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Assessment and Management of HIV Distal Sensory Peripheral Neuropathy: Understanding the Symptoms

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Abstract

Distal sensory peripheral neuropathy (HIV-DSP) affects upwards of 50% of people living with HIV. Causing often debilitating symptoms of tingling, numbness and burning, HIV-DSP can result in disability, unemployment and low quality of life. Comorbidities further complicate nursing care, heightening risk of polypharmacy and symptom exacerbation. Therefore, a neurological sensory assessment, combined with the patient's self-report of symptoms, can help nurse practitioners visualize, quantify and understand symptoms. Common pharmacological interventions include antiepileptics, antidepressants, analgesics and medical marijuana. The complexity of care for individuals with HIV-DSP merits a comprehensive approach. Implications for practice include interdisciplinary management with neurologists, podiatrists, mental health providers, and nurse-led counseling inclusive of patient safety teaching.

Keywords

HIV; AIDS; distal sensory peripheral neuropathy (HIV-DSP); people living with HIV/AIDs (PLWH); neuropathy assessment; complementary therapy; chronic pain management; polypharmacy; comorbidity

Distal sensory peripheral neuropathy (HIV-DSP)* is one of the most debilitating and common HIV complications, rendering unique healthcare needs for people living with HIV (PLWH). Upwards of 50% of PLWH experience associated symptoms of *stabbing, numbness* and *burning* (Schütz SG, Robinson-Papp, 2013), often resulting in disability, unemployment and decreased quality of life (Ellis et al., 2010). Challenges in combining essential medications, including combination antiretroviral therapy (cART) and medicine for comorbidities, render polypharmacy a serious concern for nurse practitioners (NPs) treating

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*HIV-DSP, also known as HIV-Associated Sensory Neuropathy, refers to neuropathy attributable to HIV itself and/or some HIV treatments. The term 'HIV-DSP' will be used in this manuscript and focus on lower extremity pain and associated symptoms.

PLWH (Cherry, Wadley, Kamerman, 2016). There are no U.S. Food, Drug Administration (FDA) approved medications, and their side effects, such as insomnia, drowsiness and rash, may outweigh the benefits of HIV-DSP relief. Recent reports indicate a patient-centered approach, with integrative care, accounting for the comorbidity burden (Clinical Research, 2019).

HIV-DSP management can fall by the wayside in clinical care as the pressing nature of illnesses, like diabetes and cardiovascular disease, pose a more immediate risk for PLWH. However, HIV-DSP strongly effects quality of life, making it an important aspect of clinical practice. This article aims to outline how HIV-DSP presents in patients, including influence of comorbidities on the pain experience; assessment tools to characterize the phenotype of HIV-DSP; limitations of current pain management strategies; and interdisciplinary pain management with patient safety approaches.

PREVALENCE AND RISK FACTORS

Most common risk factors for HIV-DSP are low CD4 count and past dideoxynucleoside analogues “d-drug” use, such as stavudine, didanosine and zalcitabine (Ellis et al., 2010). Subsequent viral suppression, immune recovery and d-drug termination often do not decrease neurological effects of HIV-DSP (Cashman, Höke, 2015; Phillips et al., 2010). Other risk factors include psychosocial influences, substance abuse, tuberculosis medications, nutritional deficiencies, advanced age, cART and non-communicable conditions (Nicholas et al., 2014). Psychosocial influences undermine health and pain management in HIV: depression, stress, feelings of helplessness and anxiety predicate chronic pain and disability (Lerman et al., 2015). Certain risk factors also influence each other to compound HIV-DSP risk. Substance abuse, a common maladaptive coping mechanism in HIV-DSP (Hernandez et al., 2018), as well as the disease process and tuberculosis medications, can cause nutrition deficits that further increase neurological symptom risk (Nicholas et al., 2014).

Advanced age, cART and non-communicable comorbidities can also influence health outcomes. Improvements in cART extend the life expectancy of PLWH, causing comorbid conditions to supersede the historic emphasis on opportunistic infections. Certain cARTs also cause metabolic disruptions, such as hyperlipidemia, hyperglycemia and lipodystrophy, which increase risk of developing diabetes (Hernandez et al., 2018). Eighty-four percent of HIV positive individuals are predicted to have at least one diagnosed non-communicable disease in 2030, compared to 29% in 2010 (Smit et al., 2015).

Diabetes and cardiovascular disease are the two most prevalent comorbidities that complicate HIV-DSP (Smit et al., 2015). Diabetes accounts for 10-15% of PLWH (Zuniga et al., 2017) and increases risk for blindness, neuropathy, cardiovascular disease and nephropathy (Hernandez et al., 2018). Also, as cardiovascular disease and its associated medications are predicted to be the bulk of the non-communicable illnesses and prescriptions (78% in 2030) among PLWH, drug interactions and contraindications with HIV medication will further limit traditional pharmaceutical pain management options and

necessitate the exploration of a wider range of complementary disciplines for pain management (Smit et al., 2015).

PATHOGENESIS

In most cases of HIV-DSP, the distal axons and small unmyelinated sensory fibers, followed by the large myelinated sensory fibers, degenerate and die (Dorsey, Gonce Morton, 2006). The primary cause of pain is due to peripheral ascending nerve damage and secondarily, to central descending nerve damage. Primarily, injury to ascending sensory neurons causes them to become more excitable and send sharp *burning* or *tingling* sensations (Schütz SG, Robinson-Papp, 2013) from hyperalgesia up the feet and legs (Dorsey, Gonce Morton, 2006). Secondarily, a memory of the sensation likely develops in the brainstem, which causes a chronic effect that can last for years (Dorsey, Gonce Morton, 2006). The descending pathway from the cortex and through the brainstem controls pain by balancing excitatory and inhibitory output. The imbalance between increased excitatory output and decreased inhibitory output causes more pain and less analgesia (Starkweather et al., 2016).

CLINICAL PRESENTATION

Patients with HIV-DSP experience paresthesia and dysesthesias- described as *burning, aching, shooting,* or *numbness* (Ellis et al., 2010). Symptoms start from the peripheries and move up the toes, feet, ankles and legs, bilaterally (Schütz SG, Robinson-Papp, 2013). Clinical findings show no impact on muscle strength, depressed or absent bilateral ankle reflexes and decreased pinprick/vibration sensation in the proximal limb (Schütz SG, Robinson-Papp, 2013). Patients risk imbalance and falls, as well as trouble dressing, walking and other activities of daily living (ADLs) (Kwong et al., 2019). This can affect quality of life, encumbering emotional health, employment and independence (Kwong et al., 2019). Some overlapping symptoms in diabetes and HIV neuropathy include muscle aches, fatigue and sleep disturbance (Zuniga et al., 2017). Overlapping symptoms are important to note, as complex pain presentation can influence clinical diagnosis and management in practice.

DIAGNOSIS

While there is no gold standard for diagnosis, pain management starts with a comprehensive assessment to develop a phenotype of symptoms. The assessment should honor the complexity of PLWH care and include psychosocial, medication, metabolic and functional influences, to capture the nuances of daily pain and discomfort (Bruce et al., 2017). Psychosocial assessment includes substance abuse, depression and stress as they show a positive correlation with neuropathy intensity (Lerman et al., 2015). Patient history may also reveal past medication use, including d-drugs, dapsone, metronidazole, isoniazid, vincristine, pyridoxine and thalidomide (Nicholas et al., 2007). Blood work eliminates other neuropathy causes, such as glucose intolerance, diabetes, B12 deficiency and thyroid dysfunction (Gonzalez-Duarte, Robinson-Papp, Simpson, 2008). Metabolic comorbidities that might exacerbate HIV-DSP symptoms necessitate additional evaluation and monitoring, or medication adjustments (Bruce et al., 2017). Patient reported symptoms may reveal debilitating pain or discomfort that limit function and ADLs (Kwong et al., 2019).

Patients may report a sensation in their feet that can be so intense that they "can hardly walk" (Nicholas et al., 2014), or *searing* pain when feet contact socks, bedsheets, or other non-noxious stimuli (Dorsey, Gonce Morton, 2006). Other reported sensations include "*pins and needles", burning, shooting, stocking-glove-like* sensation and *numbness*, as well as *stabbing, aching, cramping* and *tingling* (Schütz SG, Robinson-Papp, 2013; Ellis et al., 2010). Sleep disturbances, fatigue and drowsiness are also reported in HIV-DSP (Sandoval et al, 2014). A record of the patient report and subsequent patient-centered outcomes helps the clinician understand the symptoms and diagnose HIV-DSP.

Patient Report Instruments

Patient report instruments may help the clinician visualize or quantify data to see it in different dimensions. The Visual Analog Scale (VAS) is a quick and easy horizontal numerical instrument with two descriptors- *no pain* at zero and *worst pain imaginable* at ten (Zhou et al., 2007). Because it does not capture the nuances of the patient report, more descriptive instruments can accompany the VAS. Some reliable and valid instruments include the Gracely Pain Scale (GPS), Sensory Peripheral Neuropathy Screen (SPNS), Patient-Reported Outcomes Measurement Information System (PROMIS) and body pain map, discussed below.

The Gracely Pain Scale (GPS) uses a 13-point Likert style scale of sensory components that capture the worst and average pain in a 24-hour period (Gracely, McGrath, Dubner, 1978). Pain descriptors accompany the 13 levels of pain intensity. These include: (=1) *nothing,* (=2) *faint,* (=3) *very weak,* (=4) *weak,* (=5) *very mild,* (=6) *mild,* (=7) *moderate,* (=8) *barely strong,* (=9) *slightly intense,* (=10) *strong,* (=11) *intense,* (=12) *very intense* and (=13) *extremely intense* (McArthur et al., 2000). Cost-effective and easy to use, it is a popular HIV-DSP instrument: out of 13 RCTs with parallel designs in a meta-analysis, six used the GPS (while the rest used either a numerical rating, VAS, or descriptive differential scale) (Phillips et al., 2010).

The Sensory Peripheral Neuropathy Screen (SPNS) is a self-reporting sensory neuropathy instrument that has been used to evaluate AIDS patients by the NIH/NIAID AIDS Clinical Trials Group. Subjects describe symptom type (*aching/burning*, "*pins and needles*", *numbness*), location (hands/arms, feet/legs) and symptom severity on a 10-point scale (McArthur, 1998). Two sub scores are computed: the Average Severity Score, using the mean, and the Clinical Severity Grade, based on the highest symptom severity score of any symptom (McArthur, 1998).

The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity short form is universal, rather than disease-specific. It is recommended to assess pain severity and functional ability, rather than pain type (Cella et al., 2010). The instrument asks three Likert scale questions: *1. In the last 7 days- how intense was your pain at its worst? 2. In the last 7 days- how intense was your average pain?* And *3. What is your level of pain right now?* (NIH, 2019). The three questions are scored from *none* (=1), *mild* (=2), *moderate* (=3), *severe* (=4), to *very severe* (=5). Evidence shows that PROMIS is available to the public to encourage further validation of the tool across patient populations (Cella et al., 2010).

Body pain maps offer patients a visual instrument to identify and quantify their pain (van den Hoven, Gorter, Picavet, 2010). Patients report the location, frequency, duration and intensity of five HIV-DSP sensations: *aching, burning, cold, numbness* and *"pins and needles"* on a body map (Anastasi, Capili, Chung, Hammerschlag, 2010).

Neurological Evaluation/ Neurological Sensory Tests

A neurological evaluation, combined with the patient's self-report of pain, provides a comprehensive summary for practitioners. The standard neurological evaluation is comprised of a review of systems, physical exam and an assessment of motor and neurological sensory testing (NST) responses. NST focuses on lower limb assessments, including muscle strength, reflexes, and quantitative sensory testing for lower limb vibration, temperature and pain threshold. Instruments, including the Semmes-Weinstein monofilament, von Frey hairs and Rydel-Seiffer tuning fork, assess functionality of central pathways, as well as large and small nerve fibers in sensory perception (Starkweather et al., 2016).

The Semmes-Weinstein monofilament is a convenient and economical test for touch sensation. A 10-gram monofilament is applied to the test site until it buckles, then the patient states if they can feel the sensation (Feng, Schlösser, Sumpio, 2009). Assessing the plantar portion of the great toe, third metatarsal and fifth metatarsal produced 57-93% sensitivity, 75-100% specificity and 84-100% positive predictive value (PPV) (Feng, Schlösser, Sumpio, 2009).

Von Frey hairs are graded monofilaments that offer a more detailed image of sensation. The nylon hairs are applied from thinnest (0.026 g) to thickest (110 g) with enough pressure to buckle the hair (Moharic, Vidmar, Burger 2012). Von Frey hairs exhibited 37-79% sensitivity and 65-85% specificity against nerve conduction studies (Moharic, Vidmar, Burger 2012).

A Rydel-Seiffer tuning fork is placed on the skin, commonly at 64 or 128 Hz, to test for vibratory sensation. The clinician asks when the patient no longer feels vibration and records the finding on an 8-point scale (Starkweather et al., 2016). Measured at the tip of both great toes, the Rydel-Seiffer tuning fork exhibited 96% sensitivity, 45% specificity and 97% PPV (Kästenbauer et l., 2004).

Specialized and Exploratory Neurological Sensory Tests

Specialized NSTs can be used for more sensitive measures of neurological function, primarily for research purposes. While more invasive, skin biopsies may offer a detailed picture of nerve fibers on the surface of the skin. Also, exploratory research has been conducted on biomarkers, showing promise for clinical practice in the future. Outlined below are three specialized NSTs: the Medoc Pathway System, skin biopsy and biomarkers.

The Medoc Pathway System is a sophisticated specialized sensory testing computer technology that helps evaluate neuropathic sensory deficits with temperature settings. The clinician assesses sensation threshold by placing a Medoc thermode on the surface of the skin and telling the patient to press a button when they begin to feel sensation, then when it

begins to hurt (Starkweather et al., 2016). This allows the clinician to determine the vibration and pain threshold of small sensory fibers to cold, warm and hot temperatures (Starkweather et al., 2016).

Skin biopsy is a more invasive procedure that visualizes small unmyelinated nerve C fibers and quantifies epidural nerve fiber density (Zhou et al., 2007). A sensitive diagnostic instrument, skin biopsy can identify epidural denervation, regardless of symptom presentation: low nerve fiber density, of less than 11 fibers per millimeter, indicates the likelihood of developing symptoms within six to 12 months in asymptomatic patients (Gonzalez-Duarte, Robinson-Papp, Simpson, 2008). Skin biopsy appears more sensitive in identifying small C-fiber nerve damage, but not large fiber nerve damage, suggesting that it should be combined with an instrument for identifying myelinated large nerve fibers, if used (Zhou et al., 2007).

Biomarkers include cytokines, found at wound and infection locations, direct inflammatory and anti-inflammatory immune reactions (Page et al., 2018). While cytokine levels have been reportedly measured via urine and saliva, they are typically found in serum and plasma (Page et al., 2018). The ratio of pro-inflammatory and anti-inflammatory cytokines can provide a sensitive measure of the body's equilibrium (Page et al., 2018). Substance P, inflammatory cytokine interleukin and multiple proteins express differently between inflammatory and non-inflammatory neuropathy (Marchi et al., 2009). A nonsteroidal anti-inflammatory drug (NSAID) was observed to prevent the increase of inflammatory-associated proteins for inflammatory neuropathy (Marchi et al., 2009). These findings indicate biomarkers can potentially help distinguish different types of neuropathy and the treatments most effective for them.

One or more of these instruments can help the clinician to better document and communicate the patient's experience with HIV-DSP. A thorough description of pain with visual and quantitative data will help treatment and management.

TREATMENT

While clinicians have focused largely on pharmaceutical interventions, including NSAIDs, tricyclic antidepressants, opioids, antiepileptics and topical anesthetics, evidence shows minimal reduction of pain associated with HIV-DSP (Phillips et al., 2010). Furthermore, there are no FDA approved medications to treat HIV-DSP and the negative side effects of medication can outweigh the benefits. Marijuana, topical capsaicin and recombinant human nerve growth factor (rhNGF) effectively relieved pain (Phillips et al., 2010). Although legal limitations interdict marijuana prescription, a subsequent report found capsaicin ineffective and rhNGF is no longer being produced for HIV-DSP pain relief, making it clinically unavailable (Phillips et al., 2010).

Some preliminary evidence supports the use of non-pharmacological complementary therapies for pain or discomfort associated with HIV-DSP (Cherry, Wadley, Kamerman, 2016). As pharmaceuticals account for the majority of treatment costs in PLWH (Zingmond et al., 2017), complementary therapies may be a cost-effective option. Out of 19 pain

management modalities reported by PLWH, complementary therapies made up the bulk of the most effective treatments rated by patients; the six highest ranked interventions for patients, on a scale of 1 to 10, included reflexology (7.53), meditation (7.08), prescribed antiepileptics (6.85), massage (6.84), marijuana (6.82) and acupuncture (6.81) (Nicholas et al., 2007).

In a recent meta-analysis, acupuncture appeared to reduce HIV-DSP symptoms 8 weeks and 14 weeks after treatment (Dimitrova, Murchison, Oken, 2017), compared to the antiepileptic gabapentin, which appeared ineffective after four weeks of use (Phillips et al., 2010). Along with these complementary therapies, NPs can recommend CBT, which can assist in developing coping mechanisms and reducing maladaptive behaviors in pain management (Bruce et al., 2017). Pain treatment and subsequent follow up, are accompanied by safety and ADL care in HIV-DSP care and management.

MANAGEMENT

Follow up measures are crucial to the patient assessment, as the chronicity of HIV-DSP requires repeat intervention (Phillips et al., 2010). Collaboration may involve neurologists, infectious disease colleagues, podiatrists, social workers (including mental health professionals) and occupational therapists. Management includes regularly assessing and providing foot care, day-to-day advice and interdisciplinary engagement.

Foot care should be included in clinical management, as protective utility decreases in HIV-DSP, elevating risk of infection and falls (Kwong et al., 2019). NPs are critical in patient education regarding hygiene, proper footwear and fall prevention. While little research has been conducted specifically on HIV-DSP, diabetes foot care, which is ubiquitous in diabetic neuropathy nursing care, can be applied to HIV-DSP (Anastasi, Capili, Chang, 2013). The CDC (2014) recommends performing daily foot hygiene with warm (not hot) water, mild soap and light (not heavy or oily) lotion. NPs should instruct patients to evaluate their feet daily for cuts, scrapes, bruises, blisters, cracks and calluses (Chapman, 2017). If patients are unable to perform foot care themselves, NPs can refer them to a podiatrist (CDC, 2014). Patients should wear socks and wide footwear (avoiding sandals or walking barefoot) with breathable material that does not create pressure or moisture (CDC, 2014). Footwear that fits well is also important for gait and fall prevention; a cane can be encouraged if a patient stumbles often (Anastasi, Capili, Chang, 2013). To decrease fall risk, NPs can recommend installing no-slip bath mats, keeping a flashlight near the bed and removing clutter (Anastasi, Capili, Chang, 2013).

Day-to-day advice includes healthy eating recommendations, travel tips, clinical trials and advocacy opportunities. NPs can offer travel advice, for instance, like arranging for an airplane seat with extra leg room to stretch out (Foundation for Peripheral Neuropathy [FPN], 2019). Patients should plan ahead and organize lodging with clear pathways and comfortable seating, as well as destinations that cater to individuals with similar disabilities (FPN, 2019). NPs should consider resources available to their patients, such as smartphone applications, senior center activities and social support groups (FPN, 2019), as well as interdisciplinary practice.

Interdisciplinary engagement can enhance quality of life: NPs can make referrals to specialists depending on patient needs, including safety, mental health and pain management. Communicating with colleagues, such as podiatrists and neurologists, can help to decrease polypharmacy and streamline patient care. The incorporation of mental health services in HIV care has been shown to increase care retention in patients with depression and mental health diagnoses; furthermore, acceptance and feelings of self-efficacy are associated with a decrease in pain symptoms (Lucey et al., 2011). NPs should pay special attention to alcohol use, as it complicates neuropathy, depression and nutrition (Hernandez et al., 2018). An integrative approach may include nurse-led motivational counseling, self-help groups and community-based rehabilitation (Mahajan et al., 2008). Other resources include CBT, massage therapy, community meditation and acupuncture and reflexology clinics.

CONCLUSION

HIV-DSP is often a lasting burden for patients that must be managed throughout life. PLWH are getting older, resulting in comorbidities becoming the forefront of care, compounding pain symptoms and complicating treatment. NPs are instrumental in providing and coordinating ongoing care. Patient report instruments and NSTs can help the patient communicate and document progress or decline of pain. NPs can include safety measures, regular pain reassessment and integrative care aimed to relieve symptom burden and improve quality of life for patients, based on individual goals.

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HIGHLIGHTS

Distal sensory peripheral neuropathy (HIV-DSP) is one of the most common and debilitating neurologic HIV complications for people living with HIV (PLWH)

- HIV-DSP effects more than 50% of PLWH
- Symptoms include *stabbing, numbness* and *burning* sensation in lower extremities
- There are no U.S. Food, Drug Administration (FDA) approved medications for HIV-DSP
- HIV-DSP may result in disability, unemployment and impaired quality of life
- HIV and comorbidity medications cause a polypharmacy risk
- Some cARTs cause metabolic disruptions that increase diabetes risk
- The prevalence of PLWH with at least one comorbidity is predicted to be 84% in 2030
- Patient's self-report of symptoms and practitioner's neurological evaluations are essential
- Managing neuropathic pain and its sequelae requires interdisciplinary collaboration
- Management includes knowledge of polypharmacy, foot care and safety approaches

Table 1.

Pharmacologic and Non-Pharmacologic Therapies

Pharmacologic Therapies	Early initiation of cART/neurotoxic medication discontinuation
	Antiepileptics: gabapentin, pregabalin, lamotrigine
	Antidepressants: duloxetine, amitriptyline
	Medical marijuana
	Topical anesthetics: capsaicin, lidocaine
	Analgesics: NSAIDs, acetaminophen
	rhNGF
	2nd line for moderate/severe pain: time-limited opioid prescription
Non Pharmacologic Therapies	Cognitive behavioral therapy (CBT)
	Acupuncture
	Hypnosis
	Physical/occupational therapy
	Massage
	Meditation
	Physical/occupational therapy
	Reflexology
Nicholas et al., 2007;Bruce et al., 2017; Schütz SG, Robinson-Papp, 2013	