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# **The neurological complications of HIV infection.**

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## **INTRODUCTION**

This review focuses on HIV-associated cognitive disorders, HIV-associated vacuolar myelopathy, and HIV-associated sensory neuropathies because these are the most common disorders occurring in HIV/AIDS, they are potentially treatable, and the underlying pathogenic mechanisms are best understood.

## **BIOLOGY OF HIV INFECTION**

HIV-1 is a retrovirus that produces profound CD4 depletion through uncertain mechanisms, but possibly through an initial and massive depletion of gut-associated memory T cells, and then a state of chronic immune activation leading to fatigue of homeostatic T cell responses and progressive immunodeficiency. The CD4 receptor is the principal target site for HIV-1; however, specific chemokine receptors are important secondary cellular receptors (1;2). Additionally, specific lectins on dendritic cells may stabilize HIV for presentation to susceptible cells (3). HIV can infect CD4 negative cells, including astrocytes. HIV-1 strains are grouped into T-tropic (preferring replication in T lymphocytes) and M-tropic (preferring macrophages). Chemokine receptor usage is different for each, with T-tropic viruses making use of CD4 and CXCR4 (or fusin, the receptor for SDF-1), and M-tropic viruses using CCR5 (the receptor for RANTES). This is particularly relevant to the brain where M tropic viruses predominate.

Once integrated into the host cell genome, the HIV provirus may remain latent for years, apparently without affecting cellular function. With cell activation, the provirus produces retrovirus mRNA. Even during the period of clinical latency following initial infection, there is very active viral replication (4;5). With millions of replicative cycles daily, and a relatively high error rate in RNA transcription, resistant mutants can arise readily. Quiescent memory CD4+ T lymphocytes, and macrophages may serve as long-lived reservoirs for latent HIV infection (6;7).

In addition, the brain may serve as a sanctuary for unchecked HIV replication, both because

the blood-brain barrier may prevent penetration of antiretrovirals (8), and also because macrophages, the principal target cells within the CNS, may be long-lived sequestered sites for HIV (7;9). Macrophages and microglia are able to sustain a productive infection without cellular activation, while astrocytes require activation with cytokines to produce virions. The activation of circulating monocytes is probably a critical step which permits their ingress into the brain (10). HIV enters the nervous system early after infection, but productive CNS infection is rarely established until systemic immunosuppression develops, probably after reseeding of the CNS. The state of chronic immune activation with HIV disease progression leads to dysregulation of macrophages with the overproduction of a variety of proinflammatory cytokines and chemokines within the CNS and PNS. This is critical for the induction of both HIV dementia and sensory neuropathies (10;11).

## **NEUROLOGICAL MANIFESTATIONS OF HIV INFECTION**

HIV may affect the nervous system **directly**, producing distinct neurological syndromes, or **indirectly**, by causing immunodeficiency with a resultant susceptibility to opportunistic conditions. The indirect consequences of HIV/AIDS will not be discussed further in this review. Nervous system infection with HIV-1 can produce a wide spectrum of clinical manifestations, but only dementia, myelopathy or sensory neuropathies will be discussed here.

### **Direct neurological conditions resulting from HIV infection: HIV-associated dementia, myelopathy, and sensory neuropathies.**

Dementia, myelopathy and sensory neuropathies - are novel, debilitating conditions which generally do not develop until advanced HIV infection. Typically, other AIDS-defining illnesses or immunosuppression occur before these neurological syndromes. Unfortunately, little is known of these disorders in Asia and Africa.

**Hiv-1 Associated Dementia** (also termed HIV-encephalopathy/AIDS dementia complex)

**Epidemiology of HIV-D:**

HIV-associated dementia (HIV-D) rarely develops before profound immunosuppression. The lifetime prevalence of HIV-D is about 15%, and risk factors include high HIV 'set-point' early in HIV infection, low CD4+ counts (12), anemia, low body mass index, older age, constitutional symptoms (13), injection drug use (14), and female sex (15) (Table 1). In recent cohort studies, neither plasma nor CSF HIV RNA levels were associated with progression to HIV-D, however levels of plasma TNF- $\alpha$  and CSF MCP-1 were predictive (16). Longer exposure to zidovudine appears to be protective (17).

Host genetic factors may underlie susceptibility to HIV-D. The ApoE4 gene correlates with severity of dementia possibly by making neurons more vulnerable to oxidative stress (18;19), MCP-1 mutations and mutations in its receptor CCR2 (64-I allele) (20) correlate with dementia likely by influencing monocyte infiltration into the CNS (21). TNF-alpha promoter polymorphisms also correlate with HIV-D by influencing neuronal vulnerability to TNF-alpha-induced toxicity (22).

More subtle forms of cognitive impairment termed minor cognitive/motor disorder (MC/MD) exist in 20% of symptomatic HIV-seropositive adults (23), even in those treated with HAART (24). It is significant because of reduction in antiretroviral adherence (25), employability (26;27), and predicts HIV encephalitis (28).

The incidence of HIV-D declined by about 50% since the introduction of HAART, however, recent observations from our clinic at JHU suggest that incidence rates may have begun to increase again. The severity of the disease is attenuated with HAART. Cases of moderate or severe dementia in our cohort fell dramatically from about 7% in 1989 to only 1.0% in 2000.

Furthermore, the temporal progression of HIV-D appears to have been altered by HAART, with most patients now showing a static form of dementia.

Children can also be affected by HIV-D manifesting as a progressive encephalopathy (PE), with an estimated prevalence of 30% in the pre-HAART era (29) and a survival of 6-24 months (30;31). Clinical features include microcephaly, spastic paraparesis, and loss of developmental milestones. Identified risk factors include low blood CD8+ T-lymphocytes and high circulating monocytes (32).

### **Clinical features of HIV-D in adults:**

HIV-D usually develops over a few months, rarely weeks. Typically there is cognitive, behavioral, and motor dysfunction, characteristic of a subcortical dementia. Initial symptoms may be subtle, In the early stages, short term memory loss, mental slowing, reading and comprehension difficulties, and apathy are frequent complaints. Table 2 illustrates some of the salient features which differentiate HIV-D from CMV encephalitis and PML. Other mimics include cryptococcal or tuberculous meningitis, primary CNS lymphoma and depression. Confounding factors such as neurocognitive impairment due to advanced age, co-morbid disease such as diabetes, cerebrovascular disease, or concomitant hepatitis C infection can complicate the interpretation of neurological deficits in suspected HIV-D.

Gait disturbance, with stumbling and tripping, is frequent, and tremor and impairment of fine manual dexterity develop in the majority. Other findings include impaired rapid eye movements, hyper-reflexia, and release signs. New onset mania develops in 5% of patients.

Neuropsychologically, there is preferential impairment of psychomotor speed and memory. As the dementia advances, more widespread deficits develop, including a global dementia, often accompanied by myelopathy and neuropathy. Screening neuropsychological test batteries for large epidemiological studies include tests of psychomotor speed (e.g., the Symbol Digit Modalities test and the Trail Making test). Other tests include the HIV Dementia Scale although

its specificity is low (33;34)(35). In the era of HAART, the course of HIV-D has changed (36), and distinct subtypes have been proposed (Figure 1): 1) a '*subacute progressive*' dementia, in untreated patients with severe, progressive dementia; 2) a '*chronic active*' dementia, occurring in patients on HAART but with incomplete virological control and a more slowly progressive dementia; 3) a '*chronic inactive*' dementia, often found in individuals with virological suppression on HAART who have had some recovery from neuronal deficits and remain neurologically stable; and 4) a '*reversible*' dementia in patients on HAART who have initially progressive HIV-D but with effective virological suppression have reversal of neurological deficits (Table 3).

Other subtypes of HIV-associated CNS dysfunction are being recognized including: *HIV demyelinating leukoencephalopathy* in those failing HAART characterized by massive CNS infiltration of HIV infected monocytes/macrophages and extensive white matter destruction (37) . *Acute encephalopathy associated with "immune reconstitution inflammatory syndrome" (IRIS)* in which patients with initially high viral loads and low CD4 counts develop an acute infiltration of CD8 cells in the brain after HAART (38). *HIV vacuolar leukoencephalopathy* in which the histopathology is similar to HIV vacuolar myelopathy (39).

### **Diagnostic studies for HIV-dementia:**

Cerebrospinal fluid studies: CSF analysis may be required in febrile, acutely encephalopathic patients to exclude cryptococcal or tuberculous meningitis, but is not essential in the more typical non-febrile, slowly progressive forms of HIV-D. No definitive or diagnostic CSF profile for HIV-D has yet entered clinical practice; its role is more supportive. Cerebrospinal fluid abnormalities are commonly seen in HIV-D, including elevated CSF levels of HIV RNA and immune activation markers. Thus CSF levels of HIV RNA correlate with the severity of neurological deficits in untreated individuals (40;41), but levels of CSF HIV RNA or immune activation markers are attenuated in HAART-treated individuals, and do not correlate with neurological status (42). Decline in CSF HIV RNA with HAART correlates with the successful

reversal of neurological deficits (43;44). Various CSF markers of immune activation, or neuronal injury such as neopterin (45),  $\beta$ 2 microglobulin (46), quinolinic acid (47), soluble Fas (48), and protein carbonyls (49) also correlate with dementia severity, but have not been validated in HAART-treated subjects. Sphingolipid products have recently been examined with respect to specific patterns of progression of HIV-D (50).

Neuro-imaging studies: Imaging studies are frequently used both to exclude CNS opportunistic processes but also to identify characteristic radiological changes. MRI demonstrates both cortical and central atrophy, and characteristic confluent signal abnormalities within the deep white matter (see Figure 2). These represent increased interstitial water content and not demyelination, and can be reversible with HAART. Magnetic resonance spectroscopy shows increases in choline levels, reflecting astocytosis, and reductions in N-acetyl aspartate, indicating neuronal injury. These correlate strongly with the severity of HIV-D, overall functional level, CD4 cell count, plasma viral load, and CSF viral load (51). Cerebral metabolite levels can normalize after 9 months of treatment with HAART, although the changes appear to lag behind improvements in CD4 count and CSF HIV RNA levels (52).

### **Pathology of HIV-D**

HIV probably gains access to the CNS from the blood stream through the ingress of infected monocytes (10), across the blood-brain-barrier. The pathological features of parenchymal infection include a marked activation of macrophages and astrocytes, and in a proportion of HIV-D cases, multi-nucleated giant cells, representing the fusion of HIV-infected macrophages, Neuropathological changes are most prominent in the basal ganglia (53). *In situ* PCR and laser capture dissection microscopy studies have confirmed that productive infection is focused within perivascular macrophages and microglia, with a restrictive or non-productive infection of

astrocytes (54;55). Because astrocytes lack CD4 on their cell surface, this infection may be CD4-independent (56;57) Regionally, there is a preponderance of productive HIV infection within the basal ganglia, brainstem, and deep white matter (58;59). There is regional upregulation of chemokines and cytokines particularly in the basal ganglia (60) (Figure 3). Diffuse rarefaction of white matter occurs commonly, with breakdown of the blood-brain-barrier and astrocyte apoptosis (61) leading eventually to dendritic simplification and neuronal loss. Morphometric studies have shown an approximate 40% reduction in neuronal densities within frontal and temporal areas (62;63), and 50-90% within the hippocampus (64). Reduced pyramidal neuronal density correlates with dementia severity (65), and is consistent with the central atrophy observable on MRI and with the reductions in MRS N-acetyl aspartate concentrations (51;66). The selectivity of these pathological changes probably parallels differences in the distribution of perivascular macrophages in different brain regions.

### **Pathophysiology of HIV-D:**

SIV encephalitis, a reproducible model of sub-acute encephalitis (67;68), and human autopsy studies have been critical in advancing our understanding of HIV-D. The parenchymal release of proinflammatory cytokines impairs cellular functioning, and induces the neuropathological changes in HIV-D (69;70). The severity of HIV-D is strongly associated with numbers of activated CNS macrophages and with the expression of activated astrocyte- and macrophage-derived products. The density of apoptotic astrocytes also correlates with the rapidity of progression of HIV-D (61).

Infected or activated perivascular macrophages contribute to the development of HIV-D through multiple mechanisms. These cells release a number of potent toxins, including viral gene products such as tat and gp120, and a wide range of cellular gene products including pro-inflammatory cytokines such as TNF- $\alpha$ , eicosanoids, nitric oxide, platelet activating factor,

quinolinic acid and extracellular matrix-degrading proteases (70-74)(75-77). The precise role of viral proteins in pathogenesis is reviewed elsewhere (78). Viral proteins do not necessarily require a continuous presence to cause neuronal damage or glial cell activation but may act via a “hit and run” phenomenon (79). Specific neurovirulent HIV strains, characterized by increased neurotoxicity of Tat and gp120, may evolve within the CNS in individuals with HIV-D (80-82) (83;84).

The products of activated monocytes and viral proteins can activate astrocytes, leading to the release of astrocyte-derived cytokines and chemokines, altered neurotransmitter uptake and release of excitotoxins. MCP-1, stromal derived factor-1 and RANTES may be particularly important (85;86) (Figure 4).

#### **Treatment of HIV-associated dementia:**

The primary principle of antiretroviral therapy in HIV-D is to produce complete virological suppression in both plasma and the CNS (see flowchart Figure 5). It remains controversial whether particular combinations of antiretrovirals have better brain penetration and might therefore be more effective for treatment of HIV-D (87-89). Although only empirically defined, these include stavudine (D4T), zidovudine (AZT), abacavir (ABV), efavirenz (EFV), nevirapine (NVP), and indinavir (IDV).

Potent antiretroviral regimens, usually consisting of three or more antiretrovirals are now considered “standard of care” for HIV-D. Protease inhibitor-containing regimens can reverse neurocognitive deficits, both in developed countries (90;91) and resource-limited areas (92). Instructive results were derived from an “add-on” study of high-dose abacavir to background HAART therapy (93). The augmentation of HAART with one drug provided no additional improvement in neuropsychological performance or CSF HIV RNA suppression. Additionally, the reversal of neurological deficits in HIV-D was slower than anticipated with

neuropsychological improvements, continuing to accrue even after 5 months of HAART. Several ongoing cohorts, including the CHARTER and the NEAD cohorts, will explore the relationship between different patterns of HAART exposure and therapeutic responses of HIV-D. Given that aberrant immune activation is likely to play a pivotal role in sustaining or magnifying the CNS damage induced by HIV-1, attention has focused on *adjunctive* therapies targeted at attenuating the CNS effects of inflammatory products (see Table 4). These trials have been disappointing in the main except for selegiline (94;95),

**Recommendations for future research:**

1) The current definition of HIV-D and MCMD may need to be modified to include both the severity of dementia, and also its temporal progression. In all studies, the duration, regimen and virological efficacy of HAART should be reported, and especially in autopsy studies, the timing of discontinuation of HAART prior to death. 2) Studies in humans and SIV encephalitis models should focus on the development and validation of surrogate markers to predict or identify different subtypes of HIV-D. 3) A more complete understanding of the pathogenetic mechanisms of HIV-D would facilitate the development of targeted adjunctive therapies. Improved methods for increasing delivery of antiretroviral agents to the parenchyma across the blood brain barrier as well as the use of high throughput assays or assays relevant to HIV mediated neurotoxicity to identify novel neuroprotective agents. 4) A renewed emphasis should be lent to initiatives to study the effects of the newer antiretrovirals, with improved CNS penetration, on cognitive dysfunction through controlled clinical trials, not only in developed countries, but also in resource-poor areas with high HIV seroprevalence. 5) Finally the role of therapeutic vaccines needs to be explored using epitopes of HIV proteins that have been identified as causing neurotoxicity or glial cell activation.

**HIV-1 Associated Myelopathies**

The most common myelopathy associated with HIV-1 is a slowly progressive painless spastic paraparesis, with sensory ataxia and neurogenic bladder characterized by prominent vacuolar changes in the ascending and descending tracts, particularly affecting the thoracic spinal cord. This vacuolar myelopathy (VM) symptomatically affects 5-10% of patients with AIDS, but has been identified pathologically in almost 50% of cases at autopsy (96). It usually parallels the development of dementia.

Conventional spine MRIs are usually normal, or may show non-specific tract hyperintensities. Somatosensory evoked potentials have been used to track changes in the myelopathy and significantly delayed latencies of central potentials are usually restricted to the thoracolumbar spinal cord (97).

Risk factors for VM include a higher number of AIDS-defining illnesses, sensory neuropathy was five times more common in VM cases. The major pathologic finding of VM is intralamellar vacuolation in the spinal white matter, particularly in the lateral and posterior columns of the thoracic spinal cord (Figure 6). Productive HIV infection only occurs in about 6% (98). However, there is marked macrophage activation and cytokine release within the spinal cord.

Disturbances in vitamin B12-dependent transmethylation pathways may be pathogenetically important: CSF S-adenosyl methionine levels are reduced in VM (99). Cytokines particularly TNF may also be important. Finally, transgenic mice expressing low levels of Nef in oligodendrocytes developed vacuolar changes similar to VM (100).

Less common is HIV-associated myelitis which can present as transverse myelitis with contrast-enhancing intramedullary lesions (101). Other causes should be excluded particularly HTLV-1 associated myelopathy, syphilitic or tuberculous myelitis, vitamin B12 deficiency CMV myeloradiculitis and HZV-myelitis.

**Recommendations for future research:**

The principal needs are 1) for improved diagnostic imaging techniques to distinguish VM from other myelopathies, to allow for the early identification of neurological disease; and 2) improved therapies targeting the macrophage activation within the cord

#### **Treatment of HIV-associated VM:**

Antiretrovirals have not been convincingly proven effective for VM, however, high dose supplemental methionine appeared to have some benefit (102). A trial is underway with intravenous immunoglobulin. Currently, treatments are mainly aimed at relieving spasticity, improving ambulation with physical therapy, and managing the neurogenic bladder.

#### **HIV-associated sensory neuropathies**

the peripheral nervous system may be involved in diverse ways. A number of possibly immune-mediated phenomena have been described such as cranial neuropathies, polymyositis, motor-neuron disease, and inflammatory demyelinating polyneuropathies. These are discussed elsewhere (103;104).

#### **Epidemiology of HIV-SN:**

HIV-SN includes two nosological entities: distal sensory polyneuropathy (DSP) and antiretroviral toxic neuropathy (ATN). The clinical features of these entities cannot readily be distinguished, and in fact some investigators consider that the antiretroviral toxicity may simply 'unmask' an existing silent DSP. For this reason, most discussions of clinical features and epidemiology usually present the sensory neuropathies in a combined format. About 30% of hospitalized AIDS patients (105;106) were found to have clinical and electrophysiological evidence of a distal sensory polyneuropathy in the absence of antiretroviral toxicity. The prevalence was much lower in less advanced HIV infection: 2 of 798 people with CD4 cell counts of  $< 200 \times 10^6/l$  (107). In contradistinction, subclinical peripheral nerve dysfunction was present by quantitative sensory testing in 36% of patients with AIDS or AIDS-related complex (108). Incidence data from the Multicenter AIDS Cohort Study (MACS) in the pre-highly active antiretroviral therapy (HAART) era estimated an annual incidence of HIV-SN of 7% in those with CD4 cell counts  $< 200 \times 10^6/l$  (109). Up to 34% of HIV-infected children have DSP although it is less (110). Risk factors for HIV-SN have included age, nutritional deficiencies, alcohol exposure, HIV 'set-point' and low CD4 count (12). Studies in HAART-treated cohorts have not shown a relationship between these factors and the development of symptomatic sensory neuropathies (111). Data from the JHU cohort suggest that the incidence rates of HIV-SN are rising

### **Clinical features of HIV-SN:**

The symptoms of HIV-SN are dominated by pain, or at least uncomfortable 'positive' sensations. DSP and ATN cannot readily be differentiated - the etiology is usually decided by the timing with respect to exposure to offending NRTIs. The symptoms are typically bilateral, of gradual onset, and described as 'aching', 'painful numbness', or 'burning' (112). It is usually most severe on the soles of the feet, and is typically worse at night, or after walking. Patients often have hyperalgesia and allodynia. Characteristically, 'weakness' is a rare presenting symptom, and

objective weakness is absent or confined to the intrinsic foot muscles. Fasciculations are not seen, and stretch reflexes are usually absent or reduced at the ankles. Nerve conduction velocities usually show an axonal, length-dependent, sensory polyneuropathy. Quantitative sensory testing shows impairment of heat pain and cooling thresholds.

The diagnostic approach to a patient with suspected HIV-SN should include a careful antiretroviral history, and search for other potential causes of neuropathy, especially other toxic drugs, compression/entrapment neuropathies and confounding neuropathies like diabetes mellitus. Examination of epidermal nociceptive fibers with punch skin biopsy may also be helpful diagnostically when the degree of sensory loss is poorly described, or potential psychogenic factors intrude (113). Quantitative sensory testing is a research tool, and not widely available for clinical use.

#### **Pathology and pathophysiology of distal sensory polyneuropathy:**

DSP is characterized by a length-dependent axonal degeneration of sensory fibers, with minimal evidence of nerve fiber regeneration (114). Both large myelinated fibers and unmyelinated nerve fibers are lost, so DSP can therefore appropriately be classified with conditions like diabetes and amyloidosis that have prominent small sensory fiber involvement. DSP conforms to the concept of a dying back neuropathy (115), with degeneration of the rostral gracile tract (116), the CNS counterpart of the peripheral degeneration, and of the distal terminals of the peripherally directed axon. Punch skin biopsies have been used effectively to demonstrate the epidermal denervation characteristic of neuropathies which affect small caliber nerve fibers (113).

The overt neuropathological changes in DSP include inflammatory infiltrates of lymphocytes and activated macrophages (see Figure 7), decreased numbers of DRG neurons and increased frequency of nodules of Nageotte (117-120). The degree of macrophage activation within the

DRG correlates with symptomatic HIV-SN (120). Although HIV infection of DRG neurons has been demonstrated in one study using PCR *in situ hybridization* (121), it is more likely that the virus is predominantly localized in perivascular inflammatory cells and the nodules of Nageotte (117;122). The envelope glycoprotein, gp120, may produce neurotoxicity within the DRG, and *in vitro* studies have suggested that gp120 may induce apoptosis in rodent DRG culture systems (123), and lower threshold for excitation (124).

The prominent presence of pro-inflammatory cytokines, including TNF- $\alpha$ , IFN- $\alpha$ , IL-6, and other inflammatory mediators including nitric oxide, has consistently been demonstrated in DRGs in AIDS. This aberrant inflammatory response may lead to the upregulation of sodium channels within the dorsal root ganglia leading to neuronal hyperexcitability, as has been seen in animal models (125). Another theoretical mechanism derives from the loss of unmyelinated input into lamina II of the substantia gelatinosa with subsequent ingrowth of A fibers, and the aberrant processing of sensory inputs (126). The severity of pain can be out of proportion to the degree of epidermal nerve fiber loss (127) and may correspond to spontaneous activity in uninjured C fibers (120). This theory is supported by animal nerve injury experiments, in which partial injury to nerves and partial denervation of the epidermis correlates with the development of neuropathic pain .

### **Pathology and pathophysiology of antiretroviral toxic neuropathy:**

Little is known about the specific pathological changes of ATN, although sural nerve biopsies have shown severe axonal destruction, prominent in unmyelinated fibers. ATN is considered to be predominantly related to exposure to specific dideoxynucleosides (128;129). Because of the frequency of ATN, especially in advanced HIV disease, prescribing patterns have changed in the developed world, to limit the use of d4T, ddI and especially ddC. In resource-limited countries, however, generic antiretroviral combinations frequently contain d4T. Prominent mitochondrial abnormalities have been demonstrated in association with prolonged exposure to

NRTIs (130), and are considered to underlie the pathogenesis of ATN. This is further supported by evidence of increased serum lactate levels (131) and reduced serum levels of acetyl-carnitine (132) in patients with ATN and *In vitro* observations of a graded inhibition of gamma DNA polymerase by the different NRTIs (133). Specific dideoxynucleosides, (ddC, ddI and D4T) are potent inhibitors of this enzyme (133); while zidovudine, lamivudine, and abacavir, (drugs which are not associated with ATN), have only minimal effects. The effect of NRTIs on mitochondria is manifest *in vitro* as a reduction in the copy numbers of mtDNA (134) and metabolic abnormalities (135;136). In human studies, assays of mitochondrial DNA levels in peripheral blood leukocytes, and subcutaneous fat have not correlated closely (137;138) with neuropathy although they do normalize with discontinuation of the neurotoxic NRTIs.

*In vitro* studies of neuronal cultures have shown that the dideoxynucleosides inhibit neurite outgrowth in a dose-dependent manner (139;140). The neuroprotective immunophilin ligand FK506 prevents the development of neurotoxicity by ddC, as judged by amelioration of ddC-induced "neuritic pruning," neuronal mitochondrial depolarization, and neuronal necrotic death (139). This finding suggests a calcineurin-independent mechanism of neuroprotection. The mechanism of neuronal injury from ddC and other DDX agents appears to be distinct from the neurotoxicity of the envelope glycoprotein, gp120. Thus, ddC mediates injury through neuronal necrosis, while gp120 is predominantly apoptotic and mediated through Schwann cells (Figure 8).

### **Treatment of HIV-associated sensory neuropathies**

At this stage, while the pathogenic mechanisms of HIV-SN are still being clarified, no definitive restorative therapies can be offered. For ATN, it is reasonable to discontinue the offending ddI, D4T and change the HAART regimen, provided that there is an alternative regimen to offer. Failing this, a patient may need to remain on the regimen with the addition of pain-modifying agents. After discontinuation of a toxic dideoxynucleoside, symptomatic improvement can be expected in most individuals within about 3 months (129). A variety of pain-modifying agents have been used for HIV-SN, as for diabetic polyneuropathy, including tricyclic antidepressants, anticonvulsants, and narcotics. Some positive results have been achieved with high-dose topical capsaicin or topical lidocaine, especially in patients with symptoms confined to the feet. These are discussed at length elsewhere

(<http://www.mssm.edu/neurology/neuroaids/index.shtml>). Placebo-controlled trials have demonstrated a modest benefit on neuropathic pain for amitriptyline (141), and a large effect for lamotrigine in two separate studies (142;143). High-dose coenzyme Q aggravated pain in HIV-SN (144), and acupuncture was ineffective (145). In severe neuropathies narcotic analgesics may be required and long-acting narcotics such as transdermal fentanyl, morphine or oxycodone preparations, particularly useful. Specific prescribing guidelines and contracts should be used, particularly if there is any history of substance abuse. Further management details are provided in Hoke et al (146).

Regenerative strategies have been attempted for HIV-SN, utilizing recombinant human nerve growth factor, which has also been trialed in diabetic polyneuropathy. The rationale was that nerve growth factor is trophic for small sensory neurons, and in both *in vitro* and *in vivo* models stimulates the regeneration of damaged nerve fibers (147). In a study of 270 patients with HIV-SN, a modest effect on neuropathic pain and pin sensibility was demonstrated (148).

Unfortunately the clinical development of nerve growth factor has been halted, and interest has now moved to the neurophilin class of compounds, and other potentially regenerative agents.

including L-acetyl carnitine and xaliproden. *In vitro*, the hormone erythropoietin (EPO) prevented sensory axonal degeneration and DRG neuronal death by both gp120 and ddC (140;149).

**Research recommendations:**

1) The initial inciting axonal injury for HIV-SN may be multifactorial, involving multiple trigger factors ~ impaired glucose tolerance, Hepatitis C infection or nutritional effects. Further research into the relevance of these underlying comorbid disorders is needed. 2) The mechanism by which nerve injury in HIV-SN actually produces pain is unknown. Exploring this, using animal models or autopsy material may help in facilitating the design of more rational therapeutics, not only for HIV-SN but other types of sensory neuropathy. 3) As sensory neuropathies become more prevalent, there will be a greater need for the development not only of symptomatic treatments, but of agents designed to protect or rescue nerves from neurotoxicity or the effects of multifocal inflammation.

**CONCLUSION:**

There have been 20 million deaths from AIDS, and it is estimated that almost 38 million people worldwide are HIV-infected. The range of neurological manifestations associated with HIV/AIDS continues to expand, and HIV-associated dementia and sensory neuropathies will increase in prevalence with wider treatment with HAART, longer survival and more individuals living with HIV. Generic antiretrovirals in resource-limited countries frequently contain neurotoxic nucleosides analogues such as ddT, and the prolonged exposure to these regimens will induce symptomatic neuropathy, especially in vulnerable populations ~ the aged, and those with impaired glucose tolerance. One major unifying mechanism for HIV-associated neurological diseases is the importance of macrophage activation both within the CNS and PNS, and the approaches to therapy in HIV which focus on this aspect of pathogenesis and are being explored therapeutically may have important implications for other neurological disorders.



**Table 1: Putative Risk factors for HIV dementia**

Unsuppressed plasma or CSF HIV RNA

CD4 <200

Extremes of age

Female gender

History of injection drug abuse

Anemia

Low body weight

Genetic factors

ApoE4

MCP-1, CCR-2

TNF receptor polymorphisms

Table 2. Differentiation of HIV Dementia from Opportunistic Infections			
Disorder	HIV Dementia	CMV Encephalitis	PML
Features	memory, mental slowing, gait	delirium, seizures, brainstem signs	focal neurological signs
Course	several months	days-weeks	weeks-months
MRI	diffuse atrophy/ symmetrical deep WM diffuse hyperintensities	normal or periventriculitis	Scattered, assymetrical subcortical WM lesions
CSF	non-diagnostic: immune activation less marked in HAART-treated	PCR+ 90%	PCR+ 60%

Table 3. Operational definition and clinical features useful for diagnosis of HIV-D (modified from AAN 1991 Jannsen R.(150))

HIV-1 seropositivity

History of acquired and usually **progressive** cognitive/behavioral decline with apathy, memory loss, and slowed mental processing

Neurological exam: diffuse and symmetrical CNS signs including slowed eye/limb movements, apraxia, hyperreflexia, hypertonia, and release signs

Neuropsychological assessment: impairment in at least two domains including frontal lobe, psychomotor speed, and non-verbal memory

CSF analysis: exclusion of neurosyphilis, TB, and cryptococcal meningitis

CT/MRI:: diffuse cerebral atrophy with symmetrical deep white matter hyperintensities..

**Exclusion criteria:** major psychiatric disorder, intoxication or other cause for dementia; metabolic derangements, eg, hypoxia, sepsis, uremia; active CNS opportunistic processes

Table 4 Trials of adjunctive agents for HIV dementia or SIV encephalitis

<u>Agent</u>	<u>Action</u>	<u>Conclusions</u>
Nimodipine	Calcium channel	Trend for improvement in neuropsychological performance at highest dose only
Peptide T	possibly chemokine receptor blockade	No effect
OPC14117	Anti-oxidant, neuroprotectant	Positive NP performance
Thioctic acid vs selegiline]	Anti-oxidant, neuroprotectant	Selegiline + effect on NP performance
Lexipafant	PAF antagonist	Trend for improvement in verbal learning and timed gait
CPI-1189	TNFalpha antagonist	Minimal effect on NP performance. Improvement in peg board test at highest dose. Worsened SIVE !
Minocycline [Zink MC, in press JNI]	Anti-inflammatory and p38 MAP kinase inhibitor	Dramatic effects on SIVE and in vitro suppression of HIV and SIV
Selegiline	Anti-oxidant, neuroprotectant	Improvement in verbal learning. Trend for improvement in recall and psychomotor speed

Figure Legends:

Figure 1. Hypothetical Course of HIVD in the HAART era (modified from Sacktor and McArthur JN 2005)

Figure 2. T2-weighted magnetic resonance imaging (right panel) demonstrating both cortical and central atrophy, and characteristic confluent signal abnormalities within the deep white matter. CT scan (left panel) demonstrates some ventricular enlargement and white matter hypodensity.

Figure 3. Confocal photomicrograph of brain in HIV-dementia demonstrating the expression of MCP-1 colocalized with microglia (IB1a) and astrocytes (GFAP) (courtesy of Drs D. Vargas and Carlos Pardo).

Figure 4.: Pathogenic mechanisms involved in HIV dementia: Free virus and infected monocytes permeate the brain vasculature and infect microglia and astrocytes. Viral products released from these infected cells may either directly injure neurons or stimulate uninfected glial cells to release toxic cellular products. Astrocytes may also serve as a reservoir for HIV in the brain, even though infection within them is restricted, and non-productive. **NOTE TO EDITOR, THIS MAY NEED TO BE REDRAWN TO MATCH THE NEUROPATHY CARTOON.**

Figure 5 Flow chart. Management of subacute or chronic cognitive impairment in HIV/AIDS.

Figure 6. Pathologic findings in vacuolar myelopathy showing intralamellar vacuolation in the spinal white matter, particularly in the lateral and posterior columns of the thoracic spinal

cord

Figure 7. Dorsal root ganglia in HIV-SN (courtesy of Dr Carlos Pardo JHU): a) low power photomicrograph of DRG showing large sensory neurons and infiltrating inflammatory cells; b) higher power showing neuronal loss (arrow) and inflammation; c) CD68 staining indicates macrophage activation and infiltration.

Figure 8. Hypothetical model of HIV-associated sensory neuropathy. With permission of Annals of Neurology. Keswani, SJ.

**NOTE TO EDITOR, THIS MAY NEED TO BE REDRAWN TO MATCH THE DEMENTIA CARTOON.**



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