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HIV Peripheral Neuropathy and Foot Care Management: A Review of Assessment and Relevant Guidelines:

The importance of addressing this frequently overlooked aspect of HIV care.

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OVERVIEW:

Despite the decline in the incidence of central nervous system disease associated with HIV, distal sensory peripheral (DSP) neuropathy continues to be prevalent in this population, causing debilitating symptoms and affecting quality of life. Patients typically present with numbness, tingling, burning pain, and loss of sensation in the toes and soles of their feet. Although this complication causes loss of protective function and puts patients at elevated risk for injury, infection, and falls, foot care for people with HIV is often overlooked. This article reviews what is known about DSP neuropathy in HIV and discusses relevant foot care guidelines, adopted from the literature on other conditions associated with neuropathic foot disorders.

Keywords

distal sensory peripheral neuropathy; foot care; HIV; peripheral neuropathy

Peripheral neuropathy, a condition characterized by damaged sensory or motor peripheral nerves, may cause pain, sensory loss, or muscle weakness. Peripheral neuropathy may develop as a result of diabetes, physical injury, tumors, certain medications, heavy alcohol use, certain inherited disorders, autoimmune disease, vitamin deficiencies, and such infectious diseases as HIV.[1] The prevalence of distal sensory peripheral (DSP) neuropathy (often referred to as distal symmetric polyneuropathy or distal sensory polyneuropathy) in HIV patients is estimated to range from 38% to 44%.[2, 3]

Presenting symptoms of DSP neuropathy in HIV typically include bilateral and symmetric tingling, burning, or loss of feeling in the toes and soles of the feet. Symptoms tend to start at the toes and travel up the feet to the ankles and, eventually, to the lower legs, a pattern known as a “stocking” distribution. Common signs include decreased or absent ankle reflexes, impaired pain and temperature perception, reduced or absent vibration sensation in the toes, and occasional intrinsic muscle weakness.[4, 5] Patients may experience loss of

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balance, leading to falls, or have difficulty walking, bathing, or dressing. The symptoms can cause extreme discomfort, affecting employment, emotional health, independence, and quality of life.[2]

Foot care for people living with HIV is often overlooked as a clinical issue. HIV interferes with the body's immune system, increasing the risk of acquiring infections. Decreased sensation in the feet may lead to injuries and infections that go unnoticed. Tinea pedis (athlete's foot, a fungal infection that causes itching, scaling, blistering, and fissuring of the skin of the feet), onychomycosis (a fungal infection of the nail), and paronychia (a fungal or bacterial infection of the skin at the edge of the nail) frequently affect people who are immunocompromised and thus more prone to developing secondary systemic infections.[6–8] In one study, the prevalence of onychomycosis among 500 people with HIV was 23%.[7] Both onychomycosis and tinea pedis may lead to lower-extremity bacterial cellulitis.

For patients with diabetes, foot care guidelines and educational materials are ubiquitous. Although there are no specific foot care recommendations for people living with HIV, many of the principles guiding the care of patients with diabetes or cancer apply to this population as well. In this article, we integrate what is currently known about DSP neuropathy in HIV patients with the relevant guidelines for the management of other conditions that similarly render patients susceptible to neuropathic foot disorders.

PATHOPHYSIOLOGY

DSP neuropathy may be associated with the HIV infection itself or with antiretroviral toxicity. The condition is believed to be linked to axonal injury resulting from the binding of the viral envelope glyco-protein 120 to chemokine receptors and to macrophage dysregulation, which prompts the local release of proinflammatory neurotoxic cytokines.[9, 10] The drug-associated neuropathies may be mediated by disrupted DNA synthesis, which interferes with mitochondrial function.[11] With antiretroviral toxicity, symptom onset tends to be sudden and associated with the start of antiretroviral therapy (ART), usually peaking within the first three months of treatment.[12, 13]

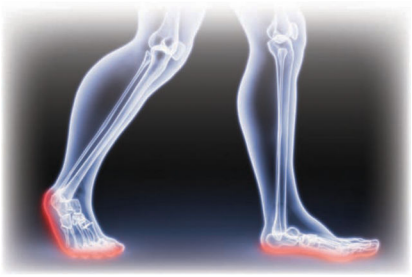
RISK FACTORS

Several factors increase the risk that people with HIV will develop DSP neuropathy and associated foot problems. These include past or current use of neurotoxic drugs, advanced age, metabolic disorders, alcohol use, nutritional deficiencies, and a low $CD4^+$ count.

Neurotoxic drugs.

Some nucleoside reverse transcriptase inhibitors (NRTIs) are associated with neuropathy.[14, 15] Because they inhibit mitochondrial DNA polymerase gamma, a key enzyme in mitochondrial replication, NRTIs may cause mitochondrial dysfunction, oxidative stress, increased production of free radicals, and tissue injury and toxicity—although other mechanisms likely contribute to the development of DSP neuropathy as well.[16, 17] For example, infiltrating activated macrophages, proinflammatory cytokines, and other mediators may play a role in damaging peripheral nerve axons and dorsal root ganglia fibers.

[18] Of the NRTIs, the dideoxynucleoside NRTIs (d-NRTIs)—didanosine (Videx), zalcitabine (Hivid; taken off the market in 2006), and stavudine (Zerit)—have demonstrated the most mitochondrial toxicity and greatest association with neuropathy. The newer NRTIs demonstrate less toxicity; their association with neuropathy remains unclear.



Although the use of d-NRTIs is being phased out in developed countries, the prevalence of neuropathy remains high.[2, 3] These drugs are still widely used in resource-limited regions of the world—particularly stavudine, the component most commonly found in the fixed-dose generic drugs.[2] The cumulative, long-term effects of exposure to d-NRTIs are not yet clear.[19, 20] A small study of patients with current or prior use of d-NRTI treatment found that subjects who had previously tolerated the drugs without developing neurotoxicity were not at significant risk for developing incident DSP neuropathy.[21] Another study found that past, but not current, d-NRTI use was associated with an increased risk of pain in HIV-associated neuropathy after adjusting for other factors.[2] Recent research on the potential contribution of protease inhibitors to the risk of neuropathy is in-conclusive.[22, 23]

People living with HIV commonly manage comorbid conditions with multiple drugs, increasing the risk of neurotoxic adverse effects and drug–drug interactions. Drugs with neurotoxic potential frequently used to treat HIV include dapsone (Aczone), hydroxyurea (Droxia, Hydrea), metronidazole (Flagyl and others), vincristine, thalidomide (Thalomid), isoniazid, linezolid (Zyvox), and ribavirin (Rebetol and others).[24]

Advanced age.

The introduction of ART greatly increased the life span of people with HIV, and advanced age has consistently been associated with DSP neuropathy in the eras both preceding and following the introduction of combination ART regimens, most often referred to as highly active ART (HAART).[2, 25] As people age, the peripheral nervous system under-goes the following changes[26, 27]:

- the density of small and large myelinated fibers decreases
- the amplitude of nerve action potentials declines
- nerve conduction slows

By 2015, half of the people living with HIV in the United States will be over age 50.[28] With the aging of the HIV population and prolonged exposure to ART, the prevalence and severity of DSP neuropathy is a growing concern.

Metabolic disorders

Metabolic disorders, such as diabetes or impaired glucose tolerance, may further increase the risk of DSP neuropathy. Population studies indicate that neuropathy affects 60% to 70% of patients with type 1 and type 2 diabetes, and risk rises with age and with the duration of diabetes.[29] It's been suggested that small-fiber neuropathy may be associated with impaired glucose tolerance and may also occur in prediabetes.[30, 31] In both diabetes and HIV, high triglyceride levels are associated with neuropathy,[32] and many people with diabetes experience neurovascular damage, which impedes blood flow to the extremities, potentially contributing to or exacerbating symptoms in those who also have HIV and DSP neuropathy.

Data suggest that the increased prevalence of glucose disorders among patients living with HIV is associated with HAART use.[33] Individuals using HAART often experience such metabolic complications as lipodystrophy, dyslipidemia, and insulin resistance, which in turn increase their risk of diabetes. New-onset diabetes occurs in an estimated 1% to 6% of HIV-infected people using protease inhibitors.[34]

Alcohol use and nutritional deficiencies.

Some people with HIV try to self-manage their neuropathic symptoms with alcohol or illegal drug use.[35, 36] Long-term, heavy alcohol use can damage nerves, while causing deficiencies in the vitamins (particularly B vitamins) and minerals essential to healthy nerve function.[37] The effects of nutritional deficiencies may be compounded by weight loss and poor diet, which are common problems in HIV owing to nausea, loss of appetite, diarrhea, and the adverse effects of medications.[38, 39] In addition, poor diet may exacerbate impaired immunity, contributing to the progression of HIV and reducing the therapeutic effect of ART.

$CD4^+$ count.

Prior to the widespread use of HAART, a higher plasma HIV-1 RNA load and lower $CD4^+$ count were associated with an increased risk of DSP neuropathy.[40] In the post-HAART era, however, an elevated viral load no longer seems to be associated with increased risk, although DSP neuropathy remains prevalent among those with advanced, untreated HIV or a lower nadir $CD4^+$ cell count.[2]

ASSESSMENT AND MANAGEMENT

It is useful to determine whether the patient has any neurologic symptoms, such as muscle, bowel, or bladder abnormalities. Documentation should include any history of drug or alcohol abuse, detailing the amount of the substance used and the duration of use; current and past medications; and an assessment of dietary and nutritional deficiencies.

All patients with HIV should receive an annual, comprehensive foot exam in which the skin, hair, nails, musculoskeletal structure, circulation, and sensation of the feet are assessed. Those diagnosed with DSP neuropathy may need more frequent foot exams. Inquire about and document any reports of leg discomfort, providing details about the following factors:

- symptom onset

- location
- duration
- the character or quality of described sensations (for example, whether pain is burning, sharp, or dull)
- the severity (using a 0-to-10-point scale)
- diurnal variation
- progression
- exacerbating or relieving factors

Sensory testing.

An assessment should also include sensory testing of the feet. Pressure sensation is assessed using a 5.07 (10-g) Semmes-Weinstein nylon monofilament on the plantar surface of the foot while the patient's eyes are closed (see How to Perform a Pressure Sensory Exam). Practice varies as to the number (one to 10) and location of sites tested for skin breakdown.[41] One study found that exams that included the first toe, third metatarsal head, and two other toes or metatarsal heads per foot produced a sensitivity of 90% to 93% for abnormal pressure sensation and required less than one minute to complete.[42]

Patients are tested for light touch with a cotton swab and for temperature discrimination with warm and cold stimuli. Pinprick sensation is tested using the sharp end of a disposable safety pin. Patients with a loss of protective sensation are at risk for injury, incomplete healing, and infection. Another useful assessment tool is the Brief Peripheral Neuropathy Screen used in several AIDS Clinical Trials Group protocols.[43] With this tool, clinicians capture both subjective and objective findings by asking patients to rate the severity of their symptoms on a scale from 1 (mild) to 10 (most severe) and evaluating their vibration perception and deep tendon reflexes.[24] Testing for reduced or absent Achilles tendon reflexes has a sensitivity of 84% and a specificity of 98% for DSP neuropathy in HIV.[43] After assessing the patient's risk and documenting all foot exam findings, consider whether the patient would benefit from referral to a foot care specialist and schedule follow-up care.

Management.

The Food and Drug Administration has not approved any therapies specifically for the treatment of HIV-associated DSP neuropathy. Current pharmacologic treatment is based on primary symptoms, with acetaminophen, nonsteroidal antiinflammatory drugs, antidepressants, anticonvulsants, topical agents, and opioids used as tolerated. Unfortunately, several drugs that are useful for other types of neuropathic pain—including the tricyclic antidepressant amitriptyline, topical lidocaine anesthetics, and the anticonvulsant pregabalin (Lyrica)—have been found to be ineffective for HIV-associated DSP neuropathy.[44, 45]

Symptom management also involves general life-style modifications, such as reducing cigarette smoking, attaining optimal nutrition, practicing meticulous foot care, and improving circulation through appropriate exercise. In 2010, the American Diabetes Association and the American College of Sports Medicine modified their positions to

suggest that people with peripheral neuropathy who have no acute ulceration may participate in modest weight-bearing exercise.[46] Moderate walking is unlikely to increase the risk of foot ulcers in people with peripheral neuropathy.

FOOT CARE EDUCATION

Nurses play a critical role in disseminating self-care information to patients. Since HIV-associated DSP neuropathy has many of the same signs and symptoms as diabetic and chemotherapy-induced neuropathies, foot care educational materials from such organizations as the American Diabetes Association, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Cancer Institute, and the American Cancer Society may be helpful to people with HIV. In studies of people with diabetes, foot care education improved patients' foot care knowledge and practice in the short term.[47]

Daily foot hygiene.

It's important to emphasize to patients that their feet need to be cleaned daily, using warm—not hot—water and a mild soap, and then towel dried thoroughly, particularly between the toes.[48] Dry skin is a common foot problem. Advise patients with dry skin to moisturize the tops and bottoms of their feet with a thin coat of lotion—not a heavy cream or oil—and to avoid getting lotion between the toes. Nurses should counsel patients to inspect their feet every day for any cuts, cracks, blisters, redness, calluses, swelling, or dryness. Corns and calluses should be gently filed with an emery board or pumice stone after a bath or shower. Toenails should be cut once a week or as needed after washing, when they are soft. They should be cut to the shape of the toes and not too short. Patients who are unable to cut their nails should be referred to a podiatrist.

Footwear and fall prevention.

Shoes should fit well and allow the toes to move. They should be wide enough to exert no pressure on the joints and long enough to allow 1 cm of space between the longest toe and the edge of the shoe when the patient is standing.[49] Shoe material should be permeable because a warm, moist environment may harbor fungal organisms. Patients should shop for new shoes at the end of the day when their feet are larger from standing and walking; until new shoes are fully broken in, they should be worn only an hour a day. Before putting shoes on, patients should always check the insides to make sure the lining is smooth and there are no sharp edges that could injure their feet. Patients should always wear socks or stockings with shoes to prevent skin irritation and blisters. Remind patients that open-toed or thong sandals do not adequately protect the feet from injury. Reinforce the importance of wearing shoes at the beach.

Many older patients wear slippers indoors. Since DSP neuropathy may cause gait and balance problems, putting patients at risk for falls, teach patients about the importance of wearing slippers that fit properly and have slip-resistant soles.[50] If a patient frequently stumbles, a walker or cane may provide needed support. To further protect against falls, advise patients to[51, 52]

- use night lights or keep a flashlight near the bed.

- roll up area rugs.
- remove any electric cords that could impede walking.
- install no-slip bath mats in the shower and tub.

Foot exercises.

To promote lower limb circulation and prevent swelling, nurses should advise patients to elevate their feet when sitting, avoid crossing their legs, and perform simple foot exercises, such as wiggling the toes and moving ankles up and down, several times a day.

CONSIDER ALL RESOURCES

Although people with compromised immune systems and reduced sensory perception are clearly at elevated risk for foot infection, foot exams are often conducted only after a patient has established foot injuries. Advanced age further escalates the risks of HIV-associated foot problems owing to reduced peripheral nerve function, gait complications, and reduced mobility.[27, 53]

Within the diabetes community, efforts to educate patients on peripheral neuropathy and foot care have been intensive and should serve as lessons for providers who care for patients with HIV. Studies have shown that the efficacy of foot care education may depend on the type of education employed.[54, 55] Nurses should take advantage of all available resources, including smartphone applications, which can set daily foot check reminders as well as provide instructional videos. By encouraging simple, preventive foot care education, nurses can promote health and overall well-being in patients at risk for HIV-associated DSP neuropathy, while reducing the potential for complications and related health care costs.

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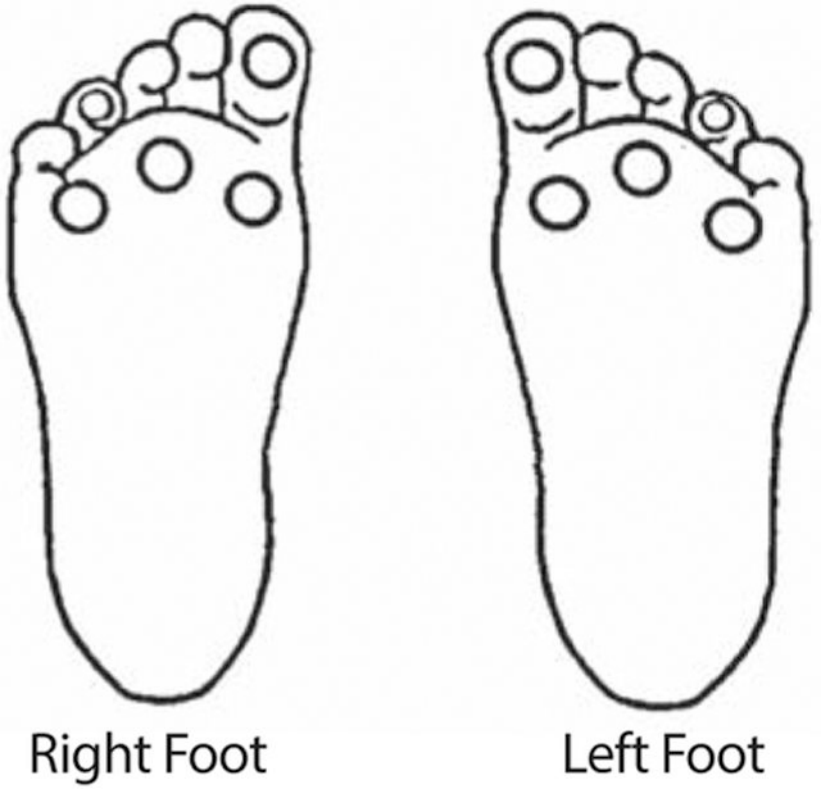
How to Perform a Pressure Sensory Exam

The National Diabetes Education Program (NDEP) of the National Institutes of Health and the Centers for Disease Control and Prevention provides the following instructions for performing a sensory exam of the feet, using a 5.07 (10-g) Semmes-Weinstein nylon monofilament "mounted on a holder that has been standardized to deliver a 10-gram force when properly applied."

Performing the exam.

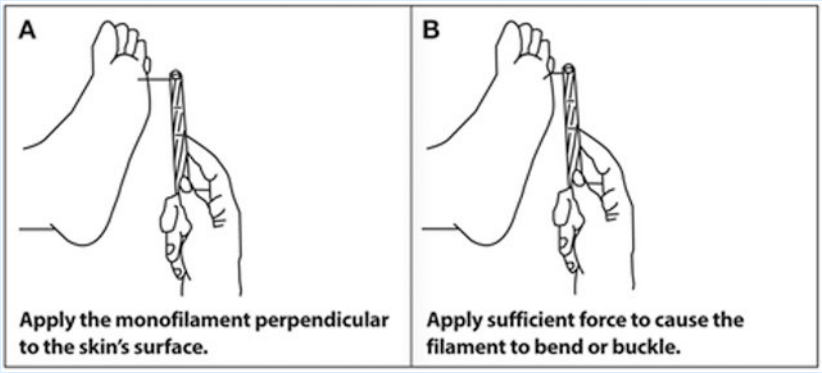
Because sensory deficits appear first in the most distal portions of the foot and progress proximally in a "stocking" distribution, the toes are the first areas to lose protective sensation.

- The sensory exam should be done in a quiet and relaxed setting. The patient must not watch while the examiner applies the filament.
- Test the monofilament on the patient's hand first so she or he knows what to expect.
- The five sites to be tested on each foot are indicated on the exam form. (The diagram below is from the NDEP's Annual Comprehensive Diabetes Foot Exam Form.)



- Label the sensory level in the five circled areas of the foot with a "+" if the patient can feel the monofilament and with a "−" if the patient cannot.

- Apply the monofilament perpendicular to the skin's surface (see diagram A below).
- Apply sufficient force to cause the filament to bend or buckle, using a smooth, not a jabbing, motion (see diagram B below).
- The total duration of the approach, skin contact, and departure of the filament at each site should be approximately one to two seconds.
- Apply the filament along the perimeter and NOT ON an ulcer site, a callus, a scar, or necrotic tissue. Do not allow the filament to slide across the skin or make repetitive contact at the test site.
- Press the filament to the skin such that it buckles on one of two times, as you say "time one" or "time two." Have patients identify at which time they were touched. Randomize the sequence of applying the filament throughout the exam.



Adapted from the National Diabetes Education Program. *Feet can last a lifetime: A health care provider's guide to preventing diabetes foot problems*. Bethesda, MD: National Institutes of Health and the Centers for Disease Control and Prevention; 2000 Nov. http://ndep.nih.gov/media/feet_hcguide.pdf.