HIV neuropathy

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Purpose of review
To present an overview of HIV-associated distal symmetric polyneuropathy (HIV-DSP) and other HIV-related peripheral neuropathies in the post-highly active retroviral therapy era.

Recent findings
HIV-DSP has become the most common neurologic complication of HIV largely due to the prolonged survival of HIV-positive patients with the advent of highly active retroviral therapy. HIV-DSP can be attributed to the disease itself or to secondary effects of certain HAART agents, and often the two disease entities cannot be distinguished. HIV-DSP can lead to significant morbidity and interfere with daily activities. Diagnosis can be obtained from a detailed history and neurologic exam revealing absent ankle jerks and abnormal, vibratory perception or decreased pinprick or temperature. Supporting studies include nerve conduction studies and skin biopsy. Although there are no United States Food and Drug Administration-approved treatments for HIV-DSP, clinicians often use off-label medications, including antidepressants, anticonvulsants, topical agents and other analogics.

Summary
The prevalence of those affected by HIV-DSP will continue to grow with the aging population of HIV-infected individuals. Compared to the diabetic neuropathy drug trials, trials in both symptomatic and disease-modifying agents for HIV-DSP have had little success. Other forms of HIV-related peripheral neuropathies are discussed briefly, and include acute and chronic inflammatory demyelinating polyneuropathy, autonomic neuropathy, polyradiculopathy, mononeuropathies, mononeuritis multiplex, cranial neuropathies, and amyotrophic lateral sclerosis-like motor neuropathy.

Keywords
HIV, HIV-associated distal symmetric polyneuropathy, peripheral neuropathy

INTRODUCTION
Highly active antiretroviral therapy (HAART) has led to the prolonged survival of HIV-infected patients. Among the many neurologic complications of HIV/AIDS, peripheral neuropathy is the most common. A review of 37 cohort and cross-sectional studies reported a variation in prevalence rates from 1.2 to 69% and annual development of neuropathy among HIV-positive patients ranging from 0.7 to 39.7 per 100 persons per year, with greater risk of neuropathy among older populations and patients with more severe disease [1].

HIV-ASSOCIATED DISTAL SYMMETRIC POLYNEUROPATHY
The most common form of HIV neuropathy is HIV-associated distal symmetric polyneuropathy (HIV-DSP) estimated to affect up to 35% of the HIV population [2]. HIV-DSP is associated with HIV infection itself or with toxic effects of antiretrovirals or ‘D-drugs’, such as stavudine (d4T), didanosine (ddl) and zalcitabine (ddC), in which case, it is known as antiretroviral toxic neuropathy (HIV-ATN) [3]. Although not commonly reported in children [4], DSP has been reported in up to 28% in a recent cohort of 182 HIV-infected children in rural South Africa [5]. The other major types of HIV neuropathy are defined by their presentation and include acute and chronic inflammatory demyelinating polyneuropathy (IDP), autonomic neuropathy, polyradiculopathy, mononeuropathies, mononeuritis multiplex, cranial neuropathies, and amyotrophic lateral sclerosis-like motor neuropathy [6].
**Clinical features**

HIV-DSP can lead to significant morbidity and its management can be complex and challenging. A recent study found that signs of neuropathy were detected by detailed neurologic exam in 35% of participants at a median of only 3.5 months after HIV transmission [7]. Many individuals with HIV-DSP may be asymptomatic, although most present with distal, symmetric symptoms of numbness, tightness, burning pain or paresthesias that may be provoked or spontaneous. Neurologic exam reveals decreased or absent ankle jerks, vibratory perception or decreased pinprick or temperature in a stocking glove distribution. Muscle atrophy and weakness are rare [8].

**Risk factors**

In the pre-HAART era, HIV-DSP was found to be associated with a lower CD4 count and a higher viral load [9]. In the HAART era, this correlation has not been well established. HIV-DSP is not related to low CD4 count [10,11] and may even be correlated with higher CD4 count [12–14]. Additionally, viral load is not related to HIV-DSP [11,13–16]. Several hypotheses have been proposed for this counterintuitive finding, including improved health and longevity in patients with higher CD4 counts may allow more time to develop DSP, [12] or that other medical conditions independent of immune status are taking a more prominent role in the post-HAART era, highlighting the growing significance of other comorbidities in HIV [14].

Other risk factors identified include greater age [13–19] and height [13,15,16,18], statin use [15], d4T exposure [13,14] and substance abuse [20]. Diabetes has been implicated as a significant risk factor for HIV-DSP [11,15,16] as well as triglyceridemia, although other individual factors comprising the metabolic syndrome have not been shown to correlate [21]. A study in Nigeria found that hemoglobin was also a risk factor for HIV-DSP [22].

**Pathophysiology**

Pathologically, HIV-DSP involves distal degeneration of peripheral nerve fibers with predominantly small myelinated and unmyelinated fibers being affected [8], although the underlying pathogenesis is unknown. As HIV does not infect Schwann cells or axons directly, indirect mechanisms have been proposed, including the dysregulation of macrophages and the release of proinflammatory cytokines, chemokines and free radicals [23]. In-vitro models have demonstrated neurotoxicity of HIV-1 envelope protein gp120 caused by interaction between the Schwann cell and the sensory neuron, as well as direct toxicity of gp120 to the axon [24].

HIV-ATN may have a faster onset and progression than HIV-DSP, although clinically it may be identical to HIV-DSP. Typically the time course from the onset of symptoms can be the only distinguishing factor. The proposed mechanism for HIV-ATN is mitochondrial toxicity, particularly the inhibition of mitochondrial DNA polymerase [25–27]. Although HIV-ATN may not be as prevalent in developed countries, it still poses a problem in developing countries that have limited access to alternative drugs. The 2010 guidelines from the WHO recommended avoidance of d4T as a first-line regimen. Despite these efforts, the latest 2013 WHO guidelines report that the international response to phasing out d4T as a first-line HAART has been variable, with some counties avoiding d4T only for pregnant women and people starting HAART. They have provided guidelines for phasing out d4T in these countries and restricting its use to cases in which other HAART drugs cannot be used [28].

**Diagnosis**

Diagnostic studies used to evaluate HIV-DSP include the clinical neurologic exam, blood tests to exclude other forms of neuropathy, such as B12 deficiency and diabetes, electromyography, quantitative sensory testing (QST) and intraepidermal nerve fiber density measurement by skin biopsy [29]. Within HIV-DSP research, several scales have been used to measure the extent of neuropathy, including the total neuropathy score (TNS) and the brief peripheral neuropathy screen (BPNS). TNS quantifies neuropathy on the basis of both the neurologic exam and QST/nerve conduction studies, whereas BPNS incorporates questions involving neuropathy.
symptoms in the lower extremities and an exam of vibration sense and ankle reflexes [10]. A modified TNS that excludes QST and includes autonomic indices may be optimal for HIV-DSP [30].

**Treatment**

The majority of clinical research, thus, far has focused on symptomatic pain management. Almost all agents have had limited success to date, and none are currently United States Food and Drug Administration (FDA) approved. Symptomatic agents most often used by clinicians are off-label that include anticonvulsants, antidepressants, topical agents and nonspecific analgesics. A recent meta-analysis of prospective, double-blind, randomized controlled trials assessing both symptomatic and disease-modifying treatments of HIV neuropathy analyzed 44 studies, 14 of which fulfilled inclusion criteria [31]. Only topical high-dose (8%) capsaicin [32], smoked cannabis [33,34] and recombinant human nerve growth factor (rhNGF) [35] showed greater efficacy than placebo. However, most agents showed no superiority over placebo, including amitriptyline (100 mg/day) [36], mexiletine (600 mg/day) [37], gabapentin (24 mg/day) [38], pregabalin (1200 mg/day) [39], lamotrigine (600 mg/day) [40,41], topical capsaicin (0.075% four times daily) [42], prosaptide (16 mg/day) [43], Peptide-T (6 mg/day) [44] and acetyl-L-carnitine (1 g/day) [45].

Capsaicin, a selective agonist for transient receptor potential vanilloid 1 receptor, is expressed on small-diameter afferent neurons [46]. A topical patch containing high-dose (8%) capsaicin was compared with a low-concentration capsaicin patch (0.1%) control, showing that a single application of high-dose capsaicin provided at least 12 weeks of pain reduction in patients with HIV-DSP [32]. A recent meta-analysis of seven randomized double-blinded, controlled studies of high-dose (8%) capsaicin patch in various neuropathic pain syndromes, including HIV-DSP, showed that 41% of HIV-DSP patients had a 30% response and 7% had complete pain relief from 2–12 weeks after treatment. They concluded that in patients who respond to the high-dose patch, analgesia starts within a few days of treatment and lasts an average of 5 months [47].

Gabapentin and pregabalin, anticonvulsants that are active at the alpha-2-delta subunit of calcium channels, are thought to decrease central sensitization by their effect on calcium influx [48]. A small placebo-controlled trial showed that gabapentin was more effective than placebo in reducing pain and sleep interference in patients with HIV-associated neuropathy [38]. Although pregabalin is the only medication that was given a level A recommendation by the American Academy of Neurology guidelines for diabetic neuropathic pain [49], a placebo-controlled trial of pregabalin failed to significantly reduce neuropathic pain in the HIV population [39]. Similarly, the tricyclic antidepressant, amitriptyline, is considered to be a first-line agent among several guidelines of diabetic neuropathy, although it was not found to be effective in HIV-DSP [36,37]. Lamotrigine was found to be effective in HIV-DSP, particularly in patients on HAART [40,41].

Of the disease-modifying trials, only rhNGF, a neurotrophin that regulates small sensory nerve fiber activity, showed a greater efficacy over placebo [50]. In this randomized control trial of 235 patients given 0.1 µg/kg rhNGF, 0.3 µg/kg rhNGF or placebo twice weekly for 18 weeks, rhNGF was superior to placebo. Punch skin biopsies performed on a subset of 60 patients at the baseline and at week 18 showed no significant treatment effect on nerve regeneration or collateral sprouting of nerve fibers [35]. A subsequent 48-week open-label trial with 200 patients confirmed findings of improved pain but did not show improvement in DSP severity [51]. As there was no evidence for a disease-modifying effect of rhNGF in neuropathy due to HIV or diabetes, further development of this agent was halted. Other disease-modifying therapies, some of which have had success in other neuropathy trials but have been unsuccessful in demonstrating efficacy in HIV neuropathy, include prosaptide, peptide T and acetyl-L-carnitine.

Smoked cannabis reduced daily pain by 34 vs. 17% with placebo in a placebo-controlled trial of 50 patients [33]. Another study with 28 patients also showed that pain relief was greater with cannabis than placebo, with the proportion of patients achieving at least 30% pain relief with cannabis vs. placebo being 0.46 and 0.18 [34].

The role of alternative and complementary treatments to HIV-DSP has also been studied. One clinical trial assessed the role of acupuncture and amitriptyline in HIV-positive patients and found no effect on neuropathy pain [36]. However, another study of acupuncture and moxibustion (burning of mugwort leaf) did find reduced symptoms of neuropathy in a small sample of 50 adults with HIV [17]. Hypnosis interventions were also found to reduce total pain scores in participants with HIV-DSP whether or not they were taking pain medications, in a small study of 36 HIV-positive patients [52]. Bilateral lower extremity night splints have also been shown to reduce neuropathic pain in HIV-positive patients [53,54].

To date, therapies for HIV-DSP in both symptomatic and disease-modifying trials have been largely
disappointing. The relative success of some agents in other types of neuropathy that has not been demonstrated in HIV-DSP trials emphasizes the multifaceted nature of the disease and the need for our evolving understanding of its pathogenesis. In an era when HIV is better controlled with HAART, our initial models of the disease may need to be reevaluated to account for other immune-mediated mechanisms that have not yet been described. Another consideration of treatment failure includes current study designs. Future research paths may need to reevaluate whether we are using the right tools (skin biopsy vs. QST) to identify HIV-DSP, or using the right scales (TNS vs. BPNS) to measure outcomes. We must also consider the possible refractory nature of the patient population and other epidemiologic factors. As HIV tends to disproportionately affect economically disadvantaged classes and minorities, multiple issues, including cultural barriers, limited access to healthcare, comorbid psychiatric disorders and substance abuse disorders, may contribute to obstacles of optimal care [55].

**OTHER HIV-RELATED NEUROPATHIES**

Mononeuropathies are common in the HIV population largely secondary to their high prevalence in the general population [56]. Focal cranial neuropathies, such as unilateral and bilateral facial palsy, can also occur [57]. The causes include tuberculosis, syphilis [58], varicella-zoster virus and meningial lymphomatosis [59]. A case of bilateral diaphragmatic paralysis in a HIV-positive patient was recently reported in the literature [60].

Symptoms of autonomic neuropathy are a common comorbidity of HIV-DSP and include orthostatic dizziness, pupillomotor and visual symptoms, diarrhea, constipation, gastroparesis, dry eyes and mouth, urinary incontinence, male sexual dysfunction and changes in body sweating [61]. A recent study investigating the relationship between autonomic dysfunction in HIV-positive patients found that autonomic dysfunction was present in up to 90% of patients with severe DSP and in only 30% of participants with little to no autonomic dysfunction. They suggested that a common pathogenesis between DSP and autonomic dysfunction may exist, and that autonomic dysfunction should be considered a part of the HIV-DSP syndrome [30*].

Inflammatory demyelinating polyneuropathy (IDP) can occur in the HIV population in the form of acute inflammatory demyelinating polyneuropathy (AIDP), otherwise known as Guillain–Barre syndrome (GBS) and the chronic form, chronic inflammatory demyelinating polyneuropathy (CIDP) [62]. AIDP is a monophasic illness with recovery typically after 3–4 weeks, whereas CIDP has a relapsing and remitting course for greater than 8 weeks. CIDP has been suggested to occur more frequently in the HIV population. Both present similarly with ascending muscle weakness, loss of reflexes and relative sparing of sensory symptoms. Cerebrospinal fluid (CSF) studies cannot be reliably used to confirm the diagnosis of IDP in patients with high CD4 counts. Whereas CSF studies in HIV-negative patients with IDP typically show albuminocytologic dissociations with elevated CSF protein without pleocytosis, HIV-positive patients that may be asymptomatic with high CD4 counts may show elevated protein with a mild lymphocytic pleocytosis [63,64]. AIDP and CIDP are typically treated with intravenous immunoglobulin or plasmapheresis in the HIV-negative population [65]. There is a role for corticosteroids in HIV-negative CIDP patients, although clinical judgment should be expressed in HIV-positive patients because of possible side-effects, including immunosuppression.

Mononeuritis multiplex (MM) is a relatively rare complication of HIV infection and usually presents with both motor and sensory symptoms in an asymmetric pattern, involving two or more peripheral nerves. Early MM has been proposed to be autoimmune in nature, whereas late MM has been suggested to be caused by cytomegalovirus (CMV) [33,56,66]. MM typically resolves after several months and does not always warrant treatment. However, with persistent symptoms, intravenous immunoglobulin, plasmapheresis or corticosteroids may help to shorten disease course [67].

Polyradiculopathy can be rapidly progressive and presents with weakness and numbness of the lower extremities, frequently with sphincter dysfunction. Like MM, CMV has been implicated and is thought to infect the cauda equina. Workup includes gadolinium-enhanced MRI, which may show meningeal enhancement of the lumbar spine, [68] and lumbar puncture to assess for CMV with polymerase chain reaction [69].

The first case of ALS-like disease in an HIV-positive patient was in 1985 in a 26-year old man with rapidly progressive upper and lower motor neuron disease [70]. Since that time, around 29 cases have been reported [71]. It is thought that there may be two forms of ALS in HIV-positive individuals; one that responds to HAART and one that does not. The differences in treatment response are abnormal CSF, young age at onset, and progression in days to weeks [72].

**CONCLUSION**

HIV produces a number of neurologic complications, the most common being HIV-DSP. Other peripheral neurologic manifestations of HIV include
MM, IDP, both acute and chronic, polyradiculopathy and autonomic neuropathy. With the advent of HAART therapy, HIV-positive patients are living longer, resulting in prolonged exposure to the HIV virus, as well as antiretrovirals. HIV-DSP presents with distal, symmetric symptoms of numbness, tightness, burning pain or paresthesias. Neurologic exam reveals decreased or absent ankle jerks, vibratory perception or decreased pinprick or temperature in a stocking glove distribution. There is currently no FDA-approved treatment for DSP, although various symptomatic therapies are used.

Future research in neuroregenerative symptomatic therapies should investigate all aspects of the disease, including the underlying pathogenesis through enhanced in-vitro and animal models. Identifying novel targets in vitro should expand from the virus itself to peripheral nerves to other axonal or Schwann cell targets. Although we currently do not have a HIV-DSP animal model, progress is being made in several areas, including gene expression in the dorsal horn and dorsal root ganglia of animal cells exposed to antiretrovirals [73, 74]. We can continue to explore other avenues of management, such as nonpharmacologic interventions for pain, other symptomatic treatments and better address psychosocial issues that may be impeding access to care.

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Conflicts of interest
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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

29.最新WHO guidelines with strategies for phasing out d4T and restricting its use to cases in which other HAART drugs cannot be used.
This study demonstrates that autonomic dysfunction is common in HIV-positive patients and may be part of the spectrum of HIV-associated peripheral nerve disorders. This study found that peripheral nerve dysfunction is the most consistent predictor of autonomic dysfunction in HIV.
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48. Meta-analysis from seven randomized double-blind studies demonstrating efficacy of capsaicin patch with onset of analgesia within a few days.