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**Diagnosing and treating HIV-associated sensory neuropathy: a global perspective**

Catherine L Cherry<sup>1,2</sup>, Antonia L Wadley<sup>1</sup>, Peter R Kamerman<sup>1</sup>

1. Brain Function Research Group, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
2. Infectious Diseases Unit, The Alfred Hospital; Department of Infectious Diseases, Monash University; and Burnet Institute, Melbourne, Australia

**Corresponding Author**

Catherine L Cherry,  
Department of Infectious Diseases,  
The Alfred Hospital,  
Commercial Rd,  
Melbourne, Victoria 3004,  
Australia

Phone +61 (3) 9076 2000  
Facsimile +61 (3) 9076 2431  
Email [kate.cherry@monash.edu](mailto:kate.cherry@monash.edu)

### **Executive Summary**

- HIV-SN remains common (20-57% prevalence), even with current HIV management strategies
- No “gold standard” diagnostic criteria, but generally easily detected using simple clinical screening tools (prioritize physician assessment +/- special tests for atypical cases)
- Symptom control is challenging and rarely complete
  - No proven, widely available and legal pharmacological strategies
  - Trials challenging: marked placebo effect, possible responder subgroups
  - Preliminary data support non-drug options including self-hypnosis, meditation, psychology, physical activity, and a positive therapeutic relationship
  - We recommend therapeutic trials of available, affordable, safe options: continuing those where benefit outweighs costs
- Work needed to understand current epidemiology, precise pathophysiology and “responder phenotypes” to available therapies

### **Abstract**

HIV-associated sensory neuropathy (HIV-SN) is a common complication of HIV and remains highly prevalent even with modern HIV management strategies; causing debilitating pain in millions globally. We review HIV-SN diagnosis and management. We suggest most HIV-SN cases are easily recognized using clinical screening tools, with physician assessment and/or specialized testing prioritized for atypical cases. Management aims to prevent further nerve damage and optimize symptom control. Symptom relief is difficult and rarely complete, with a lack of proven pharmacological strategies. Work is needed to clarify optimal use of available medications. This includes understanding the marked placebo effect in HIV-SN analgesic trials and exploring “responder phenotypes”. Limited data support non-drug strategies including hypnosis, meditation, psychology, physical activity, and a positive therapeutic relationship.

### **Key words**

HIV, neuropathy, neuropathic pain, placebo effect, non-drug strategies

## Introduction

HIV-associated sensory neuropathy (HIV-SN) was an early recognized complication of AIDS [1] and remains common in the context of current HIV management strategies [2]. Precise prevalence rates vary with the cohort surveyed and the case definition used, but recent estimates suggest that symptomatic HIV-SN is present in 20 – 57% of adults living with HIV infection [3-10]. HIV-SN is a predominantly sensory, symmetrical, polyneuropathy characterized by distal axonal loss [11]. Neuropathic pain is common among affected individuals, and is associated with substantially reduced quality of life and functional impairment [12], including reduced likelihood of employment [13]. The impact of HIV-SN is magnified by the paucity of proven, effective analgesic strategies [14].

With an estimated global prevalence of HIV infection of around thirty five million people at the end of 2013 [15], the economic and morbidity burden associated with HIV-SN is enormous. Here we review methods for diagnosing HIV-SN in a clinical setting and the limited evidence available for managing this difficult condition.

## Diagnosis of HIV-SN

Any discussion of the epidemiology, diagnosis or management of HIV-SN is hampered by the lack of “gold standard” diagnostic criteria. Some authors accept bilateral signs of neuropathy as sufficient for the diagnosis of HIV-SN [16]. For the purpose of this review, we define HIV-SN as requiring both neuropathic signs and also symptoms consistent with this diagnosis, for several reasons:

1. This review is intended to assist those involved in the clinical management of adults living with HIV, making symptomatic disease relevant.
2. Isolated neuropathic signs are common among adults with HIV infection and their prognostic significance is limited. Long term follow up of 1592 patients involved in AIDS Clinical Trials Group treatment studies showed that isolated neuropathic signs at baseline were associated with some increased risk for the development of symptomatic HIV-SN (OR 1.58). However, 83.7% of patients with isolated neuropathic signs at baseline remained symptom free after an average of 255 weeks of follow up [17].
3. We have shown that the presence of both neuropathic symptoms and signs associates with the greatest degree of pathology and peripheral nerve dysfunction on formal testing [18].

How, then, should HIV-SN best be diagnosed in a clinical context, and does this vary between sites with greater access to sophisticated testing (such as sensory threshold testing or quantitation of epidermal nerve fiber density) and sites where resources are more limited, as is the case in many places where the greatest burden of HIV care is concentrated?

The simplest diagnostic criteria for HIV-SN would be self-reported symptoms consistent with this diagnosis; requiring no special testing or even a clinical examination. Despite the apparent crudeness of this approach, relatively high diagnostic utility for HIV-SN of a single question about neuropathic symptoms has been documented in a Zambian setting [19].

However the reference standard used in this study included similar questions on symptoms, which may explain the good agreement. Self-reported distal neuropathic pain and/or paresthesia were also found to have 92% specificity and a positive predictive value of 96% for HIV-SN (as diagnosed on a total neuropathy score) in the CNS HIV Antiretroviral Treatment Effects Research Study [20]. However, the sensitivity of this symptom-based approach was low (52%), possibly reflecting the lack of pathognomonic symptoms for neuropathic pain [21] together with the fact that there may be multiple sources of pain in HIV-infected individuals [22].

Causes of distal neuropathic pain other than HIV-SN do occur in the context of HIV, some with distinct treatment implications. We would therefore not advocate using symptoms alone to diagnose HIV-SN, regardless of their high positive predictive value. For example, one group have found high rates of restless legs syndrome in HIV [23] – a condition that can be worsened by some of the drugs commonly used to treat neuropathic pain. Chronic inflammatory demyelinating polyneuropathy (CIDP), although uncommon, is also increased in HIV infection and, where possible, should be specifically excluded in any patient with atypical features, including unexpected motor findings such as weakness or muscle wasting [24].

The other end of the spectrum would be to require specialized testing to identify a lesion in the somatosensory system for a formal diagnosis of HIV-SN in all those who present with compatible symptoms. However, the number of people with HIV infection, the high prevalence of symptomatic HIV-SN and the fact that most people with HIV are receiving care at centers where specialist neurological testing is unavailable, make such a suggestion impractical. Fortunately, in most cases of HIV-SN, we suggest special tests are not necessary.

Thermal threshold testing has been investigated in the context of HIV infection. While elevated thermal thresholds are common among those with a clinical diagnosis of HIV-SN, several groups have shown that adults with HIV infection, including those *without* symptoms or signs of neuropathy, perform less well on sensory threshold testing than HIV negative controls [25-27], likely due to sub-clinical nerve damage. This limits the diagnostic utility of such testing in isolation. Similarly, although cutaneous nerve fiber density is generally reduced in those with HIV-SN, as in other types of small fiber neuropathy [28-30], the diagnostic utility of skin biopsy alone is limited for HIV-SN [31-33]. Even in those without clinical evidence of peripheral nerve disease, factors including ethnicity, age and height may influence results [34, 35]. A recent “deep profiling” study examined the utility of a comprehensive battery of diagnostic modalities in HIV infected adults with and without neuropathy – including numerous clinical assessment tools, pain scales, mental health scores, quantitative sensory testing, cutaneous nerve fiber quantitation, and neurological examination. The authors confirmed the relatively poor diagnostic utility of any of the special

tests examined for HIV-SN in isolation, demonstrating that assessment tools based on characteristic symptoms and signs perform better [11].

From these data we conclude that HIV-SN is primarily a clinical diagnosis based on the presence of compatible neuropathic symptoms and signs. The role of special tests, where available, is primarily to exclude alternative diagnoses (such as CIDP) in atypical cases, and for research purposes.

In many HIV care clinics, screening for conditions including HIV-SN is likely to be the responsibility of allied health staff, and referral to a neurologist may not always be possible. A reasonable approach to identifying the presence of neuropathic pain has been detailed by Treede and colleagues [21] and for the identification of symptomatic HIV-SN, we suggest the following:

1. Question every HIV-infected patient on whether they have pain
2. If pain is present, determine whether it follows a neuro-anatomically plausible distribution for a distal, symmetrical polyneuropathy (ie stocking-and-glove distribution)
3. Physical examination of those with symptoms compatible with neuropathy for supportive clinical signs of peripheral nerve dysfunction
4. Consider other, identifiable causes of the neuropathy (e.g., diabetes mellitus) that may require management (and can co-exist with HIV-SN)

To aid in the process, we suggest that simple, standardized tools that assess symptoms and signs of neuropathy and that were designed for use by non-medical staff (such as the ACTG Brief Peripheral Neuropathy Screen [18]) be used. In the case of the BPNS, a single day of training allowed non-physician health care workers in Western Kenya to diagnose accurately most cases of HIV-SN [36]. This then allows those with atypical findings to be prioritized for physician assessment.

### **Management of HIV-SN**

No therapy has been shown to improve the underlying pathology of HIV-SN and a single trial of recombinant human nerve growth factor found no benefit in terms of epidermal nerve fiber density [37]. Management is therefore aimed at avoiding any additional nerve damage (for example, avoiding potentially neurotoxic medications including stavudine or didanosine, providing pyridoxine in all cases if isoniazid is required, and ensuring adequate nutrition) and minimizing the patient's symptoms and their impact. Unfortunately, as with many types of neuropathic pain, analgesia is difficult to achieve and typically incomplete [38].

### Pharmacological treatment of HIV-SN pain

There is no widely available, legal and evidence-based analgesic that can routinely be offered for the management of HIV-SN pain. Several agents have been investigated in randomized, controlled trials, but the medication under investigation has rarely been found to be more

efficacious than placebo for this condition. A 2010 systematic review found some evidence of benefit only with smoked cannabis, 8% capsaicin patches and recombinant human nerve growth factor [14]. Smoked cannabis has shown consistent analgesic benefits in HIV-SN across two well-designed trials [39, 40]. However, these studies looked only at very short term (five days) efficacy, and both legal issues in many jurisdictions and mental health concerns preclude the routine recommendation of smoked cannabis for HIV-SN pain. High dose (8%) capsaicin patches are available in some countries, but are relatively costly, labor intensive to use, and their analgesic efficacy in the context of HIV-SN is limited at best, with a recent trial being negative [41] and an estimated number need to treat to achieve a 30% reduction in pain across all randomized HIV-SN trials of 11 [42]. Recombinant human nerve growth factor is not available for clinical use.

It is notable that agents used first-line to manage other types of neuropathic pain have performed disappointingly in HIV-SN studies. For example, amitriptyline, a tricyclic antidepressant, performed no better than placebo in three high quality, randomized trials. This includes a recent randomized, cross over trial of amitriptyline versus placebo performed in South Africa [43] and two trials comparing both amitriptyline and another intervention (acupuncture in one, mexilitine in the other) to placebo [44, 45]. While the data are more limited, other agents demonstrating no superiority over placebo in at least one randomized trial for the treatment of HIV-SN pain include gabapentin [46], pregabalin [47, 48] and lamotrigine [49, 50]. A trial of duloxetine was abandoned due to poor recruitment [51].

Overall, the available data do not provide strong evidence of analgesic efficacy for any widely available pain modifying agent in HIV-SN, and high quality studies of simple analgesics are lacking [14]. The data are convincing that amitriptyline is no more effective than placebo at a population level [43-45]. This is particularly disappointing, as amitriptyline is affordable, and is one of the few agents that is available for the treatment of neuropathic pain in many of the resource-limited settings where the greatest burden of HIV disease is seen [52].

Despite the lack of high quality evidence to support the pharmacological treatment of HIV-SN pain, lower quality studies and numerous clinical anecdotes suggest that some individuals may benefit from agents including amitriptyline, pregabalin and gabapentin; all of which have the advantage of being relatively free from significant interactions with antiretroviral medication. This is consistent with what is seen in other neuropathic pain conditions, where years of clinical experience provide some support for available treatment recommendations, often despite a relative lack of high quality evidence of analgesic efficacy in clinical trials [38].

There are several factors that may have contributed to the generally negative results of analgesic trials in the context of HIV-SN. The first is the magnitude of the placebo response in this group of patients. In all high quality HIV-SN trials conducted to date, the active agent

has been associated with statistically and clinically meaningful reductions in pain intensity. However, this has been confounded by similarly large reductions in pain intensity in the group receiving placebo. A recent meta-analysis of placebo responses in clinical trials of neuropathic pain states [53] reported that the magnitude of the placebo response in trials of HIV-SN was substantially larger than those reported in trials of painful diabetic polyneuropathy, post-herpetic neuralgia, and central neuropathic pain. On average, the placebo group in HIV-SN trials had a reduction in pain intensity of almost 2 points on an 11-point numerical pain rating scale (Figure 1A) and the placebo responder rate (participants with at least 50% pain relief) was 42%; double what was seen in the next highest condition, diabetic polyneuropathy (Figure 1B). This may be attributable, at least in part, to a “care effect” (discussed in more detail below), whereby this often marginalized group of patients may benefit from their interactions with investigators during trial participation. In addition, there is a general trend towards increasing placebo response rates in trials of neuropathic pain in the US, where the majority of HIV-SN trials have been performed [54].

Another factor, and one that is a matter of broader discussion in the field of neuropathic pain [55, 56], is that effect sizes of drugs trialed for neuropathic pain may be underestimated because only a subset of the individuals studied has a responsive phenotype. Large-scale analyses have demonstrated phenotypic heterogeneity within neuropathic pain syndromes, and phenotypic sub-group clustering across neuropathic pain conditions [57, 58]. There is emerging evidence that phenotypic profile contributes to treatment response [59, 60]. This includes HIV-SN pain, where responder analysis of a negative trial of pregabalin revealed that participants with increased pin-prick sensitivity were more likely to respond to treatment [48].

These challenges raise questions about whether the existing, negative analgesic studies in HIV-SN represent evidence of “failed analgesics” or, rather, “failed trials” [61]. Until better quality evidence is available, our approach to the pharmacological management of HIV-SN pain involves documenting the individual’s symptoms and their severity, a therapeutic trial of one agent at a time (chosen based on availability, side effect profile, interactions with other medication and cost), and withdrawal of any agent from which either no discernable benefit is gained, or where side effects outweigh any benefits. Many patients will end up on combination therapy, but the evidence-base to guide combination therapies for neuropathic pain states in general is inconclusive [38]. Even among individuals who benefit from medication, relief from HIV-SN pain is typically incomplete.

The absence of a clear, evidence-based guideline on how to manage painful HIV-SN may contribute to the under-treatment of diagnosed pain among people living with HIV (a group in which pain is also typically under-recognized) [22]. Against this backdrop, we recently reported that in Southern African patients with painful HIV-SN, around half of patients with moderate pain and one quarter of patients with severe pain were not receiving any analgesic

medication. Of those receiving analgesic pharmacotherapy, 84% were receiving amitriptyline and most continued to experience pain [62].

#### Non-pharmacological approaches

The lack of proven, effective drug options, the challenges of managing an ageing population living with HIV, where co-morbidities and drug interactions (including with essential antiretroviral therapies) make polypharmacy undesirable as well as costly, and the pronounced placebo effect seen in analgesic trials in HIV-SN all point to a role for non-pharmacological approaches in managing HIV-SN pain. The available data in this area are limited, but preliminary work supports the possibility of real benefits from safe, non-drug options.

An open-label pilot study in 36 adults with painful HIV-SN demonstrated sustained analgesic benefits from self-hypnosis. Participants received three once-weekly training sessions in self-hypnosis and were followed up for seven weeks post training. Overall, 72% achieved stable reductions in pain out to at least seven weeks, and the mean reduction in pain amongst responders was 44% [63]. This safe intervention is supported by an earlier case series of five patients with HIV-related pain [64] and warrants further study.

No published trial has investigated mindfulness-based therapies specifically for HIV-SN pain, but preliminary studies in Iran, Spain and the USA have all found mindfulness techniques useful in improving quality of life and physical symptoms in adults with HIV infection [65-67]. Anecdotal reports of meaningful reductions in HIV-SN pain exist (unpublished data, CL Cherry) and a pilot study in post-herpetic neuralgia supports the possible efficacy of mindfulness meditation for neuropathic pain [68]. In addition, a sample of 80 patients who meditated regularly (any style) rated the practice as having an effectiveness of >7/10 for reducing HIV-SN pain [69].

Psychological interventions may also be beneficial in managing HIV-SN pain. Prevalence of pain in HIV increases with number of psychological symptoms [70] and in HIV-SN specifically, pain catastrophizing (the tendency to amplify the threat value of one's pain) associated with increased pain intensity [71]. Furthermore, quality of life correlated more closely with level of depression than the intensity of HIV-SN pain [72]. In this context, two papers report benefits from a 12-week group cognitive behavioural therapy programme for HIV-related pain [73, 74]. Ten percent of participants reported foot pain, most likely attributable to HIV-SN, as their worst site of pain. Reduced pain intensity and improved function were reported at 12 weeks, despite patients only attending a mean of 4 sessions. Reductions in maladaptive coping strategies such as alcohol and drug use were also seen [73]; an important finding, as these behaviours are commonly used self-coping strategies for patients with painful HIV-SN in countries including the US and Puerto Rico [75].

Physical activity is one of the adaptive self-coping strategies adopted by patients with painful HIV-SN [69, 76, 77]. However, the benefits of exercise have not been fully explored for the management of pain in HIV-SN. In HIV patients generally, aerobic and resistance exercise is safe and has been shown to improve self-efficacy and depressive symptoms [78-80]. A small study in South Africa found a six week group exercise and education intervention to be effective in reducing pain intensity and interference and increasing self-efficacy and quality of life in women living with HIV [81]. However, a no-intervention group, who received the same education and repeated follow up with a consistent research assistant but no group exercise intervention, also improved compared with controls. A follow-on, multi-site study is currently underway to determine the relative contribution of education alone versus the effect of repeated time and interest from a research assistant in improving pain outcomes. Repeated follow up by a consistent research assistant was associated with improved pain outcomes in another cohort with HIV pain [82]. Referred to as the “care effect”, similar responses to empathy, independent of the placebo effect, have been seen in other painful conditions including irritable bowel syndrome [83] and low back pain [84]. In the context of HIV, this has also been associated with better medication adherence [85].

Despite the limited data currently available, non-drug strategies for management of HIV-SN pain have important potential advantages including affordability, safety and the lack of need for highly specialised staff or facilities. Several of these strategies could feasibly be used even in resource limited settings. A number of studies are currently underway that will provide a better evidence base for such approaches.

### **Conclusion and Future Perspectives**

All available evidence suggests painful HIV-SN will remain common, despite current recommendations to treat HIV early [86] and avoid the use of known neurotoxic antiretroviral agents [87]. With life expectancy of those living with HIV now approaching normal [88, 89], the high prevalence of HIV-SN together with the associated morbidity demand attention. An improved understanding of the epidemiology of HIV-SN in the era of current HIV management [2, 90] is needed to explain why particular individuals are affected. Additional work to unravel the precise pathogenesis of HIV-SN will be a critical step in developing more effective mechanisms for preventing and treating this condition [91]. While the millions affected by chronic pain from HIV-SN await these developments, work is urgently needed to improve the evidence base for when, how and in whom to most effectively use currently available therapies.

Despite improvements in the morbidity and mortality associated with HIV infection [88, 89], there remains an enormous global burden of disease. Although non-life threatening, painful HIV-SN is a common cause of substantial morbidity, with associated costs to both the individual and society. The clinical diagnosis of HIV-SN is generally not difficult, even in the resource-limited settings where the greatest numbers of people affected by HIV reside. However, management of the associated pain is extremely challenging. Pharmacological

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strategies have limited proven efficacy [14] and are not widely available on a global scale. More work is needed to understand the role of safe, non-drug therapies that could potentially be patient controlled and rolled out in most settings.

### Conflicts of interest

The authors have no conflicts of interest to declare.

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***\*\*A useful summary of the data (and its limitations) relating to pharmacologic treatment of neuropathic pain in general***

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**Figure legend**

Figure 1: Placebo responses in analgesic trials for neuropathic pain states. A) The average change in pain score from baseline on an 11-point numerical pain rating scale. B) The proportion of placebo participants with at least 50% pain relief (adapted from Cepeda *et al*, 2012). (HIV-SN: HIV-associated sensory neuropathy. PDN: painful diabetic neuropathy. PHN: post herpetic neuralgia. Central: central neuropathic pain)

