CHRONIC-TREATED HIV: A NEUROLOGIC DISEASE

JOHN BOOSS, MD

ABSTRACT The concept of slow virus diseases was developed by Sigurdsson in the 1950s in studies of infections of Icelandic sheep, including Visna, a slow (lenti) viral infection of the central nervous system. Human immunodeficiency virus (HIV) belongs to the same lentivirus subfamily of retroviruses and causes significant dysfunction of all levels of the nervous system. Highly active antiretroviral therapy should allow host control of opportunistic infections, producing a clinical state of chronic-treated HIV. However, viral persistence may occur in the sanctuary of the central nervous system. As a consequence, major disabilities in the chronic-treated phase of the HIV epidemic may include cognitive impairment, gait disorders, and various pain syndromes. Policy planning will need to take into account the long-term residential, social, and health care needs of this population.

INTRODUCTION

In genetic lineage and pathogenic behavior, human immunodeficiency virus (HIV), a retrovirus, is a "slow virus." First enunciated in the 1950s by Sigurdsson, the slow or lentiviruses (Table I) share several common characteristics.¹ These include a long interval between exposure to the virus and sustained clinical symptoms, a prolonged clinical course, and, as it turns out, a propensity to involve the nervous system. Infection of the central nervous system (CNS), which has partial isolation from the protective elements of systemic immunity, facilitates persistent infection. Visna, one of the first slow virus illnesses described by Sigurdsson, is a chronic neurologic disease of sheep that has been used as a model to study chronic viral disease of the CNS.²

HIV, after a brief illness at seroconversion, has a long interval before the appearance of life-threatening opportunistic infections or neurologic disease.

Dr. Booss is National Director of Neurology, Department of Veterans Affairs; Professor of Neurology and Laboratory Medicine, Yale University.

Correspondence to: Director of Neurology (Field Based), VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516-2700.

TABLE I Representative Lentiviral Infections

Viral Infection	Disease
Maedi	Pneumonia in sheep
Visna	Neurological disease in sheep
Caprine arthritis-encephalitis	Arthritis and encephalitis in goats
Equine infectious anemia	Fever, anemia, and weight loss in horses
HIV	Immunosuppression and neurologic disease

With the advent of highly active antiretroviral therapy, immunologic restoration has reduced life-threatening opportunistic infections significantly for many HIV-infected individuals. Such individuals can be termed to have chronic-treated HIV infection. Distressingly, it appears that HIV persists despite antiretroviral suppression of plasma viral RNA.³ It remains to be determined the extent that progressive neurologic illness will be reduced by the potent antiretroviral regimens. HIV disorders of the brain, spinal cord, and peripheral nerves may play an increasing role in the health care and social service needs of HIV-infected individuals as we move into the chronic-treated phase of the epidemic in the US.

This discussion first provides a general review of the diseases of the nervous system in the course of HIV infection. We next highlight those disorders in which HIV is the principle actor, without the intervention of another infection, and the functional disabilities they induce. The principle disabilities (dementia, difficulty walking, and chronic pain syndromes) represent major barriers to enjoyable and independent living. Brief mention is made of the policy-planning issues raised by the neurologic disabilities.

DISORDERS OF THE NERVOUS SYSTEM

OVERVIEW

The advent of acquired immunodeficiency syndrome (AIDS) was announced by the appearance of unusual opportunistic processes in immunocompromised individuals. That pattern became evident in the nervous system as well.⁴ It soon became apparent that the CNS and peripheral nervous system were prone to the direct effects of HIV itself. In addition, the peripheral nervous system is vulnerable to certain antiretroviral compounds to develop toxic neuropathy. In the face of many potential causes of illness, certain diagnostic strategies have been useful. These include anatomic localization, stage of illness, and mechanism of injury (Table II).

TABLE II Characterization of Neurological Disorders During HIV Infection

A. Localization
Brain
Focal
Abscess (e.g., toxoplasmosis)
Primary CNS lymphoma
Multifocal
Progressive multifocal leukoencephalopathy
Cytomegalovirus encephalitis
Multifocal abscesses or tumors
Diffuse
Toxi-metabolic encephalopathy
AIDS dementia complex
Spinal Cord
Vacuolar myelopathy
Myelitis
Viral: VZV, HSV, CMV
Immune mediated
Peripheral nerves
Distal symmetric peripheral neuropathy
Treatment-related toxic neuropathy
Inflammatory demyelinating polyradiculopathy
Acute: Guillain-Barré
Chronic: Progressive or relapsing
Plexitis
Mono-neuritis multiplex
Meningitis (e.g., cryptococcal)
Muscle
Myopathy: HIV, HIV/AZT
Wasting syndrome
B. By stage of illness
Seroconversion
Asymptomatic
Immunocompromised
C. By mechanism
Opportunistic Processes (infections, tumors)
HIV
Toxic therapy

OPPORTUNISTIC PROCESSES

The potential range of organisms (viral, bacterial, fungal, and parasitic) that might infect the nervous system in an immunocompromised host is broad. In actual practice, however, a restricted number of agents are encountered regularly.

Why this should be so is not clear, but it has facilitated diagnosis, therapeutic intervention, and prophylaxis. In the case of circumscribed lesions in the brain, for example, a panoply of organisms might have been predicted to produce focal cerebritis and abscess formation and cause many neoplasms to escape host control, lodging primary and metastatic tumors in the brain. In practice, however, toxoplasmosis has emerged so frequently as to allow a fairly standard diagnostic/therapeutic approach. Among intracranial neoplasms, primary CNS lymphoma has eclipsed those CNS tumors most commonly found in the immunocompetent population: primary CNS tumors, gliomas and meningiomas, and metastatic tumors from other organs such as the lung.

In the case of meningitis, *cryptococcus* is the most common opportunistic pathogen in AIDS patients rather than the more common causes of meningitis in immunocompetent subjects, such as the *meningococcus*. Other examples of relatively uncommon CNS pathogens that assume prominence in AIDS include the agents causing viral encephalitis and, separately, white matter disease. Herpes simplex virus, which is the most common cause of sporadic encephalitis in the general population, appears not to have an increased incidence in AIDS. In contrast, cytomegalovirus (CMV), which had been documented as the cause of encephalitis in only a handful of immunocompetent adults, has been a cause of opportunistic viral encephalitis in AIDS. Fortunately, as observed by the Neuro AIDS Research Consortium, there has been a remarkable decrease of HIV-associated CMV encephalitis with the advent of the highly active antiretroviral therapies (unpublished). Finally, a hitherto rare cause of white matter disease, progressive multifocal leukoencephalopathy, has been found in 4% of persons with advanced AIDS. Caused by a papovavirus, JC Virus, fewer than 300 pathologically verified cases were known prior to the HIV epidemic.

CHRONIC HIV-ASSOCIATED NEUROLOGIC DISABILITIES

Alone or combined, the major chronic HIV-induced neurologic disabilities—dementia, gait disorders, and pain—impose a severe burden on the afflicted individual. The disabilities result from a response to HIV in the brain, spinal cord, and peripheral nerves. The underlying disorders include the AIDS dementia complex, vacuolar myelopathy, and the distal symmetric peripheral neuropathy of HIV. In aggregate, the health care, housing, and social support needs of this population will place significant resource demands on society as more individuals successfully enter the chronic-treated phase of the illness.

AIDS dementia Originally termed subacute encephalopathy or subacute encephalitis of AIDS, a cognitive disorder was recognized from the beginning of the

epidemic.⁴ It was first thought to result from an opportunistic infection by CMV. However, the work of Navia and colleagues^{5,6} established it as a new entity, not the result of an opportunistic infection, but rather infection by the AIDS virus itself. They termed the disorder the AIDS dementia complex and characterized its essential features as including cognitive impairment, motor slowing, and affective impairment. Virologic studies by Shaw et al.⁷ confirmed the association with HIV, known at that time as HTLV-III (human T-lymphotrophic virus III). Clinical neuropsychometric testing has demonstrated various levels of cognitive impairment.⁸ Staging of the AIDS dementia complex from least to most severely impaired can be used.⁹ Alternatively, the term *minor motor/cognitive disorder* can be used to describe the less severe manifestation of the process.⁸ Prevalence rates in AIDS vary according to the study, but include 20% for AIDS dementia and 30% to 40% for lesser forms of cognitive disorder.⁹

While AIDS dementia results from infection with HIV, the pathogenesis remains a matter of intense investigation. In contrast to infection of the brain with certain other viral agents such as herpes simplex virus, which injures by direct destruction of cells in the brain, HIV appears to injure indirectly by inducing a self-injurious host response. A cascade of inflammatory mediators induced by components of the virus and the initial response to the virus by macrophages and microglia may result in cytotoxic injury to cells and dendrites. Investigations into pathogenesis have a direct bearing on therapy as points of intervention and protection may be exposed. A current line of clinical investigation, for example, has pursued the therapeutic response to blocking calcium channels.¹⁰

The major therapeutic issue in AIDS dementia concerns the response to suppression of systemic HIV replication. The question is whether intense suppression of circulating virus, with the consequent blocking of repetitive seeding of the brain, will allow local host defense mechanisms in the brain to restrict viral-induced injury. If not, antiviral regimens with good CNS penetration will be needed. Regrettably, only a minority of agents now in clinical use has effective CNS penetration. A related question is whether the cerebrospinal fluid viral content accurately mirrors the viral content of the brain. Because of the sanctuary nature of virus in the CNS, HIV strains may evolve independent of systemic virus, with differing antiretroviral sensitivities, requiring adjustment of therapy. Studies comparing the responses to therapy in cerebrospinal fluid and serum are under way by the Neuro-AIDS Research Consortium together with the AIDS Clinical Trials Group.

Lurking in the background is the concern that lentiviruses have evolved effective strategies to infect the CNS chronically, giving rise to the fear that HIV

may not be dislodged easily. Therapeutic strategies of local HIV containment and control of the indirect mechanisms of CNS injury will be needed if HIV cannot be eliminated from the brain.

Social policy planning in the US, responsive to the needs of persons with chronic-treated HIV infection, will be influenced directly by the effectiveness of controlling AIDS dementia. With the decrease in deaths from AIDS, absent a fall in the new infection rate, the number of persons living with HIV will increase substantially. The question concerning dementia, then, is whether it will decline proportionately to opportunistic infections or whether sanctuary-protected virus will create a disproportionate prevalence of cognitive impairment. Data in support of the latter possibility have been reported from Australia.¹¹ However, observations on more patients over a longer period are needed. The intensity, range, and volume of services needed will also be dependent on whether AIDS dementia or the minor motor/cognitive disorder is the predominant manifestation of cognitive impairment in chronically treated individuals.

Gait disorders Casual observation in outpatient HIV care departments reveals significant numbers of people with gait disorders. These include painful limping, ataxic gait that requires a cane, and weakness or paralysis that requires a wheelchair. The frequency of impaired gait among residents at Leeway, a chronic care facility for persons with HIV, was found by Selwyn et al. to be 46%.¹²

Neurologic disabilities associated with gait disorders include diseases of the peripheral nerves, spinal cord, and muscles, as well as the brain. AIDS dementia in its severe form can impair ambulation, as can the distal symmetric peripheral neuropathy, discussed below. Vacuolar myelopathy, a cause of spastic paraparesis, was originally described by Petito et al.¹³ and was often seen in the context of the AIDS dementia complex. As suggested by its name, vacuolization of myelin is found in the thoracic spinal cord. This accounts for the clinical finding of spastic weakness in the legs in association with normal strength in the arms. The columns subserving proprioception are involved in addition to the motor tracts. An interesting anomaly on clinical exam is the common observation of very brisk reflexes at the knees with absent ankle reflexes. The cause of this pattern in persons with vacuolar myelopathy is the superimposition of the distal symmetric peripheral neuropathy, ablating the ankle reflexes. There is as yet no established therapy for vacuolar myelopathy and no convincing evidence that antiretroviral therapy can reverse it. Accumulation of data is hampered by lack of agreement on baseline prevalence. All gait disorders, regardless of cause, interfere with

quality of life, and require services such as handicapped-accessible housing and transportation.

PAIN

The diagnosis and management of pain syndromes are among the most challenging problems faced by AIDS care providers. In a convenience sample in an HIV outpatient clinic, coworkers and I¹⁴ found that over 40% of consultations to a nonpain specialist neurologist were for problems related to chronic pain. Roughly equal proportions of consults concerned low back pain, vascular headache, and peripheral neuropathy. Some comments on this experience can be made. First, HIV-infected patients experience the same common maladies as do others, such as low back pain and headache. However, the acute onset headache and new onset headache are especially worrisome in HIV/AIDS because of the vulnerability of this population to meningitis, intracranial infections, and primary CNS lymphoma. Other issues that are less life threatening must be considered in HIV-infected patients, such as sinus disease and the side effects of therapy. Second, the particular circumstances encountered by this population, such as weight loss, make them more vulnerable to compressive, or traumatic, injuries to nerves.

The most common cause of neuropathy in association with HIV is distal symmetric sensory peripheral neuropathy, which is found in 10% to 35% of patients with advanced HIV.¹⁵ The most common complaints are of numbness and tingling in the feet. Findings on neurologic exam include reduced vibratory perception in the feet and absent ankle tendon reflexes. Reduced vibratory perception can extend to the knees and higher, rarely affecting the hands. Pain is reported to occur in 30% of patients with distal symmetric sensory peripheral neuropathy and commonly is treated with tricyclic antidepressants, with anticonvulsants, notably gabapentin, widely used as alternatives.

It needs to be emphasized that numerous pain syndromes are not primarily neural in origin, and there remain pain syndromes in HIV-infected individuals that will elude definition. When coupled with substance abuse patterns in some patients, providers all too frequently become frustrated and fail to meet the pain management needs of this group. Pain is currently one of the most significantly undertreated conditions in America, a circumstance that has been documented for HIV/AIDS.¹⁶

FUTURE CONSIDERATIONS

Current intense antiretroviral treatment strategies have failed to eradicate HIV fully, and a combination with immunotherapeutic interventions is now antici-

pated.¹⁷ Even so, the sanctuary nature of the CNS for lentiviruses raises the possibility that eradication of HIV from other compartments may not be accompanied by elimination from the brain. Persistent CNS infection accompanied by neuronal dysfunction may result in the gradual increase of cognitive disorders disproportionate to other HIV-associated disorders. Public policy will need to provide for this younger cohort of cognitively impaired individuals in addition to the marked increase in the elderly cohort of individuals with Alzheimer's disease anticipated early in the new millenium.

REFERENCES

1. Sigurdsson B. Observations on three slow infections of sheep. Maedi. Paratuberculosis. Rida, a chronic encephalitis of sheep with general remarks on infections, which develop slowly, and some of their special characteristics. *Br Vet J*. 1954;110:255-270, 307-322, 341-354.
2. Nathanson N. Neurologic disease produced by visna, maedi and caprine arthritis-encephalitis viruses, lentiviruses of sheep and goats. In Gendelman HE, Lipton SA, Epstein L, Swindells S, eds. *The Neurology of AIDS*. New York, NY: Chapman and Hall; 1998:179-188.
3. Fauci AS. The AIDS epidemic. Considerations for the 21st century. *N Engl J Med*. 1999; 341:1046-1050.
4. Snider WD, Simpson DM, Nielsen S, et al. Neurological complications of acquired immunodeficiency syndrome: analysis of 50 patients. *Ann Neurol*. 1983;14:403-418.
5. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Ann Neurol*. 1986;19:517-524.
6. Navia BA, Cho ES, Petito CK, Price RW. The AIDS dementia complex: II. Neuropathology. *Ann Neurol*. 1986;19:525-535.
7. Shaw GM, Harper ME, Hahn BN, et al. HTLV-III infection in brains of children and adults with AIDS encephalopathy. *Science*. 1985;227:177-182.
8. McArthur JC, Grant I. HIV neurocognitive disorders. In Gendelman HE, Lipton SA, Epstein L, Swindells S, eds. *The Neurology Of AIDS*. New York, NY: Chapman and Hall; 1998:499-523.
9. Navia BA, Price RW. Clinical and biologic features of the AIDS dementia complex. In Gendelman HE, Lipton SA, Epstein L, Swindells S, eds. *The Neurology Of AIDS*. New York, NY: Chapman and Hall; 1998:229-240.
10. Navia BA, Dafni U, Simpson D, et al. Phase I/II trial of nimodipine for HIV-related neurologic complications. *Neurology*. 1998;51:221-228.
11. Dore GJ, Correll PK, Yueming Li, Kaldor JM, Cooper DA, Brew BJ. Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS*. 1999;13: 1249-1253.
12. Selwyn PA, Fennie KP, Molde S, et al. Palliative care for people with HIV/AIDS in a dedicated skilled nursing facility. Paper presented at: Twelfth World Conference on AIDS; June 1998; Geneva, Switzerland.
13. Petito CK, Navia BA, Charles E-S, Jordan BD, George DC, Price RW. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1985;312:874-879.
14. Booss J, Guarnaccia J, Selwyn PA, Friedland GH. HIV neurology in the primary care setting. Paper presented at: Ninth International Conference On AIDS; June 1993; Berlin, Germany.
15. Marra CM, Boutin P, Collier AC. Screening for distal sensory peripheral neuropathy in HIV-infected persons in research and clinical settings. *Neurology*. 1998;51:1678-1681.

16. Breitbart W, Rosenfeld B, Passik S, Kaim M, Funesti-Esch J, Stein K. A comparison of pain report and adequacy of analgesic therapy in ambulatory AIDS patients with and without a history of substance abuse. *Pain*. 1997;72:235-243.
17. D'Aquila R, Walker B. Exploring the benefits and limits of highly active antiretroviral therapy [editorial]. *JAMA*. 1999;282:1668-1669.