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Global NeuroAIDS

Bibilola D. Oladeji^{1,2}, Sarah Yosief¹ and Kevin Robertson¹

¹Department of Neurology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

²Department of Psychiatry, College of Medicine University of Ibadan, Ibadan, Nigeria

Definition

The term NeuroAIDS encompasses all the neurological complications associated with HIV. This includes diseases that primarily result from direct infection of the CNS with HIV (HIV-associated neurocognitive disorders [HAND]), secondary conditions resulting either from the effects of associated immunocompromise (neurologic opportunistic infections or tumors) or the effects of treatment (such as the immune reconstitution syndrome [IRIS]) as well as other diseases that could be influenced but not caused by HIV (e.g., stroke).

Types of HIV-Associated Neurological Syndromes

- Primary HIV neurological diseases
 - HIV-associated neurocognitive disorders (HAND)

- Asymptomatic neurocognitive impairment (ANI)
- Mild neurocognitive disorder (MND)
- HIV-associated dementia (HAD)
 - Aseptic meningitis
 - HIV-associated myelopathy
 - HIV-associated peripheral neuropathies
 - Distal symmetric polyneuropathy (DSP)
 - Inflammatory demyelinating polyneuropathy (IDPN)
- Secondary or opportunistic neurological diseases
 - Opportunistic neurological infections
 - Viral: cytomegalovirus, progressive multifocal leukoencephalopathy, and herpes simplex encephalopathy
 - Bacterial: CNS tuberculosis
 - Fungal: Cryptococcal meningitis
 - Parasitic: Toxoplasmic encephalitis
 - Opportunistic CNS tumor
 - Primary HIV-associated CNS lymphoma
- Treatment-related neurological disease
 - Immune reconstitution inflammatory syndrome (IRIS)
 - Neurotoxic neuropathy
- Non-AIDS-related diseases
 - Stroke

Epidemiology of NeuroAIDS

HIV/AIDS remains a global public health problem with 35.3 million people infected and 2.3

million new infections worldwide in 2012 (UNAIDS 2013). The introduction of antiretroviral therapy (ART) from the mid-1990s led to a gradual reduction in the rates of new infections and increased the life expectancy of people living with HIV; it also altered the manifestations of HIV disease. The global incidence of new HIV infections has declined by 19 % since the peak of the epidemic in 1999. HIV has a wide range of effects on the nervous system, directly on the brain and spinal cord, which create cognitive, central motor, and behavioral abnormalities. In the pre-ART era, neurological disorders were a common presenting feature of HIV infection, with 7–20% of patients having neurological complications at first presentation. Severe cognitive impairment was commonly seen in patients with advanced immunosuppression; HIV-associated dementia was reported in 20–30 %, and 39–70 % developed opportunistic neurologic infections (Spudich and González-Scarano 2012; Tan et al. 2012).

Currently, in developed countries where there is widespread availability and access to combination antiretroviral therapy (cART), there has been a decline in the incidence of severe HIV-associated neurologic disorders and opportunistic infections by up to 80–90 %. For example, between 1996 and 1997, the incidence of opportunistic infections in high-income countries was 13.1 per thousand patient-years; by 2006–2007, this had reduced to 1 per thousand patient-years (Tan et al. 2012). However, the spectrum of disease-causing agents has remained largely unchanged. Despite this reduction in incidence rates, neurologic complications still remain a significant cause of excess morbidity and mortality in people living with HIV. The overall prevalence of HIV-associated neurocognitive disorders (HAND) is on the rise despite satisfactory virologic control; the current prevalence of HAND ranges from 20 % to 50 % (Brew and Chan 2014).

The picture is somewhat different in low- and middle-income countries where only an estimated 34 % of the 28.6 million eligible people in 2012 are receiving ART (UNAIDS 2013). The current picture of HIV neurological disorders

appears similar to that of the pre-ART era. The problem in low-resourced areas of the world is further compounded by limited diagnostic capabilities for HIV-associated neurologic disorders and hence a paucity of reliable data on the actual rates of CNS complications in HIV populations in low- and middle-income countries (LMIC) (Robertson et al. 2010). The little data available suggests that opportunistic infections are still the commonest neurologic complications of HIV.

The type and severity of the neurologic dysfunction related to HIV are influenced by the properties of the HIV virus, disease stage, genetic characteristics of the host, and interactions with the environment. Neurologic manifestations of HIV might be linked to HIV virus subtype. For example, HIV type 2 has less propensity to cause neurologic disease compared to type 1. Even within HIV-1 infection, different subtypes or clades have been associated with different rates of occurrence of neurologic dysfunction in preliminary studies (Sacktor et al. 2007).

Acute HIV infection is usually asymptomatic, but a few patients develop a neurologic illness. Common presentations include aseptic meningitis, facial palsy, Guillain-Barré (GB) syndrome, and transverse myelitis. As the disease progresses, with reduction in the CD4-positive cells, the risk for other conditions such as opportunistic infections, HIV-associated cognitive disorders, and peripheral neuropathies increases (Hogan and Wilkins 2011).

Pathogenesis of NeuroAIDS

HIV is able to infect the nervous system and cause central nervous system (CNS) and peripheral nervous system (PNS) disorders at any stage during disease evolution from seroconversion to late stage HIV disease. The neuropathology of HIV infection is very complex and as yet not fully understood; however, HIV is known to invade the central and peripheral nervous system soon after initial infection. The virus is believed to enter the CNS through HIV-infected macrophages and CD4+ T cells that are able to penetrate the blood-brain barrier. In the CNS, the virus

commonly infects perivascular macrophages and the microglia. CNS infection is mediated by CD4 and the chemokine receptor (CCR5) serving as viral receptors (Spudich and González-Scarano 2012).

The mechanism for HIV neurotoxicity is not yet fully understood, but it is thought to result from either direct neurotoxicity from the virus and its proteins or through sustained chronic immune activation and inflammation. Viral proteins such as glycoprotein 120 (gp-120) and transactivator of transcription (tat) have been shown to be neurotoxic. The chronic immune activation stimulates the microglia and macrophages to secrete neurotoxic products such as pro-inflammatory cytokines (tumor necrosis factor- α , interleukin-1, and interferon- α), quinolinic acid, and arachidonic acid metabolites. This results in disturbance of the blood-brain barrier and further entry of infected cells into the nervous system and eventually to decreased synaptic-dendritic density (Mirza and Rathore 2012). The common end pathway for neurotoxicity is through the excitation of *N*-methyl-D-aspartate (NMDA) glutamate receptors with potential for mediating apoptosis (Spudich and González-Scarano 2012).

HIV-Associated Neurocognitive Disorders (HAND)

HIV-associated neurocognitive disorder (HAND) is a chronic neurodegenerative condition characterized by cognitive, motor, and behavioral abnormalities. HAND is classified into three groups based on the severity of neurocognitive impairment that range from mild to severe: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) (Antinori et al. 2007). ANI is a subclinical decline in cognition, MND is a mild decline in cognition along with mild interference in everyday functioning, and HAD is significant decline in cognition along with significant functional impairment affecting routine activities. These disorders were previously known as AIDS

dementia complex (ADC) and minor cognitive and motor disorder (MCMD).

With the introduction of antiretroviral therapy, there has been a substantial change in the epidemiology of HAND with significant decline in the incidence of severe neurocognitive impairment. For example, in the USA, current incidence of HIV-associated dementia is less than 1 % compared to 7 % in 1989 (Kranick and Nath 2012). HIV-associated dementia (HAD) is associated with profound immunosuppression with low CD4 counts and the presence of other symptoms of AIDS. In low-resourced countries, where treatment is often delayed, HAD is still quite prevalent. The milder degrees of HAND (ANI and MND), on the other hand, remain common even in ART-treated patients and are no longer associated with the typical HIV disease biomarkers (viral load, CD4, and inflammatory response markers). Compared to patients without any impairment, patients with these milder forms of neurocognitive impairment have worse quality of life, reduced ability to perform everyday tasks, poor medication adherence, and reduced survival time.

The reasons for this persistence of cognitive dysfunction despite good viral control are unknown, but several explanations have been proposed. The host and viral factors that predispose to the development of HAND are also poorly understood. Recent evidence suggests that the subtype of HIV might have effect on disease progression and differ in neuropathogenicity. For example, a study from Uganda, where HIV clades A and D predominate, reported that adults with clade D infection had a more rapid progression and increased risk for dementia compared to clade A (Sacktor et al. 2007). Host factors that affect the occurrence of HAND include aging, substance abuse, and the presence of comorbid diseases such as hepatitis C virus infection (Shapshak et al. 2011).

HAND affects several areas or domains of neurocognitive functioning. The pattern of cognitive impairment observed in classic HAD is a subcortical dementia, more similar to deficits associated with disorders such as Parkinson's disease and Huntington's disease, rather than

the pattern for cortical dementia associated with Alzheimer's disease. Cortical deficits were not observed until very late in the disease as the brain became globally affected. There is emerging evidence that HAND has some additional cortical features that are mostly observed in the neuropsychological profile. The most commonly affected domains are attention/working memory, executive functioning, psychomotor speed, memory and learning, speed of information processing, and motor skills. Other domains less commonly or severely affected by HAND include language fluency and visuospatial domains. Furthermore, there is evidence that HAND is beginning to have more extrapyramidal features, sometimes overlapping with Parkinson's disease. These changes suggest that HAND is probably associated with the accelerated development of some neurodegenerative diseases and accelerated aging (Brew and Chan 2014).

Current "Frascati" criteria for the diagnosis of the milder forms of HAND require formal neurological assessment and neuropsychological testing (Antinori et al. 2007). Neuropsychological impairment is defined by performance below the appropriate normalized group mean on standardized tests. The formal criteria specify that at least five domains of functioning must be included to cover a range of cognitive abilities. ANI and MND impairment is defined as performance one standard deviation or more below the mean on at least two neuropsychological tests of different domains. HAD, however, must have impairment in performance two standard deviations below on two neuropsychological tests in two different domains.

In most clinical settings and in low-resourced settings where facilities for neuropsychological assessments are not readily available, a presumptive clinical diagnosis and use of brief screening tools are advocated. Examples of such brief screening tools include NEU screen, HIV Dementia Scale (HDS) and International HIV Dementia Scale (IHDS), and the ACTG ALLRT Neuroscreen, and even computerized screens such as CogState and CANTAB have also been utilized. However, no single tool is suitable

across all practice settings, and these tests are generally not sensitive or specific for HIV-associated neurocognitive dysfunction.

Clinically, HAND presents with difficulties in learning new information, disturbances in attention, slowing of information processing, and disturbances in executive functioning (e.g., planning, abstraction). Motor symptoms include motor slowing, ataxia, incoordination, and tremors and may later progress to weakness, spasticity, and paraparesis. Behavioral manifestations of HAND include apathy, psychomotor retardation, and irritability. Neuroradiological studies show generalized cerebral atrophy especially in the later stages of the disease; the degree of atrophy on MRI has been correlated with the degree of neurocognitive dysfunction. There is no specific laboratory diagnostic biomarker for HAND; HIV+ patients are diagnosed after ruling out confounding conditions such as CNS opportunistic infections, psychiatric disease, and age-related dementia. ART remains the most important treatment for HAND.

Peripheral Neuropathies

Neuropathy is one of the most common manifestations of HIV disease. Many forms of peripheral neuropathies have been associated with HIV including distal symmetric polyneuropathy (also called distal sensory peripheral neuropathy (DSPN)), mononeuritis multiplex, inflammatory demyelinating polyneuropathy, polyradiculopathy, and autonomic dysregulation. The commonest are distal symmetric polyneuropathy (DSP), acute inflammatory demyelinating polyneuropathy, and neurotoxic neuropathy.

Distal Symmetric Polyneuropathy: HIV-associated DSP is the commonest neurological problem of HIV in developed countries in this era of effective antiretroviral treatment. The rates have not been well studied in developing countries but appear similar to that from developed countries. The current prevalence estimates range from 19 % to 66 %. This wide variation results from widely varying definitions of HIV DSP used in studies and differences in the cohort

studied. Some studies defined DSP as one clinical sign (i.e., reduced ankle reflexes or reduced pinprick sensation or reduced vibration sensation in the feet), others required two clinical signs, and some used validated screening or diagnostic instruments (Schütz and Robinson-Papp 2013). Prior to the introduction of ART, DSP prevalence was 55 %, and almost all patients had evidence of DSP on autopsy even those without symptoms during their lifetime. Pre-cART, DSP was related to profound immunosuppression and high HIV viral load, but recent studies report that the degree of immunosuppression or viral load does not predict the development of DSP. Recent studies report that age is the most important risk factor for DSP; rates are higher in older patients.

DSP is an ascending, symmetric predominantly sensory distal neuropathy. Symptoms typically begin in the distal lower extremities – toes and feet – and may gradually ascend up to the thighs and could similarly involve the hand: glove and stocking distribution of symptoms. Patients present with pain, paresthesia, and numbness. The signs seen on examination include decreased or absent ankle jerks and decreased pinprick and vibration sensation involving the distal lower extremities. Pathological changes may be absent on electromyogram and nerve conduction studies; definitive diagnosis is made on skin biopsy which typically shows a reduction in epidermal nerve fiber density in DSP patients. It is important to rule out other potentially reversible causes of sensory neuropathy such as diabetes mellitus, renal disease, liver disease, infections (syphilis, hepatitis C), and micronutrient deficiency (vitamin B12, folate, and vitamin D). There is presently no effective treatment for DSP.

Inflammatory

Polyneuropathy: The true prevalence of this complication is not known. Two forms of inflammatory polyneuropathy have been described in HIV: acute inflammatory polyneuropathy (AIDP) and chronic inflammatory polyneuropathy (CIDP). AIDP typically occurs at seroconversion and may be the presenting symptom of underlying infection with HIV. It is indistinguishable clinically from Guillain-Barré syndrome (GBS);

Demyelinating

up to 10 % of GBS cases are related to HIV. AIDP presents as a rapidly progressive primarily motor neuropathy, most commonly starting in the lower limbs and like GBS can lead to quadriplegia with respiratory failure over days or even hours. The treatment is the same as for non-HIV-associated AIDP. Treatment consists of supportive care, intravenous immunoglobulin, or electrophoresis and possibly starting cART.

CIDP on the other hand occurs in late infection and is associated with low CD4 count. CIDP resembles AIDP, but it is more slowly progressive and may have a relapsing and remitting course. Electrophysiologic studies show slow or absent nerve conduction. The treatment for HIV-associated CIDPs is identical to that for non-HIV-related disease in addition to antiretroviral medications.

HIV Myelopathy

HIV is associated with a non-inflammatory, subacute vacuolar myelopathy (Previti and Marra 2012). Much of what is known about HIV-associated myelopathy is from the pre-cART era where it was found in up to 30 % of autopsies and more commonly in patient with other AIDS-defining conditions. It is likely that the incidence is dramatically reduced in the current treatment era. HIV vacuolar myelopathy (HIV VM) is a diagnosis of exclusion; it has to be differentiated from other causes of spinal cord disease such as direct infections (CMV, HTVL I and II, herpes simplex virus, enteroviruses, varicella zoster, syphilis and mycobacterium tuberculosis), tumors, and nutritional deficiencies (vitamin B12). While vacuolar myelopathy can develop at any stage in the progression of HIV disease, it is more common at lower CD4 levels.

Clinically it presents as a subacute or chronic weakness in the lower limbs, spasticity, hyperreflexia, sensory loss (especially loss of vibration and joint position sense), sexual dysfunction, and sphincter dysfunction. Laboratory and imaging studies are needed to exclude other spinal cord diseases. Histopathological features are prominent vacuolation in the white matter of

the dorsal and lateral columns that is most prominent in the thoracic spinal cord. There is no proven treatment for HIV myelopathy, and the condition is irreversible. The treatment is usually symptomatic; however, some patients may improve with ART.

Opportunistic Infections

Most CNS opportunistic infections (OIs) seen in people with HIV are due to reactivation of latent pathogens rather than new infections. The strongest predictor for the development of opportunistic infections is decreased CD4 count; susceptibility is increased when the CD4 count falls below 200 cell/ μl . These infections are usually comorbid, with up to 15 % of cases having more than one infection (Tan et al. 2011). In the era of cART, opportunistic infections are often unmasked at the initiation of antiretroviral therapy. Many of the OIs that commonly infect the CNS are AIDS-defining conditions; they include toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), CNS tuberculosis, and CNS cytomegalovirus. CNS OIs are associated with excess mortality. There is wide geographical variation in the occurrence of these infections. For example, the commonest CNS OIs in Asia and Pacific Regions are cryptococcal meningitis, cerebral toxoplasmosis, and tuberculous meningitis, while in Europe and North America, the commonest infections are PML, toxoplasmic encephalitis, and cryptococcal meningitis (Tan et al. 2011).

The diagnosis of CNS OIs is based on the clinical presentation, radiographic features, CSF findings, and isolation of the organism or its antibodies. In resource-rich settings, a battery of investigations which include neuroimaging studies (CT /MRI scans), CSF antibody testing or polymerase chain reactions to identify the organism, and image-guided stereotactic brain biopsy are used to confirm the diagnosis of CNS OIs. In places with limited resources, where diagnoses often depend on clinical presentation and minimal rudimentary investigations, the diagnosis of OIs is often missed or delayed contributing

further to increased morbidity and mortality. In such resource poor settings where cART and the resources to manage OIs are not yet widely available, the current medical strategy is the use of prophylactic antimicrobial regimens to reduce the occurrence of OIs.

Primary CNS Lymphoma

Primary CNS lymphoma (PCNSL) is the second most common mass lesion in AIDS; it usually arises in and is confined to the CNS. It is therefore important to rule out systemic lymphoma with secondary CNS lesions in making the diagnosis. PCNSL affected up to 5 % of patients with HIV before the advent of cART, but rates have declined substantially since, and in most developed countries, it is now a rare disease. The major risk factor for PCNSL is a low CD4 count (less than 100cells/ μl).

Primary CNS lymphoma is a high-grade B-cell non-Hodgkin's lymphoma that is associated with multiple genetic alterations and monoclonal Epstein-Barr virus infection. Factors that contribute to lymphoma development include HIV-induced immunosuppression, impaired immune surveillance, cytokine release and deregulation, and chronic antigenic stimulation. The clinical features of the tumor are usually nonspecific and may include headache, lethargy, cognitive changes, seizures, and focal signs which depend on the anatomic site of the tumor. The tumor shows up on neuroimaging (CT or MRI) as contrast-enhancing lesions surrounded by edema and a mass effect. In making the diagnosis, CSF PCR to detect the presence of Epstein-Barr virus is helpful; diagnosis confirmed with brain biopsy. The clinical outcome with current treatments for primary CNS lymphoma in HIV-infected persons remains relatively discouraging; median survival time is about 2 months.

CNS IRIS

Immune reconstitution syndrome (IRIS) is a serious complication related to immune recovery on

initiating effective antiretroviral therapy. IRIS can affect any organ system, and it occurs in 15–25 % of patients starting ART, but the rates increase to 20–45 % in patients with OIs. CNS IRIS is less common, found in only about 1 % of patients initiating ART (Kranick and Nath 2012). Even though the rates have not been well documented in low-resourced settings, it is likely to be much higher as patients in such setting usually start ART at lower nadir CD4 levels when many already have an AIDS-defining illness. For example, in a prospective study of neurological disorders occurring within the first year of starting ART in South Africa, 28 % of the sample developed CNS IRIS (Asselman et al. 2010). CNS IRIS is associated with poor outcomes and high mortality rates ranging from 20 % to 30 % depending on the underlying infection and the immune status of the individual. This excess mortality is related to raised intracranial pressure and risk of brain herniation resulting from the excessive inflammation and swelling in the brain tissue.

The important infections predisposing to CNS IRIS include cryptococcal meningitis, CNS tuberculosis, and progressive multifocal leukoencephalopathy. However, CNS IRIS has been described occasionally with other opportunistic infections and more rarely without an identifiable pathogen. In addition to the underlying OI, other risk factors for developing CNS IRIS are degree of immune suppression prior to initiating ART (indicated by a low nadir CD4 count), rate of immune recovery, and possibly some host genetic factors.

Two forms of IRIS are traditionally described: paradoxical and unmasking IRIS. In “paradoxical IRIS,” the individual is already known to have an opportunistic infection but is unable to mount an appropriate immune response against it; on initiating ART, the recovering immune system generates a heightened immune response that results in a worsening of the patients’ clinical condition. In “unmasking IRIS,” the presence of a subclinical or occult infection is revealed when the individual commences ART. The exaggerated immune response and clinical deterioration seen

in CNS IRIS are mediated by the infiltration of activated CD4+ and CD8+ T cells into the CNS.

The clinical features and time of onset for CNS IRIS vary significantly depending on the underlying OI; this suggests that pathogen-specific disease mechanisms may be responsible for IRIS seen in the context of each OI (Kranick and Nath 2012). CNS IRIS presents as paradoxical worsening of neurologic symptoms within the first 4–8 weeks of starting cART. Neuroimaging shows contrast-enhancing lesions on the MRI scan, indicating a breakdown of the blood-brain barrier. The management of patients who develop CNS IRIS is guided by the nature of the underlying OI and the severity of presenting symptoms. Since the most important risk for developing IRIS is a low CD4 cell count prior to starting of ART, early initiation of ART will be important in reducing the incidence of CNS IRIS.

Neurotoxic Neuropathy

Some ARTs are known to cause a toxic neuropathy with features similar to and difficult to distinguish from distal symmetric polyneuropathy. The antiretroviral agents classically associated with peripheral neuropathy are the dideoxynucleoside antiretroviral drugs (d-drugs) including didanosine, zalcitabine, and stavudine. These drugs have largely been removed from antiretroviral medication regimens in resource-rich countries but due to their effectiveness and lower cost are still commonly used in resource-limited settings. Toxicity related to the d-drugs is additive, and combination therapy with these drugs should be avoided. Symptoms of ART neurotoxicity usually arise within 2–3 months of initiation of treatment. These drugs are thought to produce nerve damage through their competition with thymidine triphosphate and subsequent mitochondrial dysfunction. Withdrawal of the offending ART and substitution with an alternative that does not include a d-drug is the first step in patient management. Neuropathic symptoms may improve in 1–3 months following the discontinuation of the drug.

Non-AIDS-Related Diseases

The incidence of stroke is higher in HIV populations compared to the general population (Ovbiagele and Nath 2011). This excess risk has been attributed to factors that result directly from HIV infection and others related to complications or treatment of HIV. HIV has been implicated in causing small- and medium-vessel vasculopathy, with dyslipidemia and increased inflammation.

Future Directions

Cure, Eradication, and CNS Latency: Despite the successes achieved in HIV treatment with the introduction of ART, a major limitation of the currently available medications is their inability to eradicate the HIV virus from quiescent reservoirs. Known sanctuaries for latent HIV infection include the central nervous system, the lymphoid tissue, and the testes. Strategies targeted at eliminating persistent HIV from these reservoirs and thereby achieving a cure in patients who are receiving suppressive cART are being evaluated.

Treatment of HAND in Those on ART Who Are Suppressed: Antiretroviral therapy currently is the mainstay of treatment for HAND. However, the use of cART only partially reverses the symptoms or persistence of HAND despite adequate viral suppression. Trials of several adjuvant therapies aimed at attenuating CNS inflammation or acting as putative neuroprotective agents have not yielded much success in reversing neurocognitive impairments till date. Further research is needed to provide more evidence to guide the treatment of HAND in patients whose HIV infection is suppressed on ART.

CNS Penetration: Antiretroviral agents vary in their ability to penetrate the CNS in therapeutic concentrations; the effects of the CNS penetration of cART regimens are an ongoing area of research. While studies have shown that regimens with higher rankings on CNS penetration effectiveness (CPE) are associated with lower CSF viral loads, the effects on

neuropsychological performance is as yet inconclusive (Brew and Chan 2014).

Conclusion

Despite advancements in the treatment of HIV, neurologic conditions remain an important cause of morbidity. In developed countries where there is widespread availability and access to combination antiretroviral therapy, there has been a significant decline in the incidence of more severe neurocognitive disorders and opportunistic infections (Sacktor and Robertson 2014); however, milder forms of HAND are present in up to 50 % of HIV-positive adults (Heaton et al. 2010). In low- and middle-income countries especially sub-Saharan Africa where the highest burden of HIV resides, limited resources hinder the diagnosis and treatment of neurological disorders in HIV (Joseph et al. 2013).

Acknowledgments Research training of Dr. Bibilola Oladeji was supported by the Fogarty International Center of the National Institutes of Health under Award Number D43TW009608. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Cross-References

- ▶ [HIV Associated Neurocognitive Disorders: Diagnostic Criteria & Natural History](#)

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