Selected Neurologic Complications of HIV and Antiretroviral Therapy

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Despite the marked benefits of highly active antiretroviral therapy (HAART), up to 70% of patients with HIV develop neurologic complications of the central or peripheral nervous system (Sacktor, 2000). Neurologic consequences of HIV can be divided into primary and secondary disorders. The primary neurologic complications include HIV dementia in adults, encephalopathy in children, HIV-associated (vacuolar) myelopathy, and distal peripheral polyneuropathy. Secondary disorders are due to opportunistic infections resulting from HIV immunosuppression. The focus of the presentation and this article is limited to complications in adults.

Since the late nineties, with the introduction of HAART, incidence rates of opportunistic infections are decreasing (Gona, 2006; Subsai, 2006). There has been a reduction in the number of patients presenting with HIV dementia, cryptococcal meningitis, central nervous system (CNS) toxoplasmosis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma in countries where antiretroviral treatment is readily available. However, as treated patients with HIV live longer, the prevalence of HIV-associated cognitive impairment and distal polyneuropathy has been increasing (Sacktor, 2006). In addition to the neurologic complications attributed to HIV itself, some antiretroviral medications also cause CNS and peripheral nerve adverse effects, and induce the immune restoration inflammatory syndrome (IRIS).

FIGURE 1. International HIV Dementia Scale (IHDS)

Memory-Registration — Give four words to recall (dog, hat, bean, red) — one second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words a bit later.

1. **Motor Speed** — Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.
   4 = 15 in 5 seconds
   3 = 11–14 in 5 seconds
   2 = 7–10 in 5 seconds
   1 = 3–6 in 5 seconds
   0 = 0–2 in 5 seconds
2. **Psychomotor Speed** — Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the fifth digit. Demonstrate and have patient perform twice for practice.
   4 = 4 sequences in 10 seconds
   3 = 3 sequences in 10 seconds
   2 = 2 sequences in 10 seconds
   1 = 1 sequences in 10 seconds
   0 = unable to perform
3. **Memory-Recall** — Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red);
   Give one point for each word spontaneously recalled.
   Give 0.5 points for each correct answer after prompting.
   Maximum = 4 points

Total International HIV Dementia Scale Score — This is the sum of the scores on items 1–3. The maximum possible score is 12 points. A patient with a score of ≤10 should be evaluated further for possible dementia.

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HIV Dementia

HIV dementia (HIVD), also known as AIDS dementia-complex (ADC), or HIV-1 associated dementia (HAD), produces a predominantly subcortical memory deficit with variable motor and behavioral symptoms. In patients with HIV, HAART is associated with improvement in neurocognitive and functional performance (Sacktor, 2006), so the severe form of dementia has become much less common. However, the prevalence of HIV-1 minor cognitive-motor disorder (MCMD) appears to be rising (Ghafouri, 2006).

HIVD is characterized by impaired short term-memory coupled with reduced ability in mental concentration (see Table 1). Lack of visuospatial memory may be manifested in the misplacing of objects, and a lack of visuomotor coordination reflects eye movement abnormalities. For example, the patient might be unable to follow instructions regarding where to direct his stare. There is usually difficulty in performing previously learned complex tasks, such as cutting up food or unbuttoning a shirt. There is also a marked difficulty in word-finding ability. In general, mental slowness seems to be the rule. While these changes may be subtle, they can be assessed early with the HIV dementia scale (NYCDH, 2006) (see Figure 1). Affective and behavioral symptoms often precede or simultaneously occur with memory loss. The affective symptoms are characterized by apathy, severe irritability, bouts of manic episodes or new onset psychosis, slowed speech or response time, personality changes, and social withdrawal. Motor changes are characterized by parkinsonian-like rigidity and slowness affecting movement and gait. Unsteady walk, loss of balance, dropping things, tremors, poor handwriting, and a decline in fine motor skills are usually present in late stages. In MCMD, the clinical manifestations are similar to those seen in HIVD, but the cognitive deficit and motor dysfunction are much less pronounced.

The differential diagnosis of HIVD should include infectious diseases and tumors within the CNS, systemic metabolic and endocrine illness, psychiatric conditions and substance withdrawal or intoxication (see Table 2). Because there are as yet no pathognomonic diagnostic tests, HIVD remains a diagnosis of exclusion.

The pathogenesis of HIVD is not fully understood, but HIV-1 is known to cross the blood-brain barrier in monocytes at an early stage of the infection and can persist without symptoms in the CNS for decades. Once in the CNS, HIV can infect microglia and macrophages, as well as replicate within these cells. Astrocytes and oligodendrocytes can be infected by HIV, but there is no viral replication (restricted infection). Neurons are not directly infected by HIV; however, secondary neuronal damage caused by other infected cells and activated cell lines is probably required to cause HIVD or MCMD.

TABLE 1. Clinical Manifestations of HIV-Associated Dementia

Type of Impairment	Manifestations
Affective	• Apathy (depression-like features) • Irritability • Mania, new-onset psychosis
Behavioral	• Psychomotor retardation (slowed speech or response time) • Personality changes • Social withdrawal
Cognitive	• Lack of visuospatial memory (misplacing things) • Lack of visuomotor coordination (eye movement abnormalities) • Difficulty with complex sequencing (difficulty in performing previously learned complex tasks) • Impaired concentration and attention • Impaired verbal memory (word-finding ability) • Mental slowing
Motor	• Unsteady gait, loss of balance • Dropping things • Tremors, poor handwriting • Decline in fine motor skills

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In the brain, HIV may cause direct and indirect effects. Direct mechanisms correlate with the presence in the CNS of activated, although not necessarily HIV-1–infected, microglia and CNS macrophages (Ghafouri, 2006). Indirect mechanisms consist of neuronal injury and death as a consequence of this activation, related to the release of cytokines (TNF-α), and dysfunction of various cellular channels (ie, calcium, NMDA). Since neurons are not directly infected by HIV-1, the secondary mechanisms are thought to be responsible, at least in part, for their deterioration seen in HIVD. Cerebrospinal fluid (CSF) HIV RNA and beta2-microglobulin are being used in the research setting as surrogate markers for brain infection and associated neurologic disease (McArthur, 1997), but are complicated tests not recommended for clinical use. They may also fail to discriminate among milder degrees of HIVD and MCMD (McArthur, 2004).

The CNS is an important potential reservoir of HIV due to the unique features of the blood-brain barrier and its selective permeability. There are three different compartments within the CNS in which HIV may be sequestered: the brain, the extracellular space, and the CSF. The CSF is the only compartment that is routinely accessible for measurement and provides an adequate reflection of viral activity within the other compartments.

The ability of different antiretrovirals (ARV) to cross the blood-brain barrier and thus enter the CNS varies. Therefore, an undetectable HIV viral load in blood plasma and a high CD4+ count do not necessarily reflect concomitant good virologic control within the CNS. Likewise, ARV concentrations in the cerebrospinal fluid (CSF) cannot be accurately predicted by plasma concentrations. Levels of ARV, simultaneously obtained in the CSF and the blood permit the calculation of a CNS-to-plasma ARV ratio. The lower this ratio, the less ARV penetrates from the plasma to CNS compartments. Factors governing CNS penetration include the degree of ARV protein binding (ie, only free drug crosses the blood brain barrier), molecular weight (larger molecules penetrate poorly), lipophilicity, pH, ionization, and the variable action of molecular pumps. The most effective CNS penetrators are zidovudine, stavudine, abacavir, nevirapine, indinavir and combined lopinavir/ritonavir (Kaletra®) see Table 2.

An alternative complex system has been established to assign penetration scores to groups of ARV, graded from 0.5 to 1 (Antinori, 2005). Based on these penetration scores, it is possible to predict the ability of the various drugs to reduce CSF viral load, as well as provide information regarding the resistance of the virus. Some studies have shown that cognitive performance improves when the CSF viral load is suppressed (see Figure 2) with regimens containing greater numbers of CSF-penetrating drugs (Letendre, 2004). While the correlation between neuropsychological functioning and the extent of a drug's CSF penetration and the subsequent CSF viral load reduction remains to be fully elucidated, this subject is of particular clinical relevance and interest, since HAART is currently the only treatment that has proved to be of some benefit for HIVD.

The standard of care for HIVD remains HAART, preferably with agents with optimal CNS penetration. Once the patient has advanced HIVD, some CNS damage may be irreversible. However, the aim of therapy is to at least prevent further progression if not to reverse deficits. Zidovudine (AZT) is the only agent proven to be effective in improving cognitive performance as shown in a placebo-controlled study of HIVD (Sidtis, 1993). It should be noted however, that the doses of AZT used in this early monotherapy study were 1000 to 2000 mg, much higher than those in use today. Although abacavir was studied in a placebo-controlled study for HIVD, it did not meet the primary endpoint of neuropsychologic improvement (Cysique, 2005). This study points out the methodologic challenges in performing a clinical trial of ARVs in HIVD, including the addition of a single agent versus placebo to optimized background HAART for a relatively brief study duration.

TABLE 2. Differential Diagnosis of Symptoms Presenting as Possible HIV-Associated Dementia

Central nervous system disease	Infectious • CMV encephalitis • Neurosyphilis • Cryptococcal meningitis • Tuberculous meningitis • CNS toxoplasmosis • Progressive multifocal leukoencephalopathy* • HIV minor cognitive motor disorder Tumors • CNS lymphoma • Metastatic disease Vasculitis
Systemic/metabolic/ endocrine disease	B_{12} deficiency Anemia Thyroid disease Addison's disease
Psychiatric illness	Mood disorders (major depression,* dysthymia) Delirium
Substance withdrawal or intoxication	Alcohol Opioids Chronic cannabis

* Cognitive impairment may occur as an accompanying feature of a depressive episode. The term pseudodementia is used to describe this clinical presentation, which resolves with appropriate treatment of the depressive disorder.

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Since there are likely secondary nonviral mechanisms contributing to the pathogenesis of HIVD, other non-ARV drugs have been employed in clinical trials. These drugs include calcium channel blockers (nimodipine), N-methyl-D-aspartate (NMDA) antagonists (eg, memantine), monoamine oxidase (MAO)-B antagonists (eg, selegiline), and antioxidants or free radical scavengers (vitamin E). None have been proven to be effective.

HIV-Associated Myelopathy

OF THE NEUROLOGIC COMPLICATIONS OF HIV/AIDS, HIV-ASSOCIATED myelopathy (HAM), also known as vacuolar myelopathy, may be the most underdiagnosed. The presence of HAM should be suspected in patients with any combination of increased tone in lower extremities (ie, spasticity), hyperactive tendon reflexes, lower extremity weakness or sensory symptoms, gait difficulty, or sphincter or erectile dysfunction. Since HAM is a diagnosis of exclusion, other causes of myelopathy, such as spinal cord compression from disc herniation, vitamin B_{12} deficiency, neurosyphilis, HTLV-1, toxoplasmosis, lymphoma, herpes zoster, and other causes of infectious, inflammatory or neoplastic myelopathy must be considered and rejected.

While the prevalence of HAM is unknown, autopsy series of patients dying with AIDS report pathologic evidence of HIVM of between 22% and 55% (Petito, 1985; Artigas, 1990). Pathologically, HAM is characterized by vacuolization in the lateral and posterior columns of the thoracic spinal cord and, therefore, it predominantly affects the lower extremities. Clinically and pathologically, HAM has a striking similarity to the myelopathy of vitamin B_{12} deficiency (subacute combined degeneration).

Usually, HAM manifests late in the course of HIV infection, with the development of spasticity (increased tone and brisk reflexes) in the lower extremities, with variable weakness that slowly progresses over several months. As a result of the posterior predominance of the pathologic process, vibration and proprioception are the sensory modalities that are most affected. A sensory level may be found on the trunk, as compared with the stocking sensory distribution of distal sensory neuropathy (DSP). Patients should be queried about urinary frequency and urgency, constipation, and impotence, since it is rare for patients to spontaneously offer this information. Many patients have a combination of myelopathy and DSP, resulting in brisk knee reflexes in association with absent or reduced ankle reflexes.

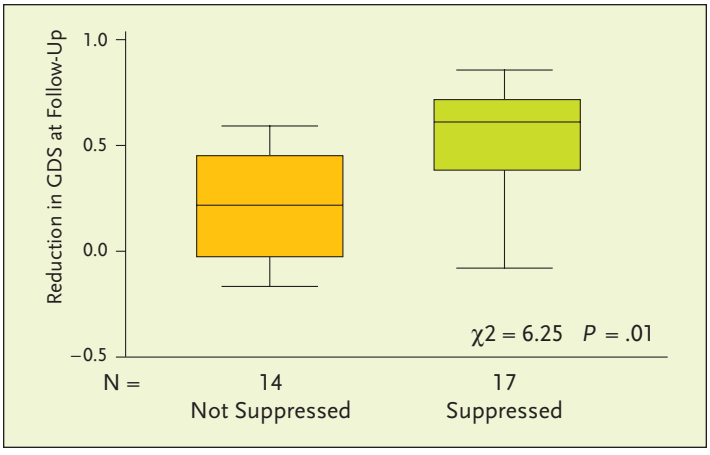

FIGURE 2. CSF HIV-RNA Suppression at Follow-Up | Median 15 Weeks
Reduction (improvement) in GDS among subjects with and without suppressed CSF HIV-RNA viral load at follow-up. Box-and-whisker plots show the median (center line), interquartile range (box), and 5th and 95th percentiles (whiskers). GDS = global deficit score; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus.
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Some patients with HAM have a slowly progressive course and remain ambulatory over a variable number of years, whereas others have a more rapid deterioration leading to severe weakness of the lower limbs and loss of sphincter control. The upper extremities remain relatively spared in most patients; if there is marked involvement of the arms, an alternative diagnosis should be considered.

The pathogenesis of HAM is unknown. Attempts to detect HIV in the spinal cord have not yielded significant results, and there is no evidence of a relationship between the presence of HIV-RNA in the CSF and the development of myelopathy (DiRocco, 1998; Geraci, 2000). Early studies provided evidence that HAM is associated with an abnormality of the vitamin B_{12}–dependent transmethylation pathway (DiRocco, 2002). While an open-label study of oral supplementation with L-methionine for HIVM provided encouraging results (Di Rocco, 1998a), a subsequent placebo-controlled trial did not show significant differences. (Di Rocco, 2004).

The treatment of HAM is mostly supportive. The increase in tone and painful spasms can be alleviated by anti-spasticity agents such as baclofen and tizanidine. The doses of these agents should be slowly increased in order to provide relief without causing excess hypotonia, weakness or somnolence. In patients with severe spasticity who do not respond to high doses of oral agents, intramuscular injections of botulinum toxin or intrathecal baclofen via a subcutaneous pump may be employed. Urinary urgency and incontinence can be improved with the use of anticholinergic drugs, and intermittent or permanent catheterization. Laxatives may help constipation. Mechanical devices and oral treatments for erectile dysfunction may be required. While the direct role of HIV in HIVM is not certain, it is always important to ensure that patients are receiving adequate ARV. A recent small pilot study in 17 patients has shown that intravenous immunoglobulin (IVIG) produced significant improvement in muscle strength in the lower extremities (P = .021) and may be a future potential treatment for this condition (Cikurel, 2006)

Distal Sensory Polyneuropathy

DISTAL SENSORY POLYNEUROPATHY (DSP) IS THE MOST COMMON NEUROlogic complication of HIV, with up to two-thirds of patients with HIV becoming affected (Schifitto, 2002; Simpson, 2006). Certain ARVs may also cause DSP, indistinguishable from that caused by HIV. The only ARVs that have been shown to be clearly neurotoxic are the dideoxynucleoside nucleoside analogues, which include didanosine (ddI), stavudine (d4T) and zalcitabine (ddC), commonly known as "d-drugs" (Simpson, 1995). Recent data indicate that certain protease inhibitors, particularly indinavir, may be neurotoxic (Pettersen, 2006).

The prevalence of HIV-DSP depends on the definition used. When both decreased ankle reflexes and increased distal vibration threshold are diagnostic criteria, 32% of the patients in a current observational cohort study have DSP (Simpson D, unpublished observations). However, when only one abnormal sign is necessary (ie, either decreased reflexes or increased vibration threshold), the prevalence increases to 56% (Simpson D, unpublished observations)

Usually, DSP presents with symmetrical numbness, tingling, and a burning sensation of the lower extremities without significant muscle weakness. Upper limb involvement may follow with progression of the neuropathy (glove and stocking distribution) (see Figure 2). Neurologic examination demonstrates reduced tendon reflexes, particularly at the ankles, diminished pinprick sensation, and increased vibration threshold distally in the lower extremities. Clinically it is difficult to dis-

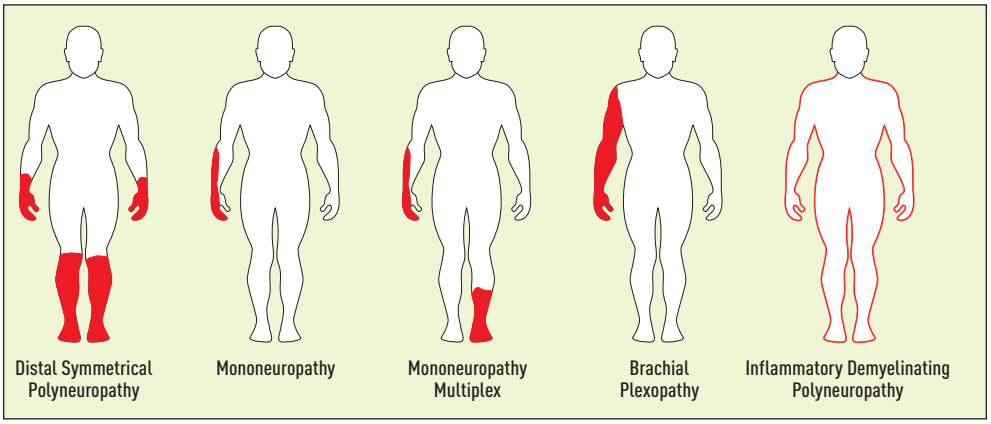

FIGURE 3. Types of Neuropathy in HIV/AIDS

Peripheral neuropathy can occur in a number of patterns, which can be elicited from bedside history and examination. The most common form is the distal symmetrical polyneuropathy, although one may see a mononeuropathy affecting only a portion of one limb, mononeuropathy multiplex affecting multiple nerves in an asymmetric fashion, brachial plexus involvement, or involvement of the entire body as is seen in inflammatory demyelinating polyneuropathy, also known as Guillain-Barre syndrome.

tinguish neuropathy due to primary HIV infection from that caused by d-drug ARV. A history of recent introduction of a d-drug, and the rapid onset of symptoms may help to implicate a neurotoxic agent rather than primary HIV related neuropathy. The best differentiating feature is resolution or improvement of neuropathic symptoms within weeks of discontinuing the potential offending drug.

Prior to the widespread use of HAART in the late nineties, risk factors for DSP included increased age, lower CD4 lymphocyte count, higher HIV plasma viral load, low hemoglobin, AIDS diagnosis, use of d-drugs, and the existence of other neurologic abnormalities (Schifitto, 2002; Tagliati, 1999; Childs, 1999; Estanislao, 2004). However, in the current HAART era, the correlation of DSP with most of these risk factors is less clear. This finding may be as result of an acquisition bias in the cohort studies from which this information is derived (Schifitto, 2005); (Morgello, 2004). It also appears that DSP may be more prevalent in patients with high plasma viral load prior to the initiation of ARV therapy (Childs, 1999).

The pathophysiology of HIV-DSP is not known. HIV does not infect primary cell types of peripheral nerves (ie, axon, Schwann cell). As with HIV-induced damage within the CNS, peripheral nerve injury may be cytokine mediated. It is thought that ARV-DSP is related to mitochondrial DNA damage (Moyle, 2005).

The diagnosis of HIV-DSP is predominantly clinical. Other causes of neuropathy should be excluded, such as diabetes mellitus, impaired glucose tolerance, vitamin B_{12} deficiency, renal or liver impairment, thyroid dysfunction or syphilis. Nerve conduction studies are not routinely required, and the results often reflect small fiber neuropathy. Sural nerve biopsies are not indicated unless there are unusual features such as asymmetric distribution or associated weakness that may indicate a vasculitic or other infectious process (ie, CMV mononeuropathy multiplex). Skin biopsy is an emerging new technique for the detection of small fiber neuropathies. It involves the measurement of intraepidermal nerve fiber density at various sites in the leg (Luciano, 2003), and can be repeated over time. The results correlate with the severity of painful symptoms (Simpson, 2006).

The management of HIV-DSP includes the identification and control of alternative underlying causes of neuropathy, such as ARV toxicity and diabetes mellitus; to provide symptomatic treatment for neuropathic pain, and to prevent further deterioration of the neuropathy with optimal virologic control. If ARV-DSP is suspected, it is desirable to withdraw the offending drug if possible. After stopping the drug, symptoms may take 4 to 8 weeks, and sometimes longer, to subside. Withdrawal of the d-drug often leads to gradual resolution of signs and symptoms in most patients, although a period of symptom intensification may occur shortly after withdrawal ("coasting phenomenon"). However, some patients continue to have residual symptoms, which may be due to irreversible damage caused by the d-drug or may be related to concomitant primary HIV neuropathy or an additional risk factor such as diabetes mellitus.

Once a patient has an established neuropathy, the standard of care is symptomatic relief of painful symptoms. There is no specific treatment for the associated numbness. The analgesic ladder recommended by the World Health Organization for pain management can be useful. This involves increasing pain medications using a stepwise approach starting with simple analgesics and building up to opioids.

However, analgesics are often not completely effective in treating neuropathic pain. Opioid analgesics are often reserved for severe or resistant pain or may not be indicated in patients with substance abuse issues. Thus, alternative medications with demonstrated efficacy for other forms of neuropathic pain are commonly used alone or in combination in HIV neuropathy.

Several studies have demonstrated that amitriptyline is effective in relieving pain in diabetic neuropathy (Max, 1987). However, a trial of amitriptyline in HIV-DSP did not demonstrate superiority to placebo (Kieburtz, 1998; Shlay, 1998). A newer antidepressant, duloxetine, which is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), has been FDA-approved for use in diabetic neuropathy. However, there are no studies evaluating its use in painful HIV-DSP.

Evidence supporting the efficacy of anticonvulsants in the treatment of pain associated with HIV-DSP is evolving (Backonja, 2002). Gabapentin is generally well tolerated, and has been shown to lower the pain significantly ($P<.05$) when compared to placebo in HIV neuropathy after four weeks of treatment (Hahn, 2004). The most frequent adverse effect is somnolence. Lamotrigine has also shown benefit in a placebo-controlled study of HIV-DSP, particularly in patients with d-drug ARV use (Simpson, 2003; Simpson 2000).

Since currently available treatments for HIV DSP are suboptimal, newer drugs are being developed and studied. Placebo-controlled studies are underway for pregabalin, an anticonvulsant with a mechanism of action similar to gabapentin. Capsaicin is an agonist of the vanilloid receptor (VR1). A small, open-label pilot study of a topical, high-concentration (8% w/w) capsaicin patch showed significant relief of pain in HIV-DSP ($P<.01$). Patients received a one-hour patch application to the most painful areas of their feet. The mean decrease in pain from baseline was 46%, with 67% of patients experiencing a 30% decrease in pain and 33% of patients with at least a 50% decrease in pain which lasted up to 12 weeks (Simpson, 2004). A large, placebo-controlled trial in 307 patients with HIV-DSP also proved significant ($P \leq .05$) and durable pain reduction for up to 12 weeks of the study (Simpson, 2006a).

In patients with refractory neuropathic pain, combination treatment

may prove more effective than monotherapy, depending on limitations related to adverse effects. A recent study in neuropathic pain due to diabetes mellitus or postherpetic neuralgia showed that better analgesic effect can be obtained by using the combination of two drugs (gabapentin and long-acting morphine sulfate), used at lower doses than either as a single agent (Gilron, 2005). Similar trials are necessary in painful HIV DSP.

It is important to recognize the symptoms and signs of neuropathy in patients with HIV, since timely detection may allow for reversal of the potentially irreversible toxic effects of d-drugs. Also, identification of possible additional risk factors for neuropathy such as diabetes mellitus, may improve the ultimate outcome. Finally, improving the virologic control in a patient who develops HIV-DSP may alleviate symptoms and help prevent deterioration (Martin, 2000). Overall, these measures can help to improve the quality of life in these patients, since the pain associated with HIV-DSP can been extremely disabling.

Other Types of Neuropathy

LESS FREQUENT TYPES OF PERIPHERAL NEUROPATHIES ASSOCIATED TO HIV are mono-neuropathy simplex (MS) or multiplex (MM), inflammatory demyelinating polyneuropathy and plexopathies (see Figure 2). Mononeuropathy is relatively rare in comparison to DSP. It is characterized clinically by motor, sensory and autonomic abnormalities in the same nerve distribution (simplex) or in multiple nerves with a non-symmetrical distribution (multiplex). These abnormalities may include involvement of cutaneous nerves, mixed nerves, and cranial nerves. Some examples are sensory abnormalities in patchy areas of the trunk and extremities (cutaneous nerve), foot drop (motor nerve), or facial palsy (cranial nerve). Tendon reflexes are preserved in uninvolved areas. Extensive nerve involvement may rapidly progress to include multiple cranial nerves. The occurrence of MM is bimodal. The first peak occurs early in the course of HIV infection, when CD4 cell counts are above 200 cells/mm^3, with a limited distribution of deficits. The second peak occurs in advanced immunosuppression, with CD4 counts of 100 cells/mm^3 or less.

Acute inflammatory demyelinating polyneuropathy (IDP) is characterized by rapidly progressive weakness, reaching its nadir within four weeks, with minor sensory symptoms and generalized areflexia. Chronic IDP has a more protracted course, usually progresses over 6 weeks, and may be monophasic or relapsing. Differential diagnosis should be made with cytomegalovirus polyradiculopathy or HIV associated neuromuscular weakness syndrome (see below).

Plexopathies are not associated directly to the HIV infection, but can be seen as a consequence of abscess formation, or intravenous drug use.

Drug Related Toxicity

DESPITE THE BENEFITS ACHIEVED WITH ARV REGIMENS, CERTAIN DRUGS contribute to neurologic and psychiatric adverse effects. Prominent among these are the neuropsychiatric adverse effects of efavirenz (EFV), a novel nonnucleoside inhibitor of HIV-1 reverse transcriptase. A controlled trial (ACTG 5097S) demonstrated that symptoms attributable to efavirenz include vivid dreams, dizziness, balance problems, unsteadiness and light-headedness (Adkins, 1998; Clifford, 2005). Suicidal ideation has been reported. Neuropsychiatric adverse reactions occur mainly during the first month of EFV therapy, usually by day seven of treatment. Fortunately, most of these symptoms resolve by day thirty with continued treatment. However, some patients are unable to tolerate the adverse effects and the medication has to be withdrawn. Of these patients, most have complete resolution of the symptoms. However some may experience continued neuropsychologic effects (Clifford, 2006). It is important that patients be queried about psychiatric comorbidity prior to starting EFV.

TABLE 3. CSF-to-Plasma Ratios of Concentrations of Drugs Detected in Paired Samples

Drug	Number of Patients	Median CSF-to-Plasma Concentration Ratio (range)
Nevirapine	16	0.626 (0.41–0.770)
Lamivudine	55	0.229 (0.00–4.900)
Stavudine	31	0.204 (0.00–0.204)
Indinavir	18	0.110 (0.00–0.470)
Abacavir	4	0.039 (0.00–2.360)
Zidovudine	18	0.020 (0.00–6.740)
Ritonavir	8	0.000 (0.00–0.520)
Didanosine	5	0.000 (0.00–0.000)
Efavirenz	11	0.000 (0.00–0.000)
Nelfinavir	9	0.000 (0.00–0.000)

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Mitochondrial toxicity related to d-drug ARV peripheral neuropathy has been discussed above. Other neuromuscular adverse events potentially related to ARV-induced mitochondrial dysfunction are myopathy and ascending neuromuscular weakness syndrome. There are several mechanisms by which ARV may interfere with mitochondrial DNA (mtDNA). The inhibition of DNA polymerase-gamma and other mitochondrial enzymes can gradually lead to mitochondrial dysfunction and cellular toxicity. However, the data indicate that inhibition of isolated DNA polymerases may not be predictive of *in vitro* or *in vivo* toxicity (Martin, 1994).

HIV-associated neuromuscular weakness syndrome (HANWS) is a severe neurologic disorder that occurs in HIV-infected individuals. It is associated with hyperlactemia and ARV exposure, especially stavudine (d4T)-containing regimens (Shah, 2003). Mitochondrial mechanisms have been suggested; however, some patients have neurologic symptoms beginning or worsening after discontinuation of ARVs, suggesting other etiologic mechanisms, such as immune-mediated processes.

Zidovudine (AZT) has been associated with the development of myopathy, although the extent of this relationship has been the subject of controversy. The incidence of HIV and ARV-related myopathy is unknown. Myopathy associated with HIV is characterized by predominant involvement of proximal lower limb muscles, with difficulty in climbing stairs and rising from chairs. Myalgia may be exacerbated by exertion. The primary laboratory abnormality is variable elevation of serum creatinine phosphokinase (CPK). Ragged red fibers, a hallmark of mitochondrial dysfunction, have been reported on muscle biopsy in AZT myopathy (Dalakas, 1990; Peters, 1993). Other features include myofibrillar alterations, degeneration and necrotic fibers, and an inflammatory infiltrate. The correlation of these findings to AZT exposure remains unclear (Morgello, 1995).

Electromyography reveals abnormal spontaneous activity and myopathic features in most patients. The clinical and pathologic features of ARV-associated myopathy are indistinguishable from the myopathy associated with primary HIV infection or polymyositis in HIV-seronegative patients. Myopathy associated with AZT may respond to the discontinuation of the drug. Prednisone or intravenous immunoglobulin may be used in severe cases, although they have not been systematically studied.

Immune Restoration Inflammatory Syndrome

THE ADVENT OF POTENT ARV REGIMENS HAS LED TO THE DEVELOPMENT OF an increasingly recognized condition, termed immune restoration inflammatory syndrome (IRIS). Following initiation of a HAART regimen, IRIS causes exacerbation of neurologic features in some patients (Venkataramana, 2006). Manifestations are related to a paradoxical clinical deterioration typically occurring within eight weeks of treatment onset. Immune restoration inflammatory syndrome is characterized by worsening clinical, laboratory, or radiologic findings despite improvement in HIV RNA level and CD4+ count. It is due to rapid improvement in the immune system that triggers an exuberant inflammatory response against previously unrecognized occult infection, autoimmune, or malignancy-related conditions. Risk factors for IRIS include low CD4+ count, the presence of latent infection, and a robust virologic and immunologic response to HAART (Crum-Cianflone, 2006). Factors that may reduce the risk of IRIS include initiation of HAART before the CD4+ cell count reaches very low levels (less than 100/µL), screening for hepatitis coinfection (since hepatitis B and C may be first recognized, or may flare, after the start of antiretroviral therapy), and performance of a chest radiograph and routine laboratory tests before initiating ARV. If an opportunistic infection is identified, many experts suggest delaying HAART for four weeks to reduce the potential for IRIS. Improvement of IRIS-related symptoms has been reported with the use of NSAIDs or corticosteroids.

Conclusions

IN BOTH DEVELOPED AND UNDEVELOPED COUNTRIES, WHERE HAART MAY or may not be readily available, primary neurologic complications are among the most common conditions observed in HIV-infected patients. This is especially the case with HIV-associated DSP, and, to a lesser extent, cognitive disorders and myelopathy. The pathogenesis of most of the primary neurologic complications of HIV remains under investigation. In patients with access to ARV, opportunistic infections involving the nervous system are far less frequent than in the pre-HAART era. However, with new ARV medications continuing to enter the market, unpredictable neurotoxic effects will likely be seen, in addition to immune-mediated conditions associated with restoration of immune function.

Unfortunately there are few specific treatments for the primary neurologic complications of HIV infection. Management includes optimizing virologic control, elimination of confounding risk factors, and removal of neurotoxic agents. These approaches, together with aggressive measures to provide symptomatic relief, can lead to marked improvement in quality of life. *prn*

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