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Review Article

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HIV-Related Neuropathy: Pathophysiology, Treatment and Challenges

Noushin Jazebi[1], Chad Evans[1], Hima S. Kadaru[1], Divya Kompella[1], Felix Fang[2], Mukaila Raji[3], Miguel Pappolla[1], Shao-Jun Tang[2], Jin Mo Chung[2], Bruce Hammock[4] and Xiang Fang[1*]

[1]Department of Neurology, University of Texas Medical Branch, Galveston, TX, USA
[2]Department of Neuroscience & Cell Biology, University of Texas Medical Branch, Galveston, TX, USA
[3]Department of Medicine, University of Texas Medical Branch, Galveston, TX, USA
[4]Department of Entomology and Nematology & Comprehensive Cancer Center, University of California Davis, Davis, CA, USA

***Correspondence to:**
Xiang Fang, MD, PhD, FAAN, FANA,
Department of Neurology & Mitchell Center for Neurodegenerative Diseases
University of Texas Medical Branch
Galveston, TX-77555
Tel: +409-772-2646
E-mail: sxfang@utmb.edu

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Abstract

HIV-sensory neuropathy (HIV-SN) is a debilitating complication in HIV patients with or without anti-retroviral treatment (ART). Common symptoms of HIV-SN include pain, decreased sensation, paresthesias and dysesthesias in a symmetric stocking-glove distribution. While HIV-1 protein such as gp120 is implicated in HIV-SN (e.g. impaired large-diameter fiber), ART itself was recently shown to contribute to HIV-SN in HIV patients and impair thin fiber. Multiple host mechanisms may play roles during the pathogenesis of HIV-SN, including neuron-glia interactions in the spinal dorsal horn (SDH), inflammation, mitochondrial dysfunction and endoplasmic reticulum stress. Concurrent infections, such as tuberculosis, also carry a higher likelihood of HIV-SN as well as environmental or genetic predisposition. Pro-inflammatory cytokines such as IL-1, IL2 receptor-alpha and tumor necrosis factor (TNF) along with abnormal lactate levels have been identified as potential players within the complex pathophysiology of this condition. In this paper, we review the pathophysiology of HIV neuropathy, focusing on the various treatment options available or under investigation. Although several treatment options are available e.g., the capsaicin patch and spinal cord stimulation, symptomatic control of HIV-SN are often challenging. Alternative approaches such as self-hypnosis, resistance exercise, cannabinoids, and acupuncture have all shown promising results, but need further investigation.

Keywords

HIV, Neuropathy, Pain, Pathophysiology, Treatment

Introduction

Data from the Joint United Nations Programme on HIV and AIDS (UNAIDS) showed that in 2016 approximately 36.7 million people worldwide were living with Human Immunodeficiency Virus (HIV) [1]. HIV-associated sensory neuropathy (HIV-SN) is a common and potentially disabling complication seen in HIV patients. Clinical manifestations of HIV-SN vary, but often present as distal symmetric polyneuropathy (DSP) often accompanied by autonomic neuropathy [2]. The potential pathological processes involves multiple pathways including inflammation, mitochondrial dysfunction and sensory nerve degeneration among others. There is neither universal consensus nor evidence-based guidelines for the treatment of HIV-SN, leaving physicians with the only

option of prescribing medications (e.g. gabapentin) used for general neuropathic pain. These treatments are nonspecific and not effective at treating HIV-SN when compared to placebos. Treatments targeting the pathogenic pathways would greatly benefit for the growing population of long-term HIV living with HIV-SN. In addition patients with HIV-SN are more likely to be prescribed opioid analgesics and the rates of opioid addiction are notoriously high among HIV patients. Thus, developing a disease-specific treatment for HIV-related neuropathic pain is critical to reduce opioid abuse in the HIV population. This article reviews the existing literature to provide a clinically relevant overview of the biomarkers and pathophysiology of HIV-SN with an emphasis on available treatments, while offering a recommendation for future clinically relevant research. Our goal is to identify the critical gaps in the current knowledge base as related to the clinical practice in diagnosis and management of HIV-SN. Further studies are warranted to advance treatment methods based on current biomarkers, in addition to symptom management.

Materials and Methods

Literature review qualifications and methods

A PubMed and Cochrane search were performed using "HIV Neuropathy" as the key words, with additional inclusion criteria to review studies in human adults over the age of 19. It was restricted to articles written in the English language and published within the past five years. The search yielded 115 articles of which 12 related to the pathophysiology and biomarkers of HIV neuropathy. Another 21 articles discussed the current and future treatment options for HIV neuropathy. A similar search was conducted on Cochrane Evidence with a yield of 370 articles. Our review will also focus on recent developments that further our understanding of the pathophysiology and potentially "druggable" biomarkers of HIV neuropathy including an in-depth discussion of inflammatory mediators, association with changes in polymorphic genes, the bidirectional relationship between HIV viral load and ART, putative pathways related to diabetes and mitochondrial DNA, CNS changes and their potential correlation with HIV neuropathy and the role of chemokine receptor and HIV-1 gp120.

Inflammatory mediators

A major pathophysiologic mechanism underlying HIV-SN is the pro-inflammatory state caused by HIV infection, figure 1 and table 1 outline the biomarkers and pathophysiology of HIV neuropathy. The HIV virus does not infect cells lacking a CD4 receptor such as neurons, dorsal root ganglia, or Schwann cells, but infect cells of the monocyte-macrophage lineage. The infected monocyte-macrophage lineage cells secrete inflammatory mediators (pro-inflammatory cytokines and chemokines). These cells also secrete the HIV envelope protein gp120, which may alter both peripheral and central neural mechanisms that underlie the expression and persistence of neuropathic pain in HIV-SN [3]. Intrathecal injection of gp120 activates microglia and astrocytes, which subsequently release pro-inflammatory cytokines that contribute to neuropathic pain [4].

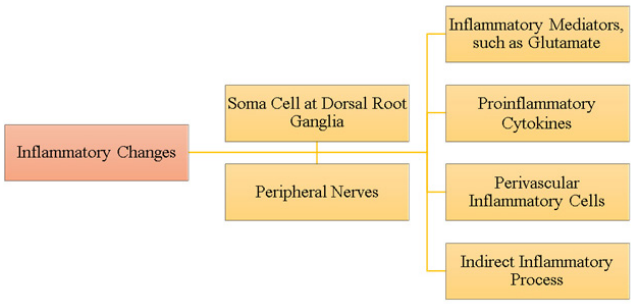

Figure 1: Pathophysiology of HIV neuropathy.

Table 1: Biomarkers in HIV neuropathy.

BIOMARKERS	COMMENT
Inflammatory mediators	Chemokines, cytokines, viral protein: envelope protein Gp-120
Iron-regulatory polymorphic genes	Reduced risk- a/w polymorphisms in TF, TFRC, BMP6, ACO1, SLC11A2, and FXN Increased risk- a/w variants in TF, CP, ACO1, BMP6, and B2M Strong association in white people: ACO1 rs2026739
Polymorphs of the KCNS1 and GCH1genes	a/w pain intensities experienced by patients in non-African patients and black, southern African patients GCH1 gene- a/w decrease pain in Europeans
Mitochondrial uncoupling protein UCP2 and UCP3	Lower prevalence of neuropathy in Caucasian type 1 diabetic and HIV patients
Mitochondrial DNA haplogroups	L0a2: associated with increased risk of neuropathy, L2a: associated with a reduced risk of peripheral neuropathy Stavudine (nucleoside reverse transcriptase inhibitor) a/w mitochondrial toxicity and high Lactate level
Neuroprotein	Increased levels of CSF neopterin, blood neopterin, and CSF monocyte chemoattractant protein (CSF MCP)-1
Pro-inflammatory cytokines	TNF-a and IFN-c: elevated levels association of IFN-c +874 A/A genotype, SNP in LN, HIV-PN, and OPN
Chemokine receptors	CX3CR1 ~ in $CD14^+$ cells CCR2, CCR5, CXCR3 and CXCR4 ~ more common on $CD3^+$ cells CX3CR1, CCR2, and CCR5 expression more common in HIV-SN^+

Significant correlations between the plasma cytokine profiles, the initiation of combination anti-retroviral therapy (cART) and HIV-SN were reported. 120 individuals that did not have pre-existing neuropathic symptoms and were about to begin cART were observed over time for the occurrence of neuropathic pain at baseline and then at 2, 4, 12, and 24 weeks after cART initiation. The authors matched the patients that developed neuropathic symptoms within the first 12 weeks of starting cART in a nested case-control design with those patients that remained symptom free for at least 24 weeks. Plasma was collected at the 2, 4, 12 and 24 week intervals to quantify cytokines and soluble receptors. Around a quarter of those 120 patients on cART, 32 to be specific, demonstrated neuropathic symptoms within 12 weeks of starting cART [5]. At the 2-week follow-up period, higher soluble interleukin (IL)-2 receptor-alpha levels and TNF receptor-II levels were also noted in the symptomatic HIV patients on cART, The ratios of pro-inflammatory *vs.* anti-inflammatory cytokines (TNF-α/IL-4 and interferon-gamma/IL-10) were significantly in favor of the pro-inflammatory cytokines in the symptomatic patients on cART compared to the asymptomatic patients on cART. The symptomatic group, the group that had neuropathic symptoms within 12 weeks of starting cART, also

showed higher CD4+ counts after 24 weeks of cART. At the 12-week follow-up, a similar increase was noted in the soluble IL-6 receptor levels in the cases. The authors concluded that cART initiation in previously treatment-naïve individuals was associated with both a cytokine 'burst' between 2 and 4 weeks after cART initiation and altered cytokine concentration in symptomatic patients before they even started cART [5].

In black Southern Africans with HIV-SN, association of TNF-α with neuropathic pain was also found. This association effect is modified by genetics, such that HIV neuropathy patients with the single nucleotide polymorphism (SNP), a gene alteration in a single nucleotide, at allele rs28445017*A were significantly more likely to have a higher pain intensity than those with the SNP allele rs28445017*G [6].

Additional evidence supports the key role of the pro-inflammatory cytokines TNF-α and IFN- γ in the pathogenesis of peripheral neuropathy in various diseases. Sykam et al. showed the association between the plasma levels of these cytokines, their single nucleotide polymorphisms (SNPs) and the development of leprosy neuropathy (LN), HIV-SN and other peripheral neuropathies (OPN). The elevated levels of plasma TNF-α and IFN-γ with several diseases associated with neuropathy suggests a common involvement of these cytokines in the susceptibility, pathogenesis, initiation and persistence of different types of peripheral neuropathy. The IFN-γ + 874 A/A genotype compared to what other genotype can lead to an 8.9 times high risk of OPN, and thus this SNP is a potential susceptibility factor in developing peripheral neuropathy and that cytokine gene polymorphisms do not necessarily exert a major influence on neuropathy but instead probably are contributing factors in increased susceptibility to HIV-SN. Since most of the HIV-SN patients showed increased levels of TNF-α and IFN-γ as compared to the healthy subjects and HIV group without sensory neuropathy, the author suggested that HIV-SN pathogenesis involves a chronic inflammation, rather than mere HIV infection or d4T drug effect alone [7].

Polymorphic genes association

Genetic polymorphisms has been proposed as susceptibility factors for HIV-SN. Polymorphisms in *TF*, *TFRC*, *BMP6*, *ACO1*, *SLC11A2* and *FXN* were found to be associated with a reduced risk, while the rs1049296 variant among other variants of *TF*, *CP*, *ACO1*, *BMP6* and *B2M* were associated with an increased risk of neuropathy [8]. Among those listed, *ACO1* rs2026739 was found to have the most significant association with neuropathic pain in the Caucasian population [8].

Based on the known association between the polymorphisms of *KCNS1* and *GCH1* and the pain intensities experienced by non-African HIV patients, Hendry et al. investigated the presence of any similar associations in black southern African populations with HIV-SN. Unlike the strong association of decreased pain with the *GCH1* in patients of European descents, no correlation was seen in the black southern African population with HIV-SN. For *KCNS1*, although no single SNP had a strong association with pain sensitivity, five haplotypes showed such an association, indicating the inclusion of the SNPs in these haplotypes [9]. In a study of 153 black Southern African patients exposed to stavudine, Goullee et al. found that *CAMKK2* exhibited the strongest associations with HIV-SN. *CAMKK2* is mainly expressed in the nervous system. As part of the calcium-calmodulin-dependent protein kinase family, its role is as an inflammatory inhibitor *via* upstream activation of AMP-activated protein kinase. This study suggested that the polymorphisms impeding the activity of *CAMKK2* may increase the risk of developing HIV-SN, while variations that increase *CAMKK2* activity may reduce the likelihood of developing the sensory neuropathy of HIV [10].

HIV infection versus ART

It is not completely clear to which extent the virus itself or the anti-retroviral treatment contribute to the pathogenesis of HIV-SN separately. A study by Dudley et al. of 67 participants from a South African HIV clinic found that of those who had undergone 5 years of ART, most had met the criteria for HIV-SN and that those with HIV-SN were more likely to develop autonomic symptoms and a decreased lower extremity functional scale (LEFS). The authors also noted that both large and small fiber nerve dysfunction accumulated over time [11]. Kokotis et al. analyzed the differences in neuropathy caused by the actual HIV viral infection and neuropathy caused by ART. Data from nerve conduction velocities, sympathetic skin responses in the palms and soles, skin biopsies and intraepidermal nerve fiber densities showed that neurotoxic treatment causes typical small fiber neuropathy with reduced intraepidermal nerve fiber density (IENFD) and reduced C-fiber conduction velocity. However, low CD4 count was linked to an impairment of myelinated fibers including reduced conduction velocities and amplitudes while IENFD was only slightly reduced in those with a low CD4 count, and in those with low CDF non-penetrating intraepidermal nerve fiber density was clearly reduced. The authors concluded that ART impairs thin fiber conduction, while the virus itself impairs large fiber conduction [12]. Wang et al. analyzed blood and CSF samples of recently HIV infected (< 1 year) and ART-naive patients and found that, while the plasma HIV RNA levels predicted and CD4+ T cell counts positively predicted, though not to a statistically significant degree, the occurrence and severity of HIV peripheral neuropathy in chronically infected patients. The authors found increased levels of CSF neopterin, blood neopterin, and CSF monocyte chemo attractant protein (MCP)-1 in patients with peripheral neuropathy [13], and suggested that peripheral neuropathy developed during the early disease states might be due to the systemic and CNS immune responses to HIV [13].

Role of diabetes and mtDNA

One way to further understand HIV-SN is by looking for protective and risk factors already publsihed in study of neuropathy-inducing conditions such as diabetes. Rudofsky et al. showed a lower prevalence of neuropathy in Caucasian type 1 diabetic patients with the mitochondrial uncoupling protein alleles *UCP2* (rs659366*A, -866G > A)

and *UCP3* (rs1800849^T, -55C > T) [14]. Considering those results, Wadley et al. investigated whether these results are similar in HIV-SN patients. After analyzing the mtDNA uncoupling protein alleles from 335 African patients, they found no such correlation with the occurrence of HIV-SN. Pathophysiological differences in the mechanisms by which neuropathy develops in diabetic and HIV-SN patients were thought to be one reason for the different outcomes [9].

In another study on ART-treated Malawian patients, Chagoma et al. explored the correlation between lactate levels and neuropathic pain in patients taking stavudine. A total of 253 patients were followed for a year and blood samples were taken for analysis during their clinic visits. The results showed that stavudine was associated with mitochondrial toxicity and that the resultant high lactate levels correlated with the severity of peripheral neuropathy and lipodystrophy [15]. However, the lactate levels seemed to decrease with longer treatment durations. Lactate is produced by astrocytes in the nervous system. Interestingly, astrocytes are specifically activated in the spinal dorsal horn of human HIV patients who developed chronic pain but not in the patients who did not suffer chronic pain, indicating a potential role of activated astrocytes in HIV-SN development [16]. In a similar study of Malawian patients who were taking stavudine, a cost-effective nucleoside reverse transcriptase inhibitor, Kampira et al. investigated the possible relationship between various mtDNA haplogroups and peripheral neuropathy. 250 non-Hispanic European and black patients on stavudine for more than six months were categorized based on the occurrence or absence of peripheral neuropathy. They found while the mtDNA haplotype L0a2 was associated with an increased risk of neuropathy, the mitochondrial DNA (mtDNA) haplotype L2a was associated with a reduced risk of peripheral neuropathy [17].

Another outcome of the CHARTER study was the association between mtDNA haplotypes and pain sensitivities in HIV patients with neuropathies. The two important locations of the SNPs were identified at positions A12810G on the African haplogroup L1c and T489C on the European haplogroup J, both of which showed associations with decreased pain in HIV neuropathy. These associations were seen independently of other predictors of HIV-SN, such as age, CD4 cell nadir and D-drug therapy. It is believed that the rates of oxidative phosphorylation differentiate the mitochondrial haplogroup. The researchers conclude that along with the adverse effects on peripheral nerves of D-drugs known to be toxic to mitochondria; their data provide evidence that the differences in HIV-SN susceptibility might be partially due to the difference in mtDNA variants within populations [18].

HIV-1 gp120

By analyzing postmortem tissues of HIV patients, Yuan et al. compared the levels of HIV proteins in the SDH of patients who did or did not manifest pain and HIV-SN [19]. They found gp120 was drastically higher in the pain-/HIV-SN-positive cohort. They generated a mouse model by intrathecally injecting gp120 to simulate the spinal increase of this protein in the pain-/HIV-SN-positive patients. Remarkably, the systematic comparison studies show that this mouse model develops all pathological phenotypes generated in the pain-/HIV-SN-positive human patients, including peripheral neuropathy, glial reactivation, synapse degeneration, and aberrant SDH activation of pain-related signaling pathways [19]. These findings strongly suggest that gp120 is the principal HIV-1 agent that causes HIV-related pain and SN [19]. Aziz-Donnelly et al. proposed that gp120 is not only a key factor in the initiation of the inflammatory cascade, but also contributes to nociception [3]. Keswani et al. found that as a chemokine activator, in animal models, gp120 was shown to induce neuronal cell death and axonal degeneration *via* independent effects on DRG and axons. Specifically, ligation of the chemockine receptor CXCR4 on Schwann cells by gp120 resulted in the release of RANTES which induced the DRG neruons to produce TNF- α and subsequent TNFR1-mediated neurotoxicity in an autocrine fashion [20]. A related study by Datta et al. demonstrated that gp120 promoted the movement of lysosomes toward plasma membranes, proceeded to induce lymphosomal exocytosis and finally increased the release of ATP into the extracellular media. They also found that lysosome de-acidification and activation of P2X4 and VNUT underlie the gp120-induced lysosome exocytosis and that these aforementioned processes lead to increases in intracellular calcium and reactive oxygen species in dorsal root ganglion neurons; this is highly suggestive of a pathogensis mechanism for HIV-SN [21]. Milligan et al. demonstrated that intrathecal administration of gp120 activates microglia and astrocytes, which, in turn, release pro-inflammatory cytokines and contribute to neuropathic pain [22].

Using compartmentalized cultures of sensory neurons, Melli et al. showed that gp120 causes axonal degeneration through two potential mechanisms: 1) indirect injury to cell bodies and requires the participation of Schwann cells and 2) direct local toxicity on the axons through the activation of the mitochondrial caspase pathway [23]. It has been reported that gp120 binds to CXCR4 on Schwann cells to cause the release of RANTES (regulated upon activation, normal T-cell expressed and secreted), which induces TNF-α-mediated neuronal apoptosis and degeneration [23].

Correlation with chemokine receptors

IENFD were variable in patients without HIV-SN, but generally lower in those with HIV-SN. It has been hypothesized that chemokines produced locally in the skin promoted infiltration of macrophages and T-cells, leading to damage of cutaneous nerves and, consequently, HIV-SN. In macrophages, those with HIV-SN had increased expression of CXCR4 while also having increased expression of CCR2, CCR5, CXCR3 and CXCR4 on $CD3^+$ B cells. Of note is that CXCR3 and CXCR4 were up regulated in all HIV patients with or without sensory neuropathy when compared to healthy controls [24]. Of note, Bhangoo et al. found that in animal models CCR2, CCR5 and CXCR4 are up regulated in the primary sensory neurons along with adjacent non-neuronal cells following a peripheral nerve injury, thus lending support to the implication that the correlation between the increased

expression of CCR2 and CCR5 is directly related to HIV-SN [19]. Furthermore, inflammatory macrophages expressing CX3CR1 and T-cells expressing CCR2 and CCR5 may also participate in peripheral nerve damage leading to HIV-SN in HIV patients [24].

Correlation with CNS changes

Using structural magnetic resonance imaging, Holzinger et al. investigated the potential association between CNS changes and peripheral neuropathic pain in HIV patients. In a total of 241 HIV patients analyzed in this multisite cross-sectional study, the severity of peripheral neuropathic pain was found to correlate with smaller total cerebral cortical volumes. Specifically, HIV-SN was associated with decreased basal ganglion volumes, and severe distal sensory neuropathy was correlated with decreased total cerebral cortical volume [10]. Structural brain abnormalities are often observed with chronic pain from various etiologies; therefore, the decrease of cortical volume observed in HIV-SN patients is likely secondary to chronic pain rather than being specific to this condition [25].

Treatment of HIV neuropathy

Medical treatments (Table 2)

ART: Centner et al. studied the evolution of sensory neuropathy after ART in HIV-infected South Africans. Results indicated that painful symptoms improved during ART *via* reduction of exposure to HIV-induced oxidative stress. The authors suggested that sensory neuropathy was due to small and large fiber dysfunction, a finding that in agreement with other studies [26].

Table 2: Treatment of HIV neuropathy.

Treatment Categories	Examples
Recombinant human nerve growth factor (rhNGF)	Prosaptide, acetyl-L-carnitine
Medical	ART, pregabalin, amitriptyline, capsaicin
Interventional	Spinal cord stimulator
Alternative treatment	Self-hypnosis, marijuana, exercise, acupuncture, night splint, analyze translational therapies, moxibustion

The occurrence of neuropathy, as demonstrated in Obiako et al. in HIV patients as treated with highly active anti-retroviral therapy (HAART). They followed 566 patients with neuropathy symptoms who were on HAART from 2006 to 2013. The frequency of neuropathy decreased from 3.9% to 0.06%, further underscoring the beneficial effect of HAART on HIV neuropathy [27]. However, another study by Olajumoke et al. found that age (older than 40 years) and stavudine-based therapy were other independent predictors of HIV-SN. Gender, height, lower CD4 count, use of HAART and duration on HAART were not associated with increased risk [28]. Of note is that Obiako studied 5240 HIV patients as opposed to Olajumoke who studied 323 and Obiako made the distinction that late presentation, low $CD4^+$ cell counts and failure of patients to start HAART early were responsible for AIDS-related mortality thus highlighting the importance of early HIV screening and treatment [27].

Chen et al. investigated the prevalence of risk factors for peripheral neuropathy in ART-exposed patients, revealing that aging, taller hight, protease inhibitor use and female sex were significant risk factors for HIV-SN and the use of statin drugs was significantly associated with lower odds of HIV-SN [29]. ART-exposed patients who switched to new regimens due to virologic failure were found to have an increased risk of HIV-SN, probably because of a longer duration of infection, uncontrolled viremia and exposure to d4T, ddI and ddC [29]. On protease inhibitor use, a paper in 2008 by Ellis et al. evaluated current and past exposure to protease inhibitors in 1159 HIV-infected individuals in a large multicenter study and found that in univariate analyses both past and present protease inhibitor exposure significantly increased the risk of HIV-SN. However, after adjusting for previously validated concomitant risk factors in multivariate models, none of the protease inhibitor exposure groups were more likely to have HIV-SN than protease inhibitor naïve individuals. Thus, the researchers concluded that the independent risk attributable to protease inhibitors is negligible [30].

Similarly, Arenas-Pinto et al. studied a cohort of sub-Saharan African patients who failed a first-line treatment and were switched to second-line treatments. Based on the results, risk factors for peripheral neuropathy included female gender, age, plasma creatinine levels, and alcohol use disorder [31]. Although there was a decrease in the number of people affected with symptomatic peripheral neuropathy in those patients switched to a second-line treatment option, there was a higher number of asymptomatic cases in this group. This decrease in symptoms was thought to be due to improvement in general health because of the administration of second-line treatment. It was also noted that the risk of TB infection is higher in HIV-positive individuals, and the use of isoniazid for TB treatment poses an increased risk of neuropathy by decreasing the levels of bioactive pyridoxine. In a study by Dean et al. ART combined with anti-tuberculosis medications, mainly isoniazid, has been shown to increase the percentage of patients experiencing neuropathic pain with the researchers ultimately suggesting caution when prescribing multiple agents known to cause nerve damage in a predisposed population [32]. Another study by Van der Watt et al. showed the association of isoniazid use, pyridoxine levels and HIV-related neuropathy. A pyridoxine deficiency was seen in patients with a TB history and those with neuropathy before the initiation of ART. This underscored the need for adequate pyridoxine supplementation before the initiation of therapy, especially in patients with a history of TB [33].

Capsaicin: Treede et al. reported optimize treatment responses to the Capsaicin 8% cutaneous patch with localized neuropathic pain. When compared with patients with mononeuropathy, postherpetic neuralgia, cervical radiculopathy and back pain, HIV-SN patients had a higher response rate to the capsaicin 8% cutaneous patch. The rates at the first and fourth weeks of treatment were found to be similar, with a slight decrease during week 12. No difference was seen with or without lidocaine pre-treatment in pain responses and sustained efficacy was observed even during the

second treatment. Notably, patients with HIV-SN alone had over 30% greater response rates than HIV-SN patients with other polyneuropathies as well. This trend was seen along with every individual polyneuropathy, indicating that this effect is not isolated to HIV-SN, specifically [34].

A meta-analysis by Mou et al. on the response time with Qutenza (capsaicin) 8% patch use and the effect of multiple treatments on neuropathic pain found that among 801 HIV neuropathy patients studied, 41% noticed more than a 30% reduction in pain, while 7% noted complete pain relief within 2-12 weeks after the treatment. The mean response time was 6.5 days after the initiation of the treatment, with results lasting an average of 5 months post treatment [35].

In a meta-analysis by Katz et al. two important predictors for HIV neuropathy were found to be the female gender and a baseline pain intensity score of ≤ 4 and a McGill Pain Questionnaire (MPQ) of ≤ 22. Subgroups of patients with these factors responded better to Qutenza as compared to others and had superior pain control. Notably, the female sex appeared to be an excellent predictor of better outcomes in patients with HIV-SN, specifically, not postherpetic neuralgia (PHN). However, the researchers believed this could be an artifact since most HIV-SN patients in this study were males [36].

Given the use of topical capsaicin for treating chronic neuropathic pain from multiple pathologies, including HIV-SN, Derry et al. reviewed the use of high concentration topical capsaicin creams for the relief of chronic neuropathic pain. In two studies involving patients with HIV-SN, substantial pain relief was noted at the 2-12 week follow-ups. The authors concluded that high concentration topical capsaicin is helpful, but not a uniquely effective therapy for chronic pain: it can be useful, but its effects are similar to other treatments for chronic pain [37].

Pregabalin and amitriptyline: Simpson et al. conducted a randomized, double-blind, placebo-controlled clinical trial to study the safety and efficacy of pregabalin (flexible doses of 150-1600 mg/day) for the treatment of HIV neuropathy. This was later followed up with an open-label extension study. Data acquired at a preplanned interim analysis point was analyzed, and the results showed that there was no significant difference between the treatment arm and the placebo arm [38].

Dinat et al. conducted a double-blind crossover trial to study the effectiveness of amitriptyline at doses ranging from 25 to 150 mg in the treatment of moderate to severe HIV neuropathy in both ART-naïve patients and ART users. The results were equivocal, and no better pain control was seen in the amitriptyline group when compared to the placebo group at the dose ranges tested [39].

Gabapentin and HIV neuropathy: Gabapentin may improve pain and sleep disturbances caused by HIV-associated sensory neuropathy. In a randomized, double-blind placebo-controlled study, Hahn et al. reported that gabapentin was more effective than the placebo at reducing pain and sleep interference in patients with HIV-SN, though the study was performed on a small number of individuals [40]. Overall, gabapentin appeared to be well-tolerated, with no serious adverse events reported and somnolence being the most common side effect. Evidence of short-term pain relief with gabapentin was found with other types of neuropathic pain, while the data remains limited with HIV-associated neuropathy. Therefore, the effectiveness of gabapentin for patients with HIV-SN remains inconclusive [41].

Opioid-based analgesics: Krashin and Merrill studied the role of opioids in HIV-related pain. Given the side effects of opioids (including immunosuppression and risks of addiction and overdose) as well as the potential interaction of opioids and ARVs in which the latter can increase the metabolism of certain opioids (i.e., buprenorphine, methadone) and induce a withdrawal syndrome [42]. Given the limited benefits of chronic opioid therapy in patients with HIV-SN, alternative treatments are preferable. HIV-infected persons are more likely to have chronic pain and be treated with opioids more frequently. This population also has a higher incidence of psychiatric illness compared with the general population, placing them at increased risk for opioid use disorder [21].

IV immunoglobulin: Rosca et al. presented a case report of a 21-year-old patient with HIV presenting with a Guillain-Barre syndrome, which was responsive to IV immunoglobulin (IVIG). The presenting symptoms of limb paresthesia, pain and muscle weakness were significantly improved with this treatment. Additionally, a decrease in viral load and improved CD4 and CD8 cell counts were noted [43]. This case report provides the basis for further evaluation of the use of IVIG in the treatment of demyelinating neuropathy in HIV patients. A pilot study by Cikurel et al. of 17 patients with HIV-SN in which each was treated with two IVIG infusion per day for a 56-day study period found improvements in strength that reached statistical significance by 28 days [44].

Interventional treatments: Two cases of severe refractory HIV neuropathic pain treated using spinal cord stimulation (SCS) were reported by Knezevic et al. After an initial trial period of spinal cord stimulation with positive results, both patients underwent a more permanent SCS procedure, after which they reported a 90% improvement in pain levels. Importantly, this led to a reduction in their use of oral opioid analgesics, indicating that this is a therapy that could reduce the risk of opioid addiction in HIV-SN patients [45]. Abd-Elsayed et al. reported three chronic peripheral neuropathy cases resistant to various conservative methods which were treated by SCS. One of these was a 60-year old HIV patient with chronic neuropathy. With a baseline visual analog scale (VAS) pain scores of 9/10, the patient improved to a VAS score of 4-10/10 with the intrathecal drug delivery system. However, with a trial of SCS, the patient reported 95% pain relief [46]. No data was available for permanent SCS implantation as the procedure was postponed due to the patient's other co-morbidities.

Scrambler therapy, a device that was approved by the FDA in 2009, causes transcutaneous electrical nerve stimulation to help chronic neuropathic pain. A case report by Smith

et al. focusing on the use of scrambler therapy to treat HIV neuropathy showed promising results. With a single treatment of scrambler therapy, a 52-year-old HIV positive patient with a long-standing history of debilitating neuropathy showed a rapid improvement in pain levels that lasted almost six months. Thereafter, a follow-up treatment session was necessary to sustain positive results [47].

Potential roles of nutraceuticals in treating HIV neuropathy

Curcumin: Evidence supports the association of food derivatives such as curcumin, bromelain from pineapple and tart cherry, in part *via* their anti-nociceptive, anti-free radical, and anti-inflammatory mechanisms. Zhu and Li investigated the anti-nociceptive role of curcumin in the chronic constriction injury (CCI) rat model of neuropathic pain, as well as the effect of curcumin on P300/CBP HAT activity-regulated release of the pro-nociceptive molecules, brain-derived neurotrophic factor (BDNF) and cyclooxygenase-2 (Cox-2). The effect of curcumin use on CCI-induced thermal hyperalgesia and mechanical allodynia was significant at doses of 40 and 60 mg/kg after seven consecutive days. In contrast, no significant analgesic effect was seen at the lower dose of 20 mg/kg. This dose-dependent effect with curcumin reduced promoter activity of BDNF and Cox-2 genes. The results indicated that curcumin exerted a therapeutic role in neuropathic pain by down-regulating p300/CBP HAT activity-mediated gene expression of BDNF and Cox-2 [48].

Bromelain: Brien et al. reviewed clinical studies on bromelain as a treatment for osteoarthritis, which found potential for trials to establish the efficacy and optimum dosage of bromelain in neuropathic pain and other inflammatory conditions [49]. A CCI neuropathic study by Bakare et al. found that bromelain mitigated neuropathic pain by enhancing the activities of nuclear transcription factors NrF-1 and NrF-2, therefore increasing the antioxidant defense system, reducing neuronal stress and structural disorganization [50].

Tart cherry extracts: The effect of tart cherry on reducing inflammatory and ROS signaling in HAPI rat microglial cells was reported by Hale et al. Pre-treatment with tart cherry decreased levels of NO, TNF-alpha and COX-2 in a dose- and time-dependent manner [51]. Carson et al. conducted a study on 12 patients with neuropathy, in which a 2-week course of tart cherry juice significantly improved non-diabetic peripheral neuropathy in the majority of patients [52]. These results favor the use of tart cherry extract as a recommended dietary supplement for those with HIV-SN.

Other alternative treatment approaches: The efficacy of hypnosis on symptom management of HIV neuropathy has been reported by Dorfman et al. Thirty-six patients volunteered for the study and were followed before, during and after a treatment intervention involving three weekly training sessions in self-hypnosis. Mean Short-Form McGill Pain Questionnaire Scale (SFMPQ) scores dropped from 17.8 to 13.2 after the treatment and continued to decline during the 7-week follow-up period [53]. Of note, all patients continued to use their regular pain medications throughout the study period.

Earlier studies in non-HIV patients showed some salutary effects of acupuncture (AC) for non-HIV neuropathy, but it is unclear if similar findings apply to HIV patients. A controlled, randomized trial by Urisini et al. provided the first evidence of a potential role for AC in the treatment of acute herpetic pain [54]. AC has been showed to decrease the pain score and muscle strength in post-zoster limb pain and paresis in shingles [55]. Lastly, Mishra et al. described a case of persistent, recurring trigeminal neuralgia in an octogenarian that was resistant to medical therapy but showed a sustained clinical response to AC [56]. Positive outcomes for AC in distinct neuropathies bodes well for its eventual clinical use and, pending validation through further research, a broader scope of potential treatment options for many neuropathies, including HIV-SN.

A randomized control pilot study by Anastasia et al. analyzed translational therapies, Acupuncture and Moxibustion as treatment options for HIV-SN. The study participants selected had a moderate level of distal sensory neuropathy. The pain in the Acu/Moxa group decreased by two pain levels after six weeks of the treatment period and decreased by three pain levels at a 15-week follow-up. The sham/placebo group noticed a pain reduction of one level after the 6-week treatment period [57].

Medical marijuana: Medical marijuana has long been used for relief from chronic pain. However, there are legal as well as ethical issues regarding the recommendation of marijuana for HIV neuropathy. In addition to working within legal constraints, physicians are ethically obliged to discuss with the patient about marijuana-associated risks and look for any substance abuse in the patient's history [58].

Smoked cannabis reduced daily pain by 34% and was well tolerated and effective at relieving chronic pain from HIV-SN in a way comparable to oral drugs used for chronic neuropathic pain [59]. A single inhalation of 25 mg of 9.4% tetrahydrocannabinol (THC) herbal cannabis three times daily for five days also reduced pain intensity as well as improved sleep [60]. THC taken four times per day for five days relieves more pain than the placebo and that proportions of subjects achieving at least 30% pain relief with cannabis versus placebo [61]. Smoked cannabis was generally well-tolerated and effective in combination with concordant analgesic therapy in patients with HIV-SN [61].

Cannabidiol oil has been used trans dermally for painful peripheral neuropathies; however, no clinical trials are available in HV-SN at the time of this writing. In a trial of 29 patients with painful peripheral neuropathy, 15 patients were randomized to the CBD group with the treatment product containing 250 mg CBD/3 fl. oz and 14 patients were randomized to the placebo group. The authors concluded that transdermal application of CBD oil resulted in significant improvement in pain and paresthesias in patients with symptomatic peripheral neuropathy [62]. A prospective randomized placebo-control trial involving adults with HIV-SN by Di et al. in which patients were randomly assigned to smoke cannabis or placebo cigarettes three times daily for five

days revealed a reducing in daily pain by 34% in the cannabis group compared to the placebo. Interestingly, in 72% of the patients that smoked their first cannabis cigarette the chronic pain from HIV-SN was reduced. This is compared to a 15% incidence of pain reduction in the placebo group. Cannabis also reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli, but had no effect on heat-induced pain [59].

In conclusion, the use of cannabis, or its derivatives, such as dronabinol, has been studied in patients with HIV/AIDS, not only for pain but also for weight increase and mood disorders. The few trials available are of low quality or too small to draw definitive conclusions at this time on HIV-SN beyond compassionate use in selected cases. However, the data are encouraging and warrants further research.

Progressive resistive exercise (PRE): A systematic review and meta-analysis of the effects of PRE on HIV-SN by O'Brien et al. suggested that PRE contributed to improved strength and psychological status in those that continued to exercise [63]. Numbness, pain and a decrease in muscle strength are often associated with HIV neuropathy and Mkandla et al. elucidated the effect of PRE on improvement in muscle strength and an overall increase in the quality of life. A bi-weekly exercise regimen for 12 weeks showed a significant improvement in the health-related quality of life in HIV patients with symptoms of HIV-SN [64]. However, there is insufficient evidence currently available to develop appropriate clinical practice guidelines for the management of HIV-SN in terms of strength training.

Discussion and Summary

Due to the increased life expectancy of HIV since the introduction of anti-retroviral treatment, the incidence of HIV-SN is currently seen in 30-60% of individuals with HIV [65, 66]. Of the biomarkers stated in table 1, gp120 has been addressed in multiple studies as have mitochondrial uncoupling protein alleles, inflammatory cytokines such as IL1R-antagonist, IL-2, TNF receptor II levels, CSF neopterin, blood neopterin and CSF monocyte chemo attractant protein (MCP)-1. The confirmation of these objective biomarkers of HIV-SN provides a current framework for diagnosis and future treatment of HIV-SN. Ideally, clinicians should engage in therapies for HIV-SN consistent with that individual patient's precise mechanism of pathology. This means that HIV-SN should be thought of as one broad condition with numerous, oftentimes overlapping, pathophysiologies. Each unique cause would therefore require a unique catered treatment ascertained by the physician. Unfortunately, this complex trial-and-error clinical intervention is a consequence of an unreached definitive consensus on the full scope of the underlying pathophysiology of the condition.

An additional challenge clinician's face is navigating the treatment of the viral infection in such a way that reduces the likelihood of HIV-SN without risking a further progression of the disease itself. There is a clear association between the increased occurrence of neuropathy and the use of specific anti-retroviral therapies like stavudine. Clinicians should be careful during the transition of a patient from ART to a new regimen, as this will increase their patient's likelihood of developing or worsening HIV-SN. Early initiation of treatment with HAART reduces the occurrence and severity of HIV neuropathy. Given the susceptibility of HIV patients to TB infection, there is also an increased risk of neuropathy due to the decreased levels of pyridoxine caused by isoniazid treatment, so pyridoxine supplementation should be used with patients at risk for HIV-SN especially if they have a history of TB. Curcumin, broelain and tart cherry extract containing foods, if not contraindicated by another concurrent medical condition, are safe and potentially helpful for patients with HIV-SN. Patients should also be encouraged to exercise. Additionally, if legal, physicians should keep in mind the increasing research supporting inhaled medical marijuana as a treatment of the symptoms of HIV-SN [33, 58, 59, 60].

Treatments that require further investigation include SCS, gabapentin, IVIG and alternative treatments such as hypnosis, acupuncture, and moxibustion. Thus, further studies based on the pathophysiological aspects of HIV neuropathy are needed to discover more effective treatment choices for such a debilitating complication of the disease.

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