient for a diagnosis of AIDS and usually occur in combination with other AIDS-defining illnesses. The manifestations of the less severe form by themselves, however, are not sufficient for an AIDS diagnosis, although they may be present in persons with AIDS. It is unknown whether the severe and minor forms of this complex represent different or the same entities or whether patients with the minor form will invariably progress to a severe form.⁽¹⁰⁾ Prospective studies will help define the natural history and response to therapy of these disorders. In addition, although both severe and minor forms of *HIV-1-associated cognitive/motor complex* tend to occur in patients with other manifestations of HIV-1 infection, there has been controversy about the frequency of these illnesses in otherwise asymptomatic, HIV-1-seropositive persons.⁽⁹⁻²⁶⁾

The essential feature of *HIV-1-associated dementia complex* is disabling cognitive impairment usually accompanied by motor dysfunction, behavioral change, or both.⁽³⁾ However, because some patients with cognitive impairment do not have clear behavioral change, and others occasionally do not have clear motor dysfunction, the criteria for *HIV-1-associated dementia complex* can be coded to describe the major features (Table 2). A patient with cognitive impairment, motor impairment and behavioral change has *HIV-1-associated dementia complex*, while a patient with cognitive impairment and motor impairment but no behavioral change has *HIV-1-associated dementia complex (motor)*; a patient with cognitive impairment and behavioral change but no motor impairment has

Patients with *HIV-1-associated minor cognitive/motor disorder* frequently have normal neuroimaging scans,⁽¹³⁾ but patients with *HIV-1-associated dementia complex* usually have cerebral atrophy and, on magnetic resonance imaging (MRI), may have nonspecific white matter changes.⁽³⁾ In patients with *HIV-1-associated minor cognitive/motor disorder* or *HIV-1-associated dementia complex*, cerebrospinal fluid (CSF) can be normal but more frequently may have pleocytosis, elevated protein, neopterin or beta-2- microglobulin.^(3,28-31) However, CSF abnormalities may be present in HIV-1-seropositive persons who are completely asymptomatic.⁽³²⁾ There are no neuroimaging, electrophysiologic, or CSF abnormalities that are pathognomic for HIV-1-associated neurological disorders.

Neuropsychological tests found to be sensitive to cognitive impairment in HIV-1 infection^(25,33,34) include those of the following domains (for most tests see reference 35): 1) attention/concentration (Trail Making A,⁽³⁶⁾ Continuous Performance Test);⁽³⁷⁾ 2) speed of processing of information (Trail Making A and B,⁽³⁶⁾ Digit Symbol Substitution on the Wechsler Adult Intelligence Scale-Revised [WAIS-R],⁽³⁸⁾ Paced Auditory Serial Addition Test,⁽³⁹⁾ Choice Reaction Time);⁽¹⁶⁾ 3) motor functioning (Finger Tapping,⁽⁴⁰⁾ Grooved Pegboard,⁽⁴¹⁾ Thumb-Finger Sequential Touch⁽⁴²⁾); 4) abstraction/reasoning (Wisconsin Card Sorting Test,⁽⁴³⁾ Halstead Category Test);⁽³⁶⁾ 5) visuospatial skills (Block Design);⁽³⁸⁾ 6) memory/learning (Rey Auditory Verbal Learning Test⁽⁴⁴⁾ or California Verbal Learning Test,⁽⁴⁵⁾ Visual Reproduction from the Wechsler Memory Scale [WMS],⁽⁴⁶⁾ Logical Prose form the WMS),⁽⁴⁶⁾ and 7) speech/language (Verbal Fluency,⁽⁴⁷⁾ Vocabulary,⁽³⁸⁾ Boston Naming⁽⁴⁸⁾, Animal Naming⁽⁴⁷⁾). Although useful, these tests have been administered predominantly to well-educated white, homosexual men in the United States, Europe, and Australia. It is unclear whether these tests are equally valid in other settings because of their limited use in persons of other social, cultural, linguistic, behavioral, and educational backgrounds. In addition, there is no clear agreement on determining impairment on neuropsychological tests. Regardless of the cutoff used to determine abnormality on a test or test battery, appropriate controls for age, education, racial/ethnic group, and sex must be used. Other factors including, alcohol or substance use and antecedent neurological (e.g., history of head trauma) or psychiatric illness (e.g., learning disability or major depression), should be analyzed as both possible confounders and cofactors. Neuropsychological tests are useful diagnostic adjuncts but, by themselves, are not capable of determining the presence of *HIV-1-associated dementia complex* or *HIV-1-associated minor cognitive/motor disorder*.

HIV-1-associated dementia complex is not invariably progressive; clinical impression suggests that it can remain static or fluctuate. It may improve with medical therapy or it may worsen abruptly in the presence of a severe metabolic disorder, such as hypoxemia from pneumonia, and then improve.

Patients with myelopathy usually complain of progressive (over weeks to months) gait disturbance, leg weakness, and urinary incontinence.^(3,49) Mild cognitive impairment may be present, but lower extremity dysfunction must be greater than cognitive impairment to meet the definition for *HIV-1-associated myelopathy*. Although some patients may have upper extremity involvement, most patients have paraparesis, lower extremity spasticity, ataxia, and extensor plantar responses. Spinal cord MRI and myelography are usually normal.

Because patients with HIV-1 infection frequently have multiple neurological illnesses, the diagnosis of one of the severe forms of *HIV-1-associated cognitive/motor complex* can be made in the presence of another possible etiology (e.g., severe depression, CNS toxoplasmosis, etc.), but the other process **cannot** be the cause of the clinical features of the *HIV-1-associated cognitive/motor complex disorder*. If another potential etiology is present, it should be reported and evaluated as a potential confounder or cofactor.

HIV-1-Associated Progressive Encephalopathy of Childhood.

Criteria for the clinical diagnosis of HIV-1-associated progressive encephalopathy of childhood are outlined in Table 3.

Table 1. Proposed nomenclature for HIV-1-associated central nervous system disorders and terms currently in use for the same disorders.

HIV-1-ASSOCIATED COGNITIVE/MOTOR COMPLEX
AIDS dementia complex (7)

I. SEVERE MANIFESTATIONS

A. HIV-1-ASSOCIATED DEMENTIA COMPLEX

Subacute encephalitis (1)

HIV-encephalopathy (8)

AIDS-related dementia (4)

B. HIV-1-ASSOCIATED MYELOPATHY HIV

encephalopathy (8)

II. MILD MANIFESTATIONS

HIV-1-ASSOCIATED MINOR COGNITIVE/MOTOR DISORDER

HIV-1-associated neurocognitive disorder (9)

HIV-associated neurobehavioral abnormalities (19)

Table 2 (cont). Criteria for clinical diagnosis of central nervous system disorders for adults and adolescents.

substance withdrawal, must be sought from history, physical and psychiatric examination, and appropriate laboratory and radiologic investigation (e.g., lumbar puncture, neuroimaging). If another potential etiology (e.g., major depression) is present, it is *not* the cause of the above cognitive, motor, or behavioral symptoms and signs.

Possible (Must have *one* of the following):

1. Other Potential Etiology Present (Must have *each* of the following)
 - a. As above #1,2,3.
 - b. Other potential etiology is present but the cause of #1 above is uncertain.
2. Incomplete Clinical Evaluation (Must have *each* of the following):
 - a. As above #1,2,3.
 - b. Etiology cannot be determined (appropriate laboratory or radiologic investigations not performed).

B. HIV-1-Associated Myelopathy

Probable (Must have *each* of the following):

1. Acquired abnormality in lower-extremity neurological function disproportionate to upper extremity abnormality verified by reliable history (lower extremity weakness, incoordination, and/or urinary incontinence) and neurological examination (paraparesis, lower extremity spasticity, hyperreflexia, or the presence of Babinski signs, with or without sensory loss).
2. Disturbance in #1 is severe enough* to require constant unilateral support for walking.
3. Although mild cognitive impairment may be present, criteria for HIV-1-associated dementia complex are not fulfilled.
4. Evidence of another etiology including neoplasm, compressive lesion, or multiple sclerosis must be sought from history, physical examination, and appropriate laboratory and radiologic investigation (e.g., lumbar puncture, neuroimaging, myelography). If another potential etiology is present, it is not the cause of the myelopathy. This diagnosis cannot be made in a patient infected with both HIV-1 and HTLV-I; such a patient should be classified as having possible HIV-1-associated myelopathy.

Possible (Must have *one* of the following):

1. Other Potential Etiology Present (Must have *each* of the following):
 - a. As above #1,2,3.
 - b. Other potential etiology is present but the cause of the myelopathy is uncertain.
2. Incomplete Clinical Evaluation (Must have *each* of the following):
 - a. As above #1,2,3.
 - b. Etiology cannot be determined (appropriate laboratory or radiologic investigations not performed).

*The severity of HIV-1-associated myelopathy should be graded as follows:

MILD Ambulatory, but requires constant unilateral support (e.g., cane) for walking.

MODERATE Requires constant bilateral support (e.g., walker) for walking.

SEVERE Unable to walk even with assistance, confined to bed or wheelchair.

Table 3. Criteria for clinical diagnosis of central nervous system dysfunction in children.

HIV-1-ASSOCIATED PROGRESSIVE ENCEPHALOPATHY OF CHILDHOODProbable (Must have *each* of the following):

1. Evidence for systemic HIV-1 infection:
 - a. Infants and children < 15 months
 - i) virus in blood or tissues or
 - ii) presence of HIV-1 antibody and evidence of cellular and humoral immune deficiency or other conditions meeting CDC case definition for AIDS
 - b. Children > 15 months
 - i) antibody or virus in blood or tissues
2. At least *one* of the following progressive findings present at least 2 months:
 - a. Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests.
 - b. Impaired brain growth (acquired microcephaly or brain atrophy demonstrated on serial CT or MRI scans).
 - c. Acquired symmetrical motor deficits manifested by *two or more* of the following: paresis, abnormal tone, pathologic reflexes, ataxia, or gait disturbance.
3. Evidence of another etiology, including active CNS opportunistic infection or malignancy must be sought from history, physical examination, and appropriate laboratory and radiologic investigation (e.g., lumbar puncture, neuroimaging). If another potential etiology is present, it is not thought to be the cause of the above cognitive/motor/behavioral/developmental symptoms and signs.

Possible (Must have *one* of the following):

1. Other Potential Etiology present (Must have each of the following):
 - a. As above #1,2.
 - b. Other potential etiology is present but the cause of #2 is uncertain.
2. Incomplete Clinical Evaluation (Must have each of the following):
 - a. As above #1,2.
 - b. Etiology cannot be determined (appropriate laboratory or radiologic investigations not performed).

Table 4 (Cont). Criteria for clinical diagnosis of HIV-1- associated peripheral nervous system disorders.

III. HIV-1-ASSOCIATED MYOPATHY

Probable (Must have *each* of the following):

1. Symptoms of proximal lower and/or upper extremity weakness, documented by physical examination.
2. No other etiology (including toxic exposure to zidovudine). EMG and muscle biopsy may be necessary to rule out certain other etiologies.

Possible (Must have *one* of the following):

1. Other Potential Etiology Present (Must have *each* of the following):
 - a. As above #1.
 - b. Other potential etiology is present and the cause is uncertain.
2. Incomplete Clinical Evaluation (Must have *each* of the following):
 - a. As above #1.
 - b. Etiology cannot be determined (appropriate laboratory investigations not performed).

Professional Societies and Designated Reviewers

American Neurological Association: Arthur Asbury, M. Marsel Mesulam, Richard Price
 American Psychiatric Association: Alexandra Beckett, Peter Bridge, Igor Grant, Marshall Folstein
 American Psychological Association: Paul Satz, Andrew Saykin, John Sidtis, Susan Torres.
 International Neuropsychological Society: Paul Satz, Andrew Saykin, John Sidtis, Igor Grant
 National Academy of Neuropsychology: Andrew Saykin.
 World Federation of Neurology: The Lord Walton, President; Arthur Asbury.

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