

# HIV-related neuropathy: current perspectives

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**Abstract:** Distal symmetric polyneuropathy (DSP) related to human immunodeficiency virus (HIV) is one of the most common neurologic complications of HIV, possibly affecting as many as 50% of all individuals infected with HIV. Two potentially neurotoxic mechanisms have been proposed to play a crucial role in the pathogenesis of HIV DSP: neurotoxicity resulting from the virus and its products; as well as adverse neurotoxic effects of medications used in the treatment of HIV. Clinically, HIV DSP is characterized by a combination of signs and symptoms that include decreased deep tendon reflexes at the ankles and decreased sensation in the distal extremities as well as paresthesias, dysesthesias, and pain in a symmetric stocking–glove distribution. These symptoms are generally static or slowly progressive over time, and depending on the severity, may interfere significantly with the patient's daily activities. In addition to the clinical picture, nerve conduction studies and skin biopsies are often pursued to support the diagnosis of HIV DSP. Anticonvulsants, antidepressants, topical agents, and nonspecific analgesics may help relieve neuropathic pain. Specifically, gabapentin, lamotrigine, pregabalin, amitriptyline, duloxetine, and high-dose topical capsaicin patches have been used in research and clinical practice. Further research is needed to elucidate the pathogenesis of HIV DSP, thus facilitating the development of novel treatment strategies. This review discusses the epidemiology, pathophysiology, clinical findings, diagnosis, and management of DSP in the setting of HIV.

**Keywords:** neuropathy, human immunodeficiency virus, acquired immunodeficiency syndrome, AIDS, distal symmetric polyneuropathy, DSP, pain

## Introduction

Human immunodeficiency virus (HIV) is a retrovirus that causes progressive failure of the immune system in humans. More than 34 million people are infected with HIV worldwide, and every year approximately 2.7 million new infections with the virus occur.<sup>1</sup> Since the early descriptions of HIV, distal symmetric polyneuropathy (DSP) has been recognized as one of the common neurologic manifestations associated with advanced stages of HIV.<sup>2</sup> With the introduction of combination antiretroviral therapy (cART) in 1996, the length of survival of individuals has dramatically improved. For many patients in resource-rich countries, HIV is no longer a rapidly progressive, fatal illness but rather a chronic condition. However, to this date, DSP remains one of the most common neurologic complications of HIV, and it is associated with significant morbidity.<sup>3–7</sup>

## Epidemiology: prevalence and incidence of HIV neuropathy

Most estimates of the prevalence of HIV DSP in the cART-era range from 50%–60%, although prevalence as low as 21% has been reported.<sup>2,6,7</sup> This variability can be in part

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attributed to the different definitions of HIV DSP, with some studies defining DSP as one clinical sign (ie, reduced ankle reflexes or reduced pinprick sensation or reduced vibration sensation in the feet), some requiring two clinical signs, and some using validated screening or diagnostic instruments.<sup>7,43,49</sup> DSP seems to be rare in children with HIV infection,<sup>8,9</sup> but in an adult, pre-cART population, almost all patients had evidence of DSP on autopsy, even those without clinical signs and symptoms during their lifetime.<sup>10</sup> The incidence of HIV DSP varies from 12–25 per 100 person-years.<sup>11,12</sup> In patient populations on neurotoxic medication, particularly stavudine, the incidence tends to be at the higher end of that range.<sup>13</sup> High doses of stavudine have been associated with a higher incidence of DSP than low doses.<sup>14</sup>

## Pathophysiology

DSP has been recognized as a common complication of HIV since the late 1980s. Nonetheless, studies investigating the macroscopic and microscopic features of HIV DSP in humans are scarce, and many of them are limited by small sample sizes as well as lack of control groups and clinical correlates. In humans, the pathologic hallmarks of HIV neuropathy include distal axonal degeneration, neuronal loss in dorsal root ganglia (DRG) of affected nerves, inflammatory cell infiltration, and reduced epidermal nerve fiber (EDNF) density.<sup>10,15</sup>

The pathogenesis of HIV DSP in humans is not completely understood, but there are several promising hypotheses. Two distinct pathophysiologic processes are thought to contribute to the development of HIV DSP: direct neurotoxicity of the virus and its products and neurotoxicity of cART medications. Both processes will be discussed below. For a more detailed review of pathogenesis, see Kamerman et al.<sup>16</sup>

## Neurotoxic effects of HIV

Two mechanisms of HIV neurotoxicity have been proposed: direct neurotoxicity through infection of neurons with the HIV, and indirect neurotoxicity through viral gene products and/or activation of an inflammatory response to HIV. While it remains controversial whether HIV can enter neurons and thus be directly neurotoxic,<sup>17</sup> there is growing evidence supporting the indirect neurotoxicity of HIV through inflammation and viral proteins. Several proteins such as trans-activator of transcription, negative regulatory factor (Nef), stromal cell-derived factor 1- $\alpha$ , and regulated upon activation, normal T cell expressed and secreted (RANTES) have been implicated in the development of HIV-related central nervous system disease, including HIV-associated neurocognitive impairment.

The strongest evidence for indirect neurotoxic effects of HIV on the peripheral nervous system stems from research investigating the role of glycoprotein (gp)120. Gp120 is a well-studied glycoprotein exposed on the surface of the HIV envelope, and its involvement in the pathogenesis of HIV DSP has been shown using *in vitro* and *in vivo* models. *In vitro*, gp120 can induce neuronal cell lysis in cultured DRG cells.<sup>18</sup> Furthermore, gp120 activates macrophages, which in turn release neurotoxic inflammatory mediators such as tumor necrosis factor- $\alpha$  and interleukin-1.<sup>19</sup> Similarly, gp120 has been shown to induce Schwann cells to release RANTES, which causes dorsal root ganglion neurons to produce tumor necrosis factor- $\alpha$ , leading to neuronal cell death through tumor necrosis factor receptor 1-mediated neurotoxicity.<sup>20</sup> *In vivo*, the application of gp120 to the sciatic nerve in rats leads to neuronal swelling<sup>21</sup> and macrophage infiltration,<sup>22</sup> similar to inflammatory processes observed in patients with HIV.<sup>23</sup> In a behavior model of pain, rats exposed to gp120 develop hypernociception, which can persist for weeks after a single application of gp120.<sup>21,22,24</sup>

Additionally, there is evidence that mitochondrial DNA damage is more pronounced in patients with HIV DSP compared to HIV patients without DSP and to HIV-negative controls. In patients with HIV DSP, the degree of mitochondrial DNA damage is higher in the distal sural nerve than in the proximally located DRG.<sup>25</sup> This spatial distribution suggests that mitochondrial dysfunction may contribute to the clinical phenotype of length-dependent neuropathy.

## Neurotoxic effects of cART

Nucleoside analog reverse-transcriptase inhibitors (NRTIs) such as didanosine, zalcitabine, and stavudine have been shown to be associated with DSP.<sup>26–29</sup> While the use of these NRTIs has significantly declined over the past decade, they continue to be part of the mainstay of HIV therapy in resource-poor countries, particularly stavudine. Symptomatic DSP due to NRTIs is cited as a reason for a change in HIV treatment regimens, as symptoms may improve after discontinuation of the offending drug.<sup>30,31</sup>

DSPs originating from HIV or NRTIs are clinically indistinguishable from one another. Nonetheless, different pathophysiologic mechanisms have been implicated in the development of the clinical phenotype. One hypothesis is that NRTIs lead to mitochondrial dysfunction through inhibition of mitochondrial DNA polymerase gamma,<sup>32,33</sup> which was first demonstrated *in vitro* using PC-12 cells.<sup>34</sup> HIV-positive patients on zalcitabine were found to have enlarged vacuolated mitochondria depleted of DNA.<sup>35</sup> In DRG cultures,

didanosine has been shown to cause cell death.<sup>36</sup> In vivo, exposure to zalcitabine leads to reduced nerve conduction velocities and amplitudes as well as axonal cell loss in rabbits.<sup>37</sup> In rats, NRTI exposure causes hypersensitivity of hind paws, dying-back of EDNFs, and macrophage infiltration into the DRG.<sup>38,39</sup>

## Synergistic neurotoxic effects of HIV and NRTIs

There is evidence from animal studies that the combination of HIV and NRTIs may lead to an increased risk of pathological findings. For instance, transgenic mice expressing gp120, as well as wild-type mice exposed to didanosine, remain free of any pathology, but gp120-transgenic mice with didanosine exposure exhibit thermal hypersensitivity, loss of unmyelinated axons, and reduced EDNF densities.<sup>40</sup> In humans, the incidence of HIV DSP is higher in patients treated with stavudine compared to those on other HIV medications.<sup>13</sup>

## Risk factors

Before the introduction of cART, HIV neuropathy was closely associated with advanced immunosuppression, which is reflected in a lower CD4 count and a higher viral load.<sup>41</sup> To this day, HIV neuropathy continues to be a predictor of death in patients of limited means living in resource-poor countries.<sup>42</sup>

In patients treated with cART, age is the most important risk factor for DSP.<sup>3,7,26,27,43–48</sup> Stavudine exposure is another risk factor that is frequently identified,<sup>7,46,48</sup> whereas the relationship to other neurotoxic medications exposure is less clear.<sup>49</sup> Several studies found an association with height<sup>26,44–47</sup> and ethnicity,<sup>26,43</sup> but these findings were not replicated by other investigators.<sup>49</sup> CD4 count in the cART-era does not seem to be related to neuropathy,<sup>43,50,51</sup> but there are several studies suggesting that a lower CD4 nadir represents a risk factor for HIV neuropathy.<sup>3,27,44</sup> Likewise, viral load is not related to HIV neuropathy.<sup>26,43,44,50–52</sup> The results regarding coinfection with hepatitis C are conflicting, with most studies not finding a relationship between hepatitis C coinfection and DSP.<sup>44,53</sup> One study showed higher rates of neuropathy in HIV patients who were coinfecting with human T-lymphotropic virus type 2.<sup>54</sup>

Diabetes mellitus (DM) and alcohol abuse are known causes of peripheral neuropathy in the general population. In patients with HIV, DM increases the risk of DSP,<sup>43,44</sup> but the results of studies regarding alcohol are inconsistent.<sup>6,43,44,50</sup> Statin use has been shown to correlate with HIV DSP.<sup>44</sup> Furthermore, substance abuse and the number of substances

used were associated with a higher incidence of HIV DSP in a recent study.<sup>49</sup> These results suggest that risk factors of peripheral neuropathy in the general population exacerbate the risk of DSP in HIV patients.

## Clinical presentation

Neuropathy in HIV is a predominantly distal, symmetric, sensory neuropathy characterized by a variety of clinical signs and symptoms. The most commonly encountered clinical signs of HIV DSP are decreased or absent ankle jerks and decreased pinprick and vibration sensation involving the distal lower extremities.<sup>2,6,7,55–57</sup> Weakness and atrophy of the extremities are rare.<sup>58</sup> HIV DSP can be asymptomatic, but many patients experience numbness, tingling, or pain in a stocking-glove distribution.<sup>7,55,59</sup> In general, the symptoms of HIV DSP are first observed in the distal lower extremities and may gradually affect more proximal areas. In advanced cases, upper extremities can be involved as well. Cramping, stabbing, aching, and burning sensations in the affected extremities have also been described.<sup>55,57</sup> The clinical manifestations of HIV DSP tend to be relatively stable over time. Distal epidermal denervation has been shown to be associated with progression of DSP.<sup>51</sup>

## Diagnosis and differential diagnosis

Diagnosis of HIV DSP remains clinically based on a combination of typical signs and symptoms in addition to a history of HIV infection and possibly NRTI exposure.

There is currently no gold standard for the diagnosis of HIV DSP, but several clinical tools have been developed to assess this condition in clinical practice and research. The most commonly used are the Total Neuropathy Score<sup>58</sup> and the Brief Peripheral Neuropathy Screen.<sup>60</sup>

The total neuropathy score combines grading of sensory, motor, and autonomic symptoms, pin and vibration sensation, muscle strength, deep tendon reflexes, sural and peroneal amplitudes assessed by nerve conduction studies (NCS), and quantitative sensory testing of vibration sensation into a composite score, which correlates with the severity of neuropathy. Although originally validated in patients with diabetic neuropathy,<sup>58</sup> it has been widely used in HIV neuropathy.

The Brief Peripheral Neuropathy Screen provides a quick and easy assessment of neuropathy at the bedside and does not require neurophysiologic testing. Its sensitivity and specificity compared to the total neuropathy score are 35%–49% and 88%–90%, respectively, with a positive predictive value of 72%.<sup>51,55</sup>

Use of NCS is not routinely necessary for the diagnosis of HIV DSP but may be useful to rule out other conditions. If obtained, NCS may reveal slowed conduction velocities and reduced sensory nerve action potentials.<sup>57,61,62</sup>

Skin biopsy of affected areas may show decreased EDNF densities and swelling of the nerve terminals.<sup>63,64</sup> The degree of pathologic changes correlates with clinical pain scores<sup>15,65</sup> and may predict worsening of symptoms in the next 1–2 years.<sup>66</sup> EDNF has been shown to correlate with age, height, body mass index, and duration of neurotoxic therapy,<sup>67,68</sup> and in some studies but not others, with CD4 count.<sup>15,65,67</sup>

In addition, quantitative sensory testing is mainly used in research settings to measure detection threshold for changes in heat, cool, vibration, and to determine pain threshold, which may be abnormal in patients with HIV neuropathy,<sup>59,69</sup> and correlate with the degree of EDNF abnormalities found on skin biopsy.<sup>63,65</sup> Abnormal results are not only found in peripheral nerve disorders but also in diseases affecting the central nervous system, which is why quantitative sensory testing is usually performed in conjunction with other studies to help differentiate between the two.<sup>70</sup>

Nerve biopsies are not routinely indicated for HIV DSP but may be considered in atypical cases, for example, those with rapid progression or with prominent motor involvement.

The differential diagnosis of HIV DSP includes other causes of peripheral neuropathy such as DM, vitamin B12 deficiency, renal or liver impairment, thyroid dysfunction, and monoclonal gammopathy. Laboratory tests to assess for these conditions are recommended so that adequate treatment can be initiated (Table 1).

## Treatment

There is currently no US Food and Drug Administration-approved treatment for HIV neuropathy. Several medications have been used off-label for symptomatic control of neuropathic pain, including anticonvulsants, topical treatments, antidepressants, and analgesics.

The rationale for the use of these medications is their proven benefit in treating neuropathic pain due to diabetic neuropathy and postherpetic neuralgia as outlined in the recommendations for the management of neuropathic pain by the International Association for the Study of Pain<sup>71</sup> and guidelines for the treatment of diabetic neuropathy by the American Academy of Neurology.<sup>72</sup> Of note, most of these agents have not been shown to be superior to placebo in clinical trials studying HIV DSP, which some authors attribute to a pronounced placebo effect in patients with HIV DSP.<sup>71</sup>

Commonly used medications include the anticonvulsants gabapentin, pregabalin, and lamotrigine; topical high-dose capsaicin patches; the antidepressants duloxetine and amitriptyline; and nonspecific analgesics such as nonsteroidal anti-inflammatory drugs, acetaminophen, and opioids (Table 2). In general, neuropathic pain remains difficult to treat, with only half of the treated population typically reporting a significant reduction in pain.<sup>73,74</sup> Complete resolution of symptoms is rarely achieved; therefore, a reduction in symptom severity by 30%–50% may be a more realistic goal of therapeutic interventions.<sup>75</sup>

The following section provides an overview of clinical drug trials in HIV neuropathy.

A double-blind, randomized trial has shown that a single application of 8% capsaicin patch can alleviate pain for several weeks.<sup>76</sup> Recently, a study comparing patients treated with a single 30-minute or 60-minute application of either high-dose (8%) capsaicin or a low-dose (0.04%) capsaicin revealed a trend toward greater pain reduction in the high-dose capsaicin group. This difference failed to reach statistical significance, which was attributed to a larger-than-expected reduction of pain in the subgroup of patients receiving the 60-minute application of low-dose capsaicin.<sup>77</sup> In prior studies, low dose (0.075%) capsaicin and lidocaine patches did not lead to improved pain control.<sup>78,79</sup>

Gabapentin reduced pain significantly and improved sleep in a small study with 24 patients.<sup>80</sup> Lamotrigine provided some pain relief in a study of 227 patients with HIV DSP, especially in those patients who were treated with neurotoxic medications.<sup>81,82</sup> A randomized, double-blind, placebo-controlled trial of pregabalin failed to demonstrate significant improvement of pain, but hyperalgesia was less pronounced in participants receiving pregabalin compared to placebo.<sup>83</sup> Amitriptyline is frequently used in diabetic neuropathy; however, it appears to be less effective in HIV neuropathy based on two randomized, placebo-controlled studies.<sup>84,85</sup>

One small study showed that smoked cannabis improved pain more than identical placebo cigarettes; however, this benefit disappeared after 7 days.<sup>86</sup> A short training program in self-hypnosis consisting of three weekly sessions was successful at reducing pain scores during a 7-week follow-up in a cohort of 36 patients with HIV DSP.<sup>87</sup>

A randomized, placebo-controlled trial of 250 patients investigating the effects of acupuncture did not show significant improvement of pain;<sup>85</sup> however, a newer study of 50 patients treated either with acupuncture plus moxibustion or a placebo procedure revealed a greater improvement of pain in the acupuncture/moxibustion group.<sup>88</sup>



**Table 1** Laboratory studies in the initial evaluation of human immunodeficiency virus patients presenting with distal symmetric polyneuropathy

|   |
|---|
| Basic metabolic panel   |
| Liver function tests  |
| Hemoglobin A <sub>1c</sub>                                    |
| Vitamin B12, folate   |
| Thyroid function tests  |
| Serum, urine protein electrophoresis and serum immunofixation |
| Hepatitis C virus serology                                    |

Recently, several trials were conducted based on newer pathophysiologic models of HIV DSP. HIV commonly uses the C-C chemokine receptor type 5 as a coreceptor to enter its target cells. Vicriviroc, a drug that binds to the C-C chemokine receptor type 5 and prevents HIV from entering cells, and therefore thought to be able to interfere with the pathophysiologic mechanisms causing HIV DSP, did not improve pain compared to placebo in a trial of 118 patients with HIV DSP.<sup>89</sup> A trial using prosaptide, a neurotrophic factor, was stopped at a planned futility analysis.<sup>90</sup> Acetyl-L-carnitine has been proposed as a booster of mitochondrial function, but it was unsuccessful in alleviating HIV DSP symptoms in a small open-label study involving 20 patients and in a randomized, placebo-controlled trial of 90 patients.<sup>91,92</sup> Although neurotrophic growth factor did lead to some improvement of DSP symptoms in an open-label study of 200 patients and a randomized placebo-controlled trial of 270 patients, it is associated with significant adverse effects at the injection sites, and it is currently not available clinically.<sup>93,94</sup> Trials of memantine, mexilitine, and peptide T were unsuccessful.<sup>84,95,96</sup>

In terms of nonpharmacologic treatment options, a pilot study demonstrated improved pain score and sleep index scores after using bilateral night splints for three weeks in 22 patients with HIV neuropathy.<sup>97</sup>

Lastly, medical management of potentially contributing comorbid conditions, such as DM, vitamin deficiencies, and alcohol abuse, should be optimized.

## Other forms of neuropathy associated with HIV

In addition to DSP, HIV can be associated with other disorders of the peripheral nervous system such as mononeuropathies, mononeuritis multiplex, inflammatory demyelinating polyneuropathy, progressive polyradiculopathy, and autonomic neuropathy.<sup>98–100</sup>

HIV-infected individuals, particularly those with DSP, may be at increased risk for superimposed mononeuropathies. The most common mononeuropathies include median neuropathy

at the wrist (ie, carpal tunnel syndrome), ulnar neuropathy at the elbow, and peroneal neuropathy at the fibular head. Facial nerve palsy, often referred to as Bell's palsy, is commonly an idiopathic, presumably inflammatory condition. However, in the setting of HIV, particularly with advanced immunosuppression, other etiologies should be considered including varicella zoster virus, meningeal lymphomatosis, aseptic meningitis, syphilis, or tuberculosis. In such patients, a more comprehensive work-up may be warranted to distinguish these etiologies from idiopathic forms.<sup>101–103</sup>

Mononeuritis multiplex manifests as painful, progressive, sensory and motor deficits in multiple nerve distributions that may become confluent. It is a rare complication of HIV, and while the symptoms can be self-limited, a rapidly progressive variant caused by cytomegalovirus infection of peripheral nerves has been described in the setting of advanced immunosuppression.<sup>104–106</sup>

Two forms of inflammatory demyelinating polyneuropathy (IDP) have been described in HIV patients: an acute form of IDP, or Guillain-Barré syndrome, with rapidly progressive symptoms, and a chronic form characterized by slower progression or by a relapsing–remitting course.<sup>107</sup> Clinically, both forms present with ascending muscle weakness and areflexia in addition to paresthesias. In HIV-negative patients with IDP, cerebrospinal fluid studies typically reveal albuminocytologic dissociation; that is, an elevated cerebrospinal fluid protein level in the absence of significant pleocytosis. In HIV-positive patients, a mild lymphocytic pleocytosis with elevated protein levels is commonly found in asymptomatic patients with high CD4 counts,<sup>108,109</sup> and is therefore less specific for IDP in this patient population.

The clinical picture of polyradiculopathy is characterized by progressive sensory, motor, and reflex changes in a radicular distribution. In HIV patients, progressive polyradiculopathy may be secondary to infectious or neoplastic etiologies such as lymphoma, cytomegalovirus, treponema pallidum, or mycobacterium tuberculosis.<sup>110–113</sup>

Manifestations of autonomic neuropathy include orthostatic hypotension, gastroparesis, diarrhea and constipation, xerostomia, xerophthalmia, urinary incontinence, sexual dysfunction, sweating abnormalities, and sluggish pupillary

**Table 2** Pharmacological treatment of neuropathic pain

|  |
|--|
| Discontinuation of neurotoxic medication             |
| Anticonvulsants: gabapentin, lamotrigine, pregabalin |
| Topical anesthetics: capsaicin, lidocaine            |
| Antidepressants: duloxetine, amitriptyline           |
| Analgesics: NSAIDs, acetaminophen, opioid analgesics |

**Abbreviation:** NSAIDs, nonsteroidal anti-inflammatory drugs.

reaction.<sup>114</sup> Recent studies suggest that autonomic neuropathy is a common comorbidity of HIV DSP, affecting more than half of all HIV DSP patients and is associated with predictors of mortality as summarized by the Veterans Aging Cohort Study Index.<sup>100,115,116</sup>

NCS and electromyography, cerebrospinal fluid studies, neuroimaging and autonomic function tests may be helpful to distinguish between HIV DSP and these other less common forms of neuropathy.

## Conclusion and future directions

HIV DSP is the most common neurologic complication of HIV. Several mechanisms may be involved in the pathogenesis of HIV DSP such as neurotoxic effects of the virus and its gene products as well as neurotoxic medications used for the treatment of HIV. Clinically, HIV DSP is characterized by sensory symptoms such as dyesthesias and paresthesias with symmetric involvement of the distal extremities. Signs of HIV DSP include decreased deep tendon reflexes and decreased sensation in a stocking-glove distribution. While the diagnosis of HIV DSP remains largely clinical, other conditions that lead to distal sensory neuropathies need to be excluded. The treatment of HIV DSP remains difficult. Topical medications such as high-dose capsaicin patches, and anticonvulsants have yielded the most promising results thus far. Additional research is needed to elucidate the mechanisms leading to HIV DSP, which in turn will allow for the development of targeted treatment strategies.

## Disclosure

The authors report no conflicts of interest in this work.

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