Primary neurological manifestation of HIV/AIDS

INTRODUCTION

In the past 30 years we have learned much about the biology and treatment of human immunodeficiency virus (HIV). Emphasis on prevention and a laudable global effort to increase access to treatment are encouraging developments. In 2010, UNAIDS reported declining new HIV infections in many countries most affected by the epidemic. Between 2001 and 2009, HIV incidence fell by more than 25% in 33 countries, 22 of which were in sub-Saharan Africa. Countries that were most affected in sub-Saharan Africa—Ethiopia, Nigeria, South Africa, Zambia, and Zimbabwe—have either stabilized or are showing signs of decline. Unfortunately, in 7 countries, 5 of them in Europe and Central Asia, HIV incidence increased by more than 25%. However, realizing that 33.3 million people live with HIV, HIV remains a major health challenge, particularly in sub-Saharan Africa where 22.5 million (68% of the global total) live.

Neurological complications of HIV infection continue to cause significant morbidity. Reports from a growing number of countries confirm tragic persistence of cognitive and neuropathic complications of HIV. Our descriptions in this course are often based on more detailed observations made in the Western world. However, reports from the developing world are increasingly replicating the experience from the West, suggesting that neurological conditions are important throughout the global epidemic. While no firm evidence contradicts this expectation, the importance of viral and host genetics in determining disease manifestations is undeniable, as is knowledge that these factors are different in various parts of the world. It is also certain that co-infections influence the course of HIV disease, and these are well known to differ in the developing world, again providing factors that may well alter the natural history of HIV neurological disease.

NeuroAIDS issues may be considered as primary complications, including conditions that are in some way the direct consequence of the HIV infection, or secondary complications (Box 19.1). The primary complications include a spectrum of HIV-associated neurocognitive disorders (HAND), HIV-associated myelopathy, and HIV-associated peripheral neuropathy. Secondary complications result as a consequence of the immunodefficient state of the host (Box 19.1). Neurological infections that fall into this category include cryptococcal meningitis, toxoplasmic encephalitis, cytomegalovirus encephalitis and radiculomyelitis, progressive multifocal leukoencephalopathy, and varicella zoster complications. This course will focus on the primary neuroAIDS complications while many of the secondary complications are described elsewhere in the text.

The frequency of neurological complications has changed as the epidemic has evolved, being profoundly impacted by therapeutic practices and perhaps by varying underlying risks in various affected populations. Both the primary HIV-associated complications and the secondary complications occur more frequently in advanced stages of HIV, when the immune system is most impaired. HIV-associated dementia (HAD), HIV-associated myelopathy, and peripheral neuropathy all are seen most commonly after the CD4 count drops below 200 cells/mm$^3$. Often primary neurological manifestations are not noticed when early development of opportunistic illnesses supervene, masking the anticipated course of disease progression. As more subjects in developing countries are managed to prevent and treat secondary complications we anticipate a rapid emergence of clinical recognition of primary HIV-associated neurological complications. Furthermore, with more successful HIV therapy, most patients retain a higher level of...
immunity and live longer, resulting in an actual increase in the prevalence of HAND in populations of long-term survivors.

Diagnostic rules in the setting of HIV deserve some special cautions. While in most fields of medicine, a single disease should be sought to understand most patients’ complaints. In AIDS, neurological complications often are superimposed on an ongoing process with a different etiology. Drug toxicity may add other facets to neurological conditions. Clinical features often reflect the sum of deficits from multiple pathophysiologic perturbations. In addition, AIDS patients are susceptible to the same neurological diseases as patients who do not have HIV infection and thus the clinician must not always leap to unusual diagnoses in the setting of HIV disease, considering as well conditions common in the immunocompetent population.

EPIDEMIOLOGY

Neurological complications of HIV infection are common manifestations of the AIDS illness [1]. Pre-combination antiretroviral therapy (cART) era investigations documented that two-thirds of patients with AIDS developed HAD. Although, after successful introduction of antiretroviral therapy, the incidence of frank dementia declined significantly, milder cognitive difficulties and HIV-associated peripheral neuropathies have persisted. The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, a multicenter NIH study, evaluated over 1,500 HIV-infected individuals in the USA and found 53% had cognitive impairment [2]. The risk of impairment was higher in those with comorbidities. The same study also found evidence of peripheral neuropathy in more than half of the subjects. Early studies in Uganda support the prevalence of neurologic impairment in less developed settings [3]. A recent report found HAND in 23.5% of HIV-infected patients seen at HIV care centers in South Africa [4].

PATHOPHYSIOLOGY, PATHOGENESIS, AND GENETICS

Primary HIV-associated complications result from infection in the nervous system, and respond to antiretroviral therapy. The mechanism by which HIV infection leads to HAD is likely multifactorial. HIV enters the brain and CSF almost immediately after systemic infection, probably via HIV-infected monocytes, which then differentiate into macrophages. The virus can be recovered from the nervous system throughout the illness. However, productive infection is almost exclusively localized in monocytes and macrophages and mainly occurs late in the disease. Neurons are rarely if ever infected, and astroglial cells, while they may be infected, do not seem to support replication. The consequences of astroglial infection remain uncertain. However, recent research supports an association of HAD with astrocyte infection, suggesting that these cells controlling the environment in the brain could be critical and require further study [5]. It seems likely that much of the pathological consequence of the HIV infection in the brain is driven by immune response to infection rather than directly correlated to the viral load in the CNS. Cytokine production is more closely linked with the degree of HAD than the viral load. However, repli-cative HIV infection in the CNS, reflected by increasing HIV RNA viral loads in the CSF, has been loosely associated with primary HAD prior to the cART era [6]. Pathologic changes are found in the deep gray matter of the brain, in white matter, and eventually in the cortex, resulting in loss of neurons and simplified dendritic structures [7].

While most people are susceptible to HIV, infection requires both CD4 receptors and chemokine receptors. Viral isolates may evolve in a host from CCR5 receptor dependent (R5) to viral tropism using the CXCR4 (X4) co-receptors. Generally, primary brain isolates are of the R5 class consistent with the fact that CCR5 is the predominant receptor on monocytes and macrophages, the primary cells with replicative infection in the brain. It is interesting that some people are protected from HIV infection by a genetic mutation in the CCR5 chemokine receptor that prevents it from participating as a co-receptor for cellular infection. A leukemia patient who received a bone marrow transplant from a donor with a non-binding CCR5 cell surface protein has been reported as showing evidence of a cure of HIV infection 3 years after receiving the transplant, including no evidence of the virus on brain biopsy [8].
Understanding factors predicting the subset of HIV-infected persons who develop neurological disease is a fundamental problem of great significance. There are likely to be both host and viral factors that predispose to development of the primary HIV complications. Understanding these should provide greater understanding of the diseases as well as opportunities to protect people from their consequences.

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND)

Clinical features

HIV-associated neurocognitive disorders (HAND) include a spectrum of cognitive impairments that range from asymptomatic neurocognitive impairment (ANI) to a severe form, HAD. Early on, it had been noted that HAND varied in severity and affected different domains of brain function, resulting in a variety of cognitive, motor, and behavioral manifestations. A consensus nomenclature for study of HAND was developed in 2007 by experts who presented a modified comprehensive classification of HAND [9]. In this classification, three HAND conditions are characterized: ANI, HIV-associated mild neurocognitive impairment (MND), and HAD. The work group emphasized the possibility of bidirectional temporal changes in diagnosis. These conditions should be classified using a variety of specific clinical and laboratory-based methods, depending upon the resources available where the patients are being evaluated. Ideally, baseline neuropsychological (NP) assessment should be part of the clinical evaluation. Where NP testing is not available, presence of cognitive impairment involving two or more ability domains may be suggested by quantitative neuropsychological testing using demographically appropriate normative cutoffs. Tools of value for screening include the HIV Dementia Scale, the International HIV Dementia Scale, Mattis Dementia Rating Scale, and the Montreal Cognitive Assessment (MoCA). Recent interest in use of the MoCA includes availability in multiple languages, balanced simple assessment of several domains, and low cost (free access at http://www mocatest.org).

ANI and MND must both have documented neurocognitive impairment, but only in the case of MND does this impact on activities of daily living. The Frascati-proposed diagnostic criteria defines ANI and MND by performance at least 1 standard deviation (SD) below the mean of demographically adjusted normative scores in at least two cognitive areas (attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory, including learning and recall, simple motor skills, or sensory perceptual abilities), with MND having evidence of functional impairment in daily living. HAD has a more profound impact on motor, cognitive, and behavioral problems that develop in advancing HIV infection (Box 19.2). Early signs and symptoms of HAND may be subtle, but evolution to HAD occurs mainly in untreated HIV. Before cART, patients often presented with insidious onset of reduced work productivity, poor concentration, mental slowing, and forgetfulness. The cognitive decline was often characterized by slowed thought and speech, which the patient as well as examiners may recognize. Habits of reading and recreation are impacted early, while productivity drops. Apathy and withdrawal from hobbies and social activities are common and must be differentiated from depression. Motor slowing is also typical, and has provided convenient means of documenting advancing neurological involvement. Imbalance, clumsiness, and weakness are common motor complaints. Behavioral changes are less common, but may be dramatic manifestations of the neurological involvement. Flattened affect is typical, and develops even without overt affective disorder. Other manifestations include sleep disturbance, psychosis, and seizures. Occasional frank psychotic episodes develop.

As the disease advances, global dementia with memory loss and language impairment develops, culminating in a virtual vegetative state. Neuropsychological evaluation reveals features suggestive of a subcortical dementia, such as is seen in Parkinson’s disease. Early in the course of CNS disease, patients develop psychomotor slowing, memory loss, and word-finding difficulties. As the stage of the disease advances, severe psychomotor retardation and language impairment become obvious, leading to akinetic

<table>
<thead>
<tr>
<th>Box 19.2 Salient clinical features of HIV-associated dementia</th>
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<tr>
<td><strong>Cognitive changes</strong></td>
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<tr>
<td>- Reduced concentration, inability to focus thoughts or finish tasks</td>
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<td>- Decreased reading, less interest in TV</td>
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<td>- Decreased memory, making lists, needing reminders</td>
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<td>- Speech changes, slowing, sometimes word-finding difficulty</td>
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<td><strong>Motor changes</strong></td>
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<td>- Slow initiation of movement</td>
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<td>- Imbalance, clumsiness</td>
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<td>- Weakness</td>
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<td>- Sometime myoclonus</td>
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<td>- Changes in bladder function, urgency, incontinence</td>
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<td><strong>Behavioral changes</strong></td>
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<td>- Personality changes, flat affect</td>
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<td>- Depressed appearance</td>
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<td>- Sleep disturbance, generally hypersomnia</td>
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<td>- Rarely psychotic thought</td>
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mutism. Clinicians sometimes comment on parallels with Parkinson’s disease, and indeed the earliest regions of the brain affected in HIV include the basal ganglia. More recent studies reveal that loss of dopamine transporters in basal ganglia correlate with progressive cognitive disability. The greater dopamine transporter decrease in the putamen than in the caudate parallels that observed in Parkinson’s disease [10].

While this description is important in untreated populations, it is almost never encountered in treated patients. HAND is most commonly seen today as either ANI or MND in early stages of the disease, or in treated patients, function may reveal subtle changes best documented by formalized neuropsychological testing. While progression to HAD on treatment is exceedingly rare, a new uncommon condition of an acute or subacute encephalitis occurring while patients are on therapy, potentially consistent with HIV cerebral immune reconstitution inflammatory syndrome (IRIS), has been described. This causes white matter changes in scans, and on brain biopsy is characterized by intense CD8 lymphocyte infiltration. Corticosteroid therapy as well as enhanced HIV therapy may be most effective in managing this serious encephalitic complication [11].

**Diagnosis**

Diagnosis of HAND is achieved by excluding alternative causes and recognizing patterns of illness associated with primary disease. While challenging in advanced patients, these conditions are even harder to fulfill in milder conditions, particularly when many co-morbid issues might also contribute to the findings. These conditions are generally clearer when the HIV disease is advanced, as defined by low CD4 counts (most often < 250 cells/mm$^3$). While HAND is now often diagnosed in patients with a higher CD4 count, it remains problematic to ascribe neurologic problems to the viral disease in well-controlled patients with an intact immune system. Nevertheless, most investigators believe evidence supports HAND even in the presence of virologically successful antiretrovirals (ARV) and functional immune reconstitution.

Recommended investigations for HAND include assessing HIV control by current and nadir CD4 count and viral load measurements, including CSF viral loads. Brain MR and CT imaging studies are most important for ruling out alternative diagnoses, but may support a diagnosis of HAND when typical atrophy or white matter disease is demonstrated (Fig. 19.1). MR spectroscopy has been extensively used in the research setting seeking non-invasive means of monitoring CNS disease. Markers of gliosis or inflammation appear to occur early with late loss of neuronal markers. Some reports correlate these measures with treatment as well as disease progression, but to date MR spectroscopy has been of little practical use in tracking the CNS disease in the clinic. Functional MRI is not yet widely applied, but early studies suggest that before performance deteriorates, recruitment patterns change, engaging larger brain regions to perform tasks in affected individuals. Brain perfusion measured with MR by arterial spin labeling studies has suggested that HIV infection results in decreased perfusion to the brain which is only partially corrected by ARV [12]. Positron emission tomography (PET) has revealed abnormalities in subcortical metabolism early, with advancing hypometabolism globally in later stages; however, use of PET is limited due to costs and complexity.

CSF is rarely completely normal in HAND but the mild lymphocytic cellular response and mild elevation of protein most often encountered are not diagnostic. Elevated immunoglobulins, not rarely with oligoclonal banding, may be detected. Even after complete viral suppression with cART, there is the suggestion that there remains at least somewhat elevated inflammatory response in the CSF [13]. Careful analysis of CSF helps to exclude other etiologic causes of altered neurologic status. In untreated patients more elevated HIV viral loads in CSF are typical but not diagnostic of primary HIV neurological disease, but the association of cognitive impairment with viral load appears even less reliable in the era of cART. CSF cytokine elevations have correlated with HAD, but the more common mild HAND manifestations do not have substantial elevations.

There is a critical need for better-validated, quantitative biomarkers of early neuroAIDS disease, particularly means of determining which subjects may suffer progressive deterioration and thus be candidates for interventions and clinical trials.

**Treatment**

There is no specific therapy available for cognitive decline in AIDS. Optimal therapy of HIV is a uniform goal once the diagnosis is established. Because lower nadir CD4 has been
suggested to increase the risk of HAND, neurological manifestations are a good rationale driving expert recommendations for earlier and more aggressive use of ARV in HIV infection. The central importance of antiretroviral therapy with relation to CNS manifestations is undeniable. Prior to introduction of ARV, the prevalence of HAD was typically at least 60–70% in advanced disease. Introduction of zidovudine was associated with improvement in cognitive performance and in a small placebo-controlled trial of high doses of zidovudine in subjects with active dementia [14]. In the early years of HIV therapy, incidence of HAD dropped to ~7% per year, with roughly 20% prevalence in the population. HAD has become rare in patients responding well to ARV with controlled viral loads, with estimated incidence now much less than 5%. Thus, amelioration of marked cognitive impairment can be added to the other major benefits of cART. However, even the lower incidence of dementia when coupled with much longer survival has resulted in stable or even increasing numbers of cognitively impaired patients in some clinics [1].

Antiretroviral drugs may vary in their effectiveness in the CNS compartment with several, particularly highly protein-bound protease inhibitors, probably having limited access to the brain. Determining whether designing therapy for CNS penetration could improve cognitive outcomes is an active topic for investigation [15]. The CNS penetration effectiveness (CPE) ranking of different ARV agents derived from information about the properties of individual ARV is used to study this issue. At present observations are not conclusive regarding the value of CPE for managing therapy. Some reports show correlation between poor penetration score and higher CSF viral loads [16]. However, other studies do not uniformly support the importance of CPE since mild HAND may be seen unrelated to CPE scores [17]. Neuroprotective strategies distinct from ARV continue to be investigated but none have been demonstrated to be effective beyond HIV therapy.

The latest expert recommendations for HIV therapy continue a trend toward earlier initiation of ARV at higher CD4 counts, often in patients < 500 cells/mm³ (http://aidsinfo.nih.gov). There is general support for aggressive and consistent use of cART once symptomatic disease, including neurological disease, is identified. Data analysis from the CHARTER study showed an association of HAND with lower nadir CD4 rather than current CD4 status. A challenge for therapeutic development resides in balancing the degree and durability of viral response with the cost and complications of the therapy, including side effects and secondary toxicities. With declining toxicity, earlier therapy has become more attractive and now dominates treatment recommendations. Treatment of HIV within the CNS may be even more difficult than systemic infection, since the virus is harbored in longer-lived cells and may be exposed to lower and less effective levels of ARV due to the blood–brain barrier. The quantity and quality of information on CNS efficacy of HIV therapy is suboptimal. CNS penetration of ARV may contribute to efficacy, while active transport of other drugs out of the central compartment could drive outcomes [18]. Despite these theoretical concerns, decline in the incidence of neurological complications has closely followed improvement in systemic HIV therapy, and concerns about CPE of therapies remain to be validated. Thus, the clinician’s first task is to construct the most effective and best-tolerated HIV therapy overall. If HAND is present, it is reasonable to consider CPE in the choice of therapies, but this should not yet be considered an overriding consideration, pending more information about this approach to therapy. Based primarily on CSF penetration (which is not necessarily the same as brain penetration), optimal nucleoside reverse transcriptase inhibitors (NRTIs) include zidovudine, stavudine, and abacavir. Nevirapine appears to cross the blood–brain barrier well and is theoretically a favorable drug from the non-nucleoside reverse transcriptase inhibitors (NNRTIs) class, but there is also documentation of therapeutic efficacy with elavirenz [19]. From the protease inhibitors (PIs) class of ARV, indinavir is the least protein bound and has best evidence of efficacy in the CNS, but is rarely prescribed due to side effects and frequent dosing. Relatively better PI drugs for CPE include ritonavir-boosted lopinavir or darunavir. The newer CCR5 antagonist maraviroc and the integrase inhibitor raltegravir both seem to have moderately good CPE scores, making them reasonable additions to salvage regimens with drug-resistant virus.

Measuring the efficacy of primary neuroAIDS therapy remains more challenging than systemic therapy. In cases of clear-cut neurological impairment, a rather dramatic clinical improvement may at times be noted, and the benefits of therapy are easily appreciated. However, with more subtle disabilities, it is much harder to document a response to therapy. For clinical trial development of treatment, repeated well-validated neuropsychometric measures to reflect the clinical response to therapy are generally employed. Viral load in CNS, which generally is lower than systemic values, has poor correlation with severity of neurological disease and often provides little guidance for therapy. However, occasional cases of CSF viral replication even when viremia is controlled are reported, and neurological improvement may be directed by the characteristics of the CSF virus [20].

Driven by the concern that viral infection is not eliminated from the brain by antiviral therapy, considerable effort has been placed in protective strategies to block presumed neurotoxic brain damage [21]. To date, small controlled studies have evaluated the toxicity, safety, and tolerability of different presumed protective drugs and failed to demonstrate neuroprotective properties. Recent trials of minocycline have also failed to reverse cognitive deficits during controlled trials [22]. At present no adjuvant therapy can be recommended outside of the clinical trial setting.
Clinical features

HIV-associated sensory neuropathy (HIV-SN) is a major source of morbidity among AIDS patients, affecting approximately 30% of AIDS patients. Other potentially treatable peripheral nerve diseases occur in HIV related to other infectious agents and immune-mediated mechanisms. However, the most common forms of distal sensory polyneuropathy (DSN) are HIV-SN and antiretroviral toxic neuropathy (ATN). These two forms are phenotypically identical. They present as a length-dependent neuropathy with distal to proximal development of symptoms. A mixture of negative symptoms including numbness and sensory loss along with positive dysesthetic and painful aching or burning is typical. Symptoms are generally worse at night and can be aggravated by innocuous stimuli, such as bed sheets or wearing shoes. Abnormalities on neurological examination are limited to sensory nerve function and include reduced or absent ankle reflexes and increased vibratory and pin sensation thresholds. International studies in Southeast Asia have confirmed that taller patients are more likely to suffer neurotoxic neuropathy, and thus an algorithm making greater effort to avoid stavudine in tall patients would make sense [23]. In the USA and Europe, the decline in use of stavudine and didanosine has been accompanied by a reduction in toxic neuropathies, but the overall burden of neuropathies remains high in most HIV clinics, and is particularly troublesome in international sites where frequent use of stavudine continues. A study from South Africa revealed a 57% prevalence of symptomatic neuropathy among stavudine-exposed South Africans [24].

Diagnosis

Without a definitive test, diagnosis of HIV-associated neuropathy requires typical presentation and exclusion of alternative diagnoses. The typical pattern of symmetric distal sensory loss is characteristic. Asymmetric neuropathies, or those with substantial motor involvement, suggest an alternate diagnosis. Physiologic testing may be of limited value in HIV-SN. Affected patients can often test normally on routine nerve conduction study. This reflects the prominent small-caliber sensory nerve involvement in HIV-SN while nerve conduction tests preferentially evaluate larger nerve fibers. Skin biopsy and visualization of epidermal nerve fibers is a useful diagnostic tool in research settings and theoretically could allow monitoring treatment aimed at nerve regeneration [25]. Reduced fiber density, increased frequency of fiber varicosities, and fiber fragmentation are prominent features of skin biopsy from patients with HIV-SN. A clinically similar syndrome is often caused by dideoxynucleoside drugs used to treat HIV, including didanosine (DDI), stavudine (D4T), and in the past by zalcitabine (DDC). While both DSN and ATN can coexist in a single patient, temporal profile of symptoms in relation to introduction and termination of neurotoxic medications can help in distinguishing the active pathophysiologic process. PIs have also been associated with neuropathy, although this association has not been consistent, or strong [26].

Predisposing conditions for neuropathy, including diabetes, nutritional deficiency, alcohol abuse, or prior chemotherapy, may contribute to development of symptomatic neuropathy. Prior to cART, DSN was associated with advanced HIV disease, with lower CD4 count and higher viral load. Advancing age remains a consistent and significant risk factor of increasing importance with the aging of HIV patients [27]. In the developing world, ATN is still important. Symptoms typically begin from a few weeks to 6 months after introduction of toxic medications. Symptoms may worsen at least for a few weeks after discontinuation of the offending agent, followed by at least partial improvement in most, but not all, patients.

The main pathologic features that characterize DSN and ATN include “dying back” axonal degeneration of long axons in distal regions, loss of unmyelinated fibers, and variable degree of macrophage infiltration in peripheral nerve and dorsal root ganglia. Marked activation of macrophages as well as the effect of proinflammatory cytokines appears to be the main immunopathogenic factor in DSN [28]. Interference with DNA synthesis and mitochondrial abnormalities produced by nucleoside antiretroviral drugs have been postulated as pathologic factors involved in ATN.

Treatment

Treatment for HIV-SN includes optimizing the environment for the nerves by assuring excellent nutritional status and minimal toxic insults. In case of ATN, the suspected agent should be discontinued or at least the dose should be reduced. In the current era, it is rarely necessary to continue toxic nucleosides when there is access to the full selection of ARVs. Symptomatic therapy is often needed for pain. Several drugs often used for neuropathic pain are apparently less effective in HIV-SN. Currently, the only therapies shown to be effective against pain by randomized, placebo-controlled clinical trials are smoked tetrahydrocannabinol [29] and lamotrigine [30]. Gabapentin in doses of 1,800 to 3,600 mg/day has provided helpful amelioration for chronic pain, but it is often necessary to employ long-acting narcotic drugs to provide reasonable quality of life in the face of troubling pain. A randomized clinical trial testing pregabalin, a related anticonvulsant used for neuropathic pain syndromes, failed to confirm activity in the face of a very potent placebo response [31].
A sometimelaetheneuromuscularsyndromeseen after lac-
tic acidosisremains important in developing countries where
 stavudine is used extensively [32]. It typically occurs several
weeks after lactic acidosis associated with d-drug toxicity
[33]. Patients develop severe weakness and subacute painful
 neuropathic symptoms. Reflexes are depressed, and muscle
biopsies suggest mitochondrial myopathy as well as neuro-
pathic changes. It occurs more commonly in women than
 men. Eye movements may be restricted. Supportive therapy,
and avoidance of mitochondrial toxins allow recovery of
many of these patients, but notable mortality has been
associated with this condition.

**HIV-1-ASSOCIATED VACUOLAR
MYELOPATHY**

**Clinical features**

Vacuolar myelopathy is the most common chronic mye-
lopathy associated with HIV infection. It occurs during
the late stage of HIV infection, when CD4 counts are very
low. It is often seen in conjunction with HAD, peripheral
neuropathies, opportunistic CNS, and peripheral nervous
system infections. In the early years of HIV when therapy
was quite limited, myelopathy was clinically noted in up
to 20% of adult HIV patients, while pathologic study of
the spinal cord indicated involvement in over half of AIDS
autopsies. Pathophysiologic data are limited but it has been
suggested that infiltration of the cord with HIV-infected
cells secreting neurotoxic factors, neurotoxic HIV proteins,
or underutilization of vitamin B12 could underlie this dev-
astating disorder. The vacuolar degeneration of heavily my-
elinated tracts including the corticospinal tract results in
progressive spastic diplegia (paraplegia), often with urinary
bladder involvement and sensory ataxia. Both dorsal col-
umn and spinothalamic sensory deficits are often observed
in these patients.

**Diagnosis**

Laboratory studies focus on exclusion of treatable causes
like vitamin B12 deficiency and compressive myelopathy.
It is critical not to ascribe myelopathy to HIV without im-
ing the spinal cord for treatable compressive lesions. A
negative imaging study with MRI, normal level for vitamin
B12, and negative HTLV-1 status are important exclusions
before HIV-associated vacuolar myelopathy is accepted as
a diagnosis.

**Treatment**

Treatment for myelopathy is best addressed by optimized
ARV. The high prevalence of this disorder in untreated
HIV disease is substantially different from the experience
in the era of cART where myelopathy is very rarely encoun-
tered in treated subjects. When treatment is started in pa-
tients beginning to demonstrate signs of myelopathy, it is
arrested and partially reversed in many cases. In addition
to ARV treatment, care in nutrition is likely to contribute
to better outcomes.

**CONCLUSION**

Primary neurological complications at every level of the
nervous system have been a significant part of the impact
of HIV infection throughout the world. While these mani-
festations may be veiled by the acute illnesses complicating
untreated disease, they are present in the much larger group
of people suffering HIV in developing countries, and are
likely to be noted more prominently as therapy is intro-
duced. Because the actual manifestations of these diseases
are likely to be dependent on both viral and host genetics,
each having significant differences in various parts of the
world, it will be critical to study the presentation and course
of these complications in the different settings where HIV
is prevalent, as unique features that could influence
outcomes are likely to emerge.

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