Chapter

# HIV-Associated Sensory Neuropathy

*Fitri Octaviana, Ahmad Yanuar Safri, Darma Imran and Patricia Price*

## Abstract

As advances in the treatment of HIV are now allowing patients a longer life span, further comorbidities become apparent. This includes sensory neuropathy (HIV-SN) which can affect a patient's quality of life. Here, we review factors influencing HIV-SN in patients receiving antiretroviral therapy that promotes this condition and in the modern era when these therapies have been withdrawn. This has halved the incidence of HIV-SN, but the condition remains significant in the lives of many sufferers. Genetic polymorphisms that influence pathogenesis of HIV-SN have indicated likely mechanisms, but studies of skin biopsies and animal models are needed to confirm the roles of the encoded proteins.

**Keywords:** HIV sensory neuropathy, inflammation, neuronal repair

## 1. Introduction

Management of HIV patients is now focused on their quality of life as antiretroviral therapy (ART) increases life expectancy. However, with longer lives, a growing number of patients experience a neurological disorder that predominantly affects small fibers. HIV-associated sensory neuropathy (HIV-SN) may arise not only as a result of HIV infection itself but also as a side effect of ART. The clinical pictures triggered by HIV infection or ART are very similar and include neuropathic pain, tingling sensation, and numbness [1–3]. HIV-SN is one of the most common complications of HIV infection.

The incidence and prevalence of HIV-SN vary widely—perhaps because most studies do not distinguish between neuropathy due to HIV itself and due to ART regimens with different risk profiles. Cross-sectional studies including patients receiving ART identify HIV-SN in 16–50% of HIV patients [4–6]. ART that includes the non-nucleotide reverse transcriptase inhibitor (NNRTI), stavudine (d4T), is associated with high prevalence of HIV-SN. The prevalence in Melbourne was up to 42%, whereas in Kuala Lumpur and Jakarta, the reported level was lower, 19 and 34%, respectively [7]. Stavudine is no longer in first-line therapy, and the prevalence of HIV-SN is almost halved (14.2%) compared to data from the same clinic in Indonesia when patients received stavudine [8].

In untreated patients, the risk factors for HIV-SN were severe HIV disease marked by low numbers of $CD4^+$ T cells and high viral loads (HIV RNA) in plasma. In the era of ART (including stavudine), the risk factors of HIV-SN included older age, height, <50 $CD4^+$ T cells/$mm^3$, malnutrition, and concurrent diabetes [1, 7, 9, 10]. HIV-SN

was also more common in African-Americans [3] and Hispanics [11]. Genetic polymorphisms may alter risk for HIV-SN in Africans [12–14], Asians [15], and Caucasians [16]. These factors are discussed in more detail here.

## 2. Clinical features and diagnostic criteria

There are two forms of HIV-SN—distal symmetrical polyneuropathy in HIV (DSP) and antiretroviral toxic neuropathy (ATN). DSP arises at later stages of HIV infection, while ATN is caused by neurotoxic effects of antiretroviral drugs [10, 17]. These two forms cannot be distinguished clinically, so they are grouped as HIV-SN when seen in patients receiving ART.

The most frequent symptoms of HIV-SN are pain, numbness, and burning sensations. The symptoms can be progressive, predominantly affecting the soles of the feet and may become more severe at night. Physical examination may reveal hyperalgesia and allodynia, with absent physiological reflexes and sensory loss in the distal limb segments, including sensitivity to vibration [1, 9–11]. Clinical symptoms usually occur first on the lower limbs for several months but may spread upward. Since HIV-SN predominantly affects small nerve fibers, the clinical signs can also manifest as autonomic neuropathy with postural hypotension and urinary dysfunction [18]. Guidelines for the diagnosis and management of HIV-SN are available [e.g., https://www.hiv.va.gov/provider/manual-primary-care/peripheral-neuropathy.asp] but require adaptation to accommodate differences between patient populations, structures of medical care, and available resources.

Perhaps, the optimal tool to screen HIV-SN is AIDS Clinical Trial Group Brief Peripheral Neuropathy Screening Test (ACTG BPNST). This test has been used in many countries including Australia, the USA, India, South Africa, and Indonesia. It is relatively inexpensive, is fairly easy to do, and takes less than 10 minutes to perform but has low sensitivity. A study comparing BPNST to modified Total Neuropathy Scores (mTNS) in HIV patients on ART (including d4T, ddI, ddC) found that the sensitivity of BPNST was 49%, whereas the specificity was high at 88% [17]. Peripheral neuropathy can be diagnosed if there is ≥1 symptom assessed in the BPNST list and one of the following signs: decreased Achilles reflexes or decreased sensibility to vibration when a tuning fork is held on a toe. This definition means that patients with two abnormal signs but no symptoms are not considered to have HIV-SN. This may contribute to variations in the prevalence of peripheral neuropathy in HIV reported in various studies. Some studies consider this intermediate group as asymptomatic peripheral neuropathy with the assumption that they can become symptomatic in time. Ellis et al. defined peripheral neuropathy as a decrease in Achilles tendon reflexes or decreased perception of vibration in both legs. The sensitivity increased by 80% but the specificity decreased to 59% [19].

Clinically, peripheral neuropathy can also be classified as small- or large-fiber neuropathy. The latter manifests as the loss of joint position and vibration sense and sensory ataxia, whereas small-fiber neuropathy manifests as neuropathic pain, impairment of temperature sensing, and autonomic function. A nerve conduction study (NCS) can include sensory and motor nerve conduction and help in documenting sensory motor deficits that mainly affect large-fiber nerves [20]. As HIV-SN is a predominately small-fiber neuropathy, NCS is often normal [21]. In HIV-SN patients, ATN- and HIV-associated DSP often cannot be distinguished since patients can have both types at same time. However, there are some evidences that ATN primarily impairs small-fiber nerves, whereas HIV-associated neuropathy (DSP) has been linked to large-fiber nerves [22, 23].

Stimulated skin wrinkling (SSW) test is a method to assess small nerve fiber function using exposure to eutectic mixture of local anesthetic. It has been shown to correlate with intraepidermal nerve fiber density (IENFD) in patients with a sensory neuropathy [24] and has high sensitivity compared to other assessments of small-fiber neuropathy in diabetic patients [25]. Skin wrinkling occurs as a result of vasoconstriction in the glabrous skin, mediated by postganglionic sympathetic fibers [26]. Other assessments that have been used to detect small-fiber neuropathy in HIV-SN patients include quantitative sudomotor axon reflex tests (QSART) [27], quantitative sensory tests (QST) [18], and sympathetic skin responses (SSR) [22, 23].

Skin biopsies are the gold standard for the detection of damage to small-diameter sensory nerves, including non-myelinated and myelinated intraepidermal nerve fibers. Lower nerve fiber densities have been demonstrated in patients with HIV-SN [18]. Studies have used several different techniques. The European Federation of Neurological Societies recommended a biopsy of the skin to a depth of 3 mm by using a skin punch biopsy on the distal limbs to calculate the linear density or nerve fibers with a minimum of 50 μm-thick slices, fixed in a 2% solution of paraformaldehyde-lysine-periodate (2% PLP). Immunohistochemical staining techniques recommended are bright-field immunohistochemistry and indirect immunofluorescence [28]. PGP9.5 immunofluorescence allows nerves to be visualized using a confocal microscope [29]. Smaller intraepidermal nerve fiber densities (IENFD) in HIV-SN patients correlated with the clinical and electrophysiological severity [30]. Skin biopsies can also be used to identify cells and mediators that contribute to SN. These are discussed later in this chapter.

## 3. Clinical factors influence the risk of HIV-SN

Analyses of the risk factor of HIV-SN require that we consider the condition in three distinct eras—(1) pre-ART, (2) the use of combination ART that included stavudine (d4T), and (3) the use of non-neurotoxic ART. In the pre-ART era, the risk factors for developing HIV-SN included HIV disease severity, low $CD4^+$ T-cell counts, high viral load, and older age [31, 32]. In the second era, the risk factors are older age, height, low nadir $CD4^+$ T-cell counts, HIV duration, malnutrition, diabetes mellitus, dyslipidemia, and the use of neurotoxic drugs (usually stavudine; see **Table 1**; [7, 14, 15, 33, 34]). Stavudine is no longer recommended by the WHO as first-line ART and is now rarely used anywhere in the world, but HIV-SN has

| Demographic risk factors | Genetic risk factors |
|---|---|
| Low nadir $CD4^+$ T-cell count<br>HIV duration<br>Age<br>Height<br>High plasma HIV RNA<br>Diabetes mellitus<br>Malnutrition<br>Neurotoxic drugs<br>• NRTI: stavudine, didanosine<br>• Protease inhibitors: indinavir, ritonavir, saquinavir | Race (more common in African populations)<br>Polymorphisms in<br>• Mitochondrial DNA (mtDNA)<br>• *HFE* (affecting iron metabolism)<br>• Cytokine genes (*IL4, IL10, IL12B*)<br>• *TNF* gene block (central MHC)<br>• *P2X4R, P2X7R* (purinergic receptors)<br>• *CAMKK2* (affecting neuronal repair) |

**Table 1.**
*Genetic and demographic risk factors affecting HIV-SN in patients receiving ART.*

not disappeared. The risk factors of HIV-SN in patients on ART without stavudine are almost the same as in the pre-ART era—high plasma viral load and older age [8]. Isoniazid is widely used as therapy for tuberculosis and has been recognized as a risk factor for neuropathy for a long time. It remains weakly associated with HIV-SN even though patients receiving isoniazid are also given B6 supplementation to prevent neuropathy. Protease inhibitor (PI) exposure may be a risk factor of HIV-SN. Lopinavir, indinavir, and ritonavir, but not nelfinavir, were associated with neuropathy in one study [35].

## 4. Genetic risk factors

The risk of HIV-SN cannot be correlated with a single genetic variant, so candidate genes are discussed separately (see **Table 1**). It is of interest to determine if any aligns with the greater sensitivity of individuals of African descent [13, 14, 36].

### 4.1 Genes in linkage disequilibrium with TNF or encoding components of pathways regulated by TNF

In patients receiving stavudine, haplotypic combinations of alleles of single-nucleotide polymorphisms (SNP) spanning the tumor necrosis factor (TNF) block in the central major histocompatibility complex (MHC) associate with variations in the prevalence of HIV-SN, but the associations were different in Africans and Asians [12]. For example, a polymorphism in intron 10 of BAT1 (marking an MHC haplotype associated with several inflammatory disorders) and a polymorphism in the promoter region of the *TNFA* gene (TNF-1031) were associated with an increased risk of HIV-SN in Caucasians [37]. TNF-1031*2 is associated with an increased risk of HIV-SN in Indonesian HIV-positive patients who receive stavudine [15, 16]. However, in Africans, different SNP alleles were found in linkage disequilibrium with TNF-1031*2, so TNF-1031*2 was not associated with HIV-SN. These findings link HIV-SN with an unknown SNP in the TNF block marked by (but distinct from) TNF-1031. The link between HIV-SN and inflammation was supported by studies linking *IL4* genotypes with HIV-SN in Africans receiving stavudine [13].

### 4.2 The *P2X7R*, *P2X4R*, and *CAMKK2* gene cluster: Inflammation and neuronal repair

Goullee et al. linked SNP in three genes *P2X7R*, *P2X4R*, and *CAMKK2* with HIV-SN in African patients treated with stavudine. In a logistic regression model which included demographic analyses, SNP in *CAMKK2*, and to a lesser extent *P2X7R* and *P2X4R*, demonstrated independent associations with HIV-SN ($p < 0.0001$; $R^2 = 0.19$) [14].

The P2X7R receptor is expressed by microglia and may be involved in neuropathic pain, as its ablation or inhibition in animal models of neuropathy can reduce responses to painful stimuli [38]. Conversely, stimulation of P2X7R will increase the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα [39] as well as pro-inflammatory chemokines such as CXCL2 and CCL3, which have been implicated in neuropathic pain [40, 41].

In animal studies, P2X4R was activated in spinal microglial cells in rats with induced pain [42]. Mice with disrupted *P2X4R* genes showed reduced pain response in two models of chronic pain (inflammatory and neuropathic) [43]. P2X4R is upregulated after peripheral nerve injury which results in increased activity of

mitogen p38 [44]. This process initiates the release of brain-derived neurotropic factor (BDNF). BDNF induces neuronal hyperexcitability through interaction with the TrkB receptor [45, 46].

The *CAMKK2* gene encodes calcium-/calmodulin-dependent protein kinase 2 (CaMKK2), which acts as a pervasive second messenger of $Ca^{2+}$ in many cellular functions such as energy balance, neuronal differentiation, and inflammation [47]. CaMKK2 plays a role in neural plasticity and neurite growth by activating another protein kinase CaMKI [48]. *CAMKK2* and *P2X4R* polymorphisms affect TNFα production in vitro. This suggests a mechanism for their impact on HIV-SN [49]. Hence, polymorphisms in *CAMKK*2 may affect inflammation or neuronal growth.

### 4.3 Mitochondrial haplotypes and iron metabolism

The process of mitochondrial toxicity induced by ART is not a simple drug toxicity, but mitochondrial DNA (mtDNA) SNP has a role in developing HIV-SN in patients receiving NRTI. SNP in African mtDNA haplogroup L1c and European haplogroup J is associated with decreased prevalence of HIV-SN compared with all other haplogroups [36]. Moreover, Thai persons belonging to mtDNA haplogroup B were more likely to develop HIV-SN [50].

HIV-1 *Nef* protein may influence iron levels via interactions with the hemochromatosis protein HFE in humans [51]. In an observational prospective study, Kallianpur et al. suggested that disruption of iron homeostasis due to HIV infection might damage neurons and potentially lead to HIV-SN. They presented evidence that the *HFE* C282Y mutation may be a protective factor in HIV patients using NRTI [52]. They subsequently linked polymorphisms in iron management genes with increased risk (*TF, CP, ACO1, BMP6, B2M*) and reduced risk (*TF, TFRC, BMP6, ACO1, SLC11A2, FXN*) of HIV-SN [53].

## 5. The pathophysiology of HIV-SN

The pathophysiology of HIV-SN is not completely understood, but there are several promising theories. It remains unclear whether HIV inflicts direct damage in the nerve body of dorsal root ganglia (DRG) or damages nerve fibers; both will lead to the development of distal axonopathies. HIV causes distal axon degeneration, reduction of nerve fiber in DRG, infiltration of inflammation cells, and reduction of the intraepidermal nerve fiber (IENFD) count [2]. As HIV itself cannot directly infect nerve bodies, destruction of neuron in HIV-SN may be caused by neurotoxic agents released by activated macrophage and satellite glial cells (TNF-α, IL-1β, chemokines), viral proteins with neurotoxic properties (gp41, gp120, Tat, Vpr), infection of perineural cells, or combinations of these processes [54–58]. A study in simian immunodeficiency virus macaque model confirmed that HIV infection activates perineuronal inflammatory cells (including macrophages and lymphocytes) in trigeminal ganglia and DRG during the early stage of infection. In the later stage, neuronal damage becomes evident, and regenerative capacity of small epidermal nerve is impaired [59].

HIV infection may cause macrophages to respond to the axonal degeneration (even in mild cases) causing inflammation of the nerves and DRG. Pro-inflammatory mediators were released by Schwann cells at DRG and may accumulate adjacent to peripheral nerves, activate apoptotic pathways and cause damage to the nerves directly or indirectly (reviewed in [55]). The gp120 virus protein may act directly on chemokine receptors expressed on neurons and cause

pain [60]. A histopathology study of skin biopsies from HIV-SN patients on ART without stavudine confirmed the presence of inflammatory macrophages and T cells expressing some chemokine receptors (CX3CR1, CCR2, CCR5), along with reduced IENFD [61].

HIV protein gp120 is a component of the viral glycoprotein sheath. The entry of the HIV virus into cells requires the interaction of gp120 with CD4 glycoprotein and a chemokine receptor (usually CXCR4 and/or CCR5) which may be expressed on neurons or infiltrating inflammatory cells. Several chemokine receptors, such as CCR2, CCR5, and CXCR4, and $CX_3CR1$ (fractalkine receptor) are located in primary afferent neurons or secondary neurons of the spinal dorsal horn. Chemokines and gp120 can cause pain through direct effects on chemokine receptors expressed by nociceptive neurons [62]. For example, binding of gp120 to CXCR4 receptors increases the release of CCL5, which binds CCR5 and triggers the release of TNFα and other neurotoxic substances. These interactions activate an influx of $Ca^{2+}$, kinase cascades, and STAT3 signaling leading to the signs and symptoms of HIV-SN. The pathways have been reviewed previously [61, 63].

The pathophysiology of HIV-SN in patients on stavudine may reflect damage to the mitochondria of neurons and axons via damage to mitochondrial DNA (mtDNA) [64]. Inhibition of mtDNA gamma polymerase, mtDNA intercalation, and damage in stress response of mitochondria has been demonstrated in vitro in cultures of T-lymphoblastoid cells [65]. This finding is further supported by differences in haplotypes or SNP in mtDNA in Europeans, Hispanics, and Africans that may contribute to differences in the prevalence of HIV-SN [36, 52, 66, 67].

## 6. Therapeutic options

Management of HIV-SN aims to avoid further nerve damage and minimize the patients' symptoms especially neuropathic pain. Some studies showed that smoked cannabis is effective and has analgesic value to relieve pain in HIV-SN patients [68, 69]. However, due to legal issues in many countries, the recommendation of smoked cannabis has been controversial. Other pharmacological treatments recommended for neuropathic pain are amitriptyline, pregabalin, and gabapentin [70]. However, these medications were not superior to the placebo in HIV-SN patients [71–73]. Another option is non-pharmacological treatment such as acupuncture and hypnosis. However, acupuncture was not superior to the placebo to improve pain in HIV patients [74]. A small study showed that hypnosis showed benefit to reduce the pain score in HIV-SN patients [75].

## 7. Conclusions and future directions

Despite the withdrawal of the most toxic drugs from recommended ART regimens, HIV-SN remains a common neurological complication of HIV disease. The risk factors of HIV-SN have changed with changes in ART from the patient's age and height to the efficacy of ART and the use of protease inhibitors. Genetic polymorphisms that influence pathogenesis of HIV-SN will provide candidate molecules, which may contribute to pathogenesis, but studies of skin biopsies from patients are needed to confirm the roles of the encoded proteins. Animal models may reveal mechanisms for neuropathy and pain by HIV proteins but do not mimic the complexities of HIV disease in patients.

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## Author details

Fitri Octaviana[1,2*], Ahmad Yanuar Safri[1,2], Darma Imran[1,2] and Patricia Price[1,3,4]

1 Neurology Department, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

2 Neurology Department, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

3 School of Biomedical Sciences, Curtin University, Bentley, Australia

4 School of Physiology, University of Witwatersrand, Johannesburg, South Africa

*Address all correspondence to: fitri.octaviana@gmail.com

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