

*HIV-1 Associated Peripheral Neuropathologies in HIV and Aging

HIV-1-associated peripheral neuropathy is currently the most common neuro-AIDS condition. Distal sensory polyneuropathy (DSP) is the most common type of peripheral neuropathy in the HIV infected. Others include progressive polyradiculopathy (most commonly occurs with advanced immunosuppression and usually caused by CMV), mononeuropathy multiplex that occurs in early HIV infection), autonomic neuropathy (which may be caused by central or peripheral nervous system abnormalities), and diffuse infiltrative lymphocytosis syndrome. With regard to DSP, one type of DSP is due to HIV infection itself, and another type is due to antiretroviral (ARV) toxicity, predominantly from the dideoxynucleosides (didanosine and stavudine). Mechanisms of disease are incompletely understood, with some evidence implicating gp120-mediated neuronal apoptosis for viral-induced DSP and mitochondrial toxicity with or without DNA polymerase γ involvement in dideoxynucleoside toxicity-induced DSP (Ng et al., 2011). However, data have implicated the protease inhibitors as well in toxicity-induced DSP (Lichtenstein et al. 2005), and protease inhibitor exposure has been noted as an unrecognized risk factor for the development of DSP (Pettersen et al., 2006). In addition, dapsone, isoniazid, metronidazole, vincristine, thalidomide, and hydroxyurea all appear to increase the risk of DSP. Patients report pain, numbness, and dysesthesias occurring first in the feet and gradually ascending – though infrequently to the level of the finger tips. Motor symptoms are minimal. The symptoms typically show a limited response to

treatment. HIV-associated DSP occurs more frequently in older patients (Chen et al., 2013). However, DSP is not as clearly shown to be related to markers of HIV disease progression -- as was the case in the era prior to effective ART. While there is a current association with age, diagnosis of AIDS, and exposure to neurotoxic ARVs, there is not one with clinical HIV disease stage, time from diagnosis, current CD4 cell count (across the entire range), or plasma viral load. Aging is independently associated with deterioration of light touch in both the soft and callous skin of the foot (Mitchell and Mitchell, 2000). DSP causes significant, ongoing pain, is associated with decreased ARV adherence (threatening control of systemic HIV disease), and has been demonstrated to be a true risk factor for falls in older people (Munhoz et al. 1995). It has also been associated with the comorbidity of HIV-associated neurocognitive impairment. Isolating the source of neuropathic pain is a particular concern in the older HIV infected patient, who may be suffering from several conditions causing pain and may not be able to distinguish the specific component of neuropathic pain well. In fact, the prevalence of pain amongst HIV-infected patients generally had been reported to range from a point prevalence of 54% to 83% over a three-month recall period, with moderate-to-severe intensity in one to two and a half different anatomical sites (Parker et al., 2014). Older patients diagnosed with DSP should have their pain assessed with standardized pain scales and should receive specific attention to ARV toxicity, maximal pain control, and regular reviews of ARV adherence. A number of comorbidities may

increase the likelihood of HIV-associated DSP. Diabetes is capable of substantially raising the risk for DSP. This is a significant clinical concern, given the impact of ARV toxicity-associated insulin resistance and diabetes in the setting of HIV infection. Moreover, ongoing studies have shown an association between high triglyceride levels and DSP. In addition, patients with HCV co-infection are at risk for DSP, though this comorbidity is more likely in the younger age range. Treatment is of two types, causal and symptomatic. Regarding causal treatment, avoiding neurotoxic medications, correcting vitamin B6, B12 and folate deficiencies, and considering thiamine replacement are important, if the patient is malnourished. It should also be noted that overdosing with B6 supplementation can cause a peripheral neuropathy. It should also be noted that the use of statin drugs has been associated with significantly lower odds of a DSP diagnosis (Chen et al. 2013). Regarding symptomatic treatment, it is useful to consider non-pharmacological treatments to reduce pain, e.g., advising patients to avoid extended periods of standing or walking, to wear looser shoes, to soak their feet in ice water, to take safety precautions to reduce fall risk by compensating for sensory loss. Therapeutic shoes may also be prescribed. Regarding medications, the antidepressants have been used frequently, particularly low doses of amitriptyline. However, the antidepressants as a class have not always been shown to have specific analgesic efficacy for DSP in trials that were considered to be well controlled (Goodkin et al. 1989, 1996;1998). While amitriptyline has been suggested to be equivalent to nortriptyline in efficacy for neuropathic pain (Liu et al., 2014), amitriptyline was specifically not shown to be more effective than placebo in ACTG 242 for HIV-associated DSP (Kiebert et al. 1998)—

suggesting that nortriptyline may be preferred in the setting of HIV infection. Some credence has been given to the notion that the specific sub-group of serotonergic and noradrenergic reuptake inhibitor (SNRI) antidepressants (such as venlafaxine and duloxetine) might be more efficacious for pain; however, this cannot be considered to be empirically confirmed. The anticonvulsants have also been used, with gabapentin as well as pregabalin being touted for efficacy. A randomized, double-blind, placebo-controlled trial of pregabalin failed to demonstrate significant improvement of pain, but hyperalgesia was less pronounced in participants receiving pregabalin compared to placebo (Simpson et al., 2010). Carbamazepine has been used as well but represents a concern regarding drug-drug interactions. Regarding other drugs for symptomatic treatment, some controlled evidence does show a therapeutic effect of lamotrigine in a small trial (Simpson et al., 1998) followed by a subsequent larger study (Simpson et al. 2003); however, a meta-analysis reported that lamotrigine was not more effective than placebo. Lidocaine gel (5%) initially showed promise in an open label study but failed in a controlled clinical trial (Estanislao et al. 2004). A high-dose capsaicin patch has shown controlled evidence for its use in a sample of good size (Simpson et al. 2008). A trial of the neurotrophic factor, prosaptide, was terminated on the basis of a planned futility analysis (Evans et al., 2007). Acetyl-L-carnitine was unsuccessful as a booster of mitochondrial function in treating HIV-associated DSP in a small open-label study of 20 patients (Osio et al, 2006) and in a randomized, placebo-controlled trial of 90 patients (Youle et al., 2007). Although nerve growth factor (NGF) did show improvement of symptoms of HIV-associated DSP in an open-label study of 200 patients (Schifitto et al., 2001) and a randomized placebo-

controlled trial of 270 patients (McArthur et al., 2000), it was associated with significant injection site reactions and is not currently available for clinical use. Memantine (Schifitto et al., 2006), mexilitine, and peptide T (Simpson et al., 1996) have been studied with no apparent effect. More recently, the CCR5 antagonist, vicriviroc, was not found to improve pain in a placebo-controlled trial of 118 patients with HIV-associated DSP (Yeh et al., 2010). Thus, use of the foregoing medications frequently does not achieve a level of pain control that satisfies the patient, and treatment with opioid analgesics (e.g., tramadol, morphine, oxycodone, methadone) can and should be undertaken, as necessary, to maximize pain control and optimize ARV adherence and activities of daily living while minimizing side effects in all patients at need (including those with a history but no current evidence for substance dependence). Use of the WHO Ladder is a generally acknowledged approach, which can be effectively supplemented by formal pain contracting and monitoring of efficacy with brief, standardized pain scales (such as the Visual Analogue Scale) and of abuse and diversion with urine toxicology screens.

References:

Estanislao L, Carter K, McArthur J, Olney R, Simpson D, and the Lidoderm-HIV Neuropathy Group: A randomized controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. *J Acquir Immune Defic Syndr*. 2004;37(5):1584-1586.

Goodkin K, Feaster D, Baldewicz T: Meta-analysis: A time for closer scrutiny in applications to pain research? *Pain Forum*. *J of the Am Pain Soc*. 1998; 7(2):100-103.

Goodkin K, Vrancken M, Feaster D: On the putative efficacy of the antidepressants in chronic, benign pain syndromes: An update. *American Pain Society Journal (Pain Forum)*. 1995; 4(4): 337-347.

Goodkin K, Gullion C: Antidepressants for the relief of chronic pain: Do they work? *Annals of Behavioral Medicine* 1989; 11(3):83-101.

Kieburtz K, Simpson D, Yiannoutsos C, Max MB, Hall CD, Ellis RJ, Marra CM, McKendall R, Singer E, Dal Pan GJ, Clifford DB, Tucker T, Cohen B and the ACTG 242 Protocol Team. A randomized controlled trial of amitriptyline and mexilitine for painful neuropathy in HIV infection. *Neurology*, 1998; 51(6) 1682-

8.

Lichtenstein KA, C. Armon, A. Baron, A.C. Moorman, K.C. Wood, S.D. Holmberg, and the HIV Outpatient Study Investigators. 2005. Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV outpatient study cohort. *Clin Infect Dis*. 40:148-157.

Mitchell, P.D., and T.N. Mitchell. 2000. The age-dependent deterioration in light touch sensation on the plantar aspect of the foot in a rural community in India: implications when screening for sensory impairment. *Leprosy Rev*. 71:169-178.

Munhoz, C.D., L.B. Lepsch, E.M. Kawamoto, M.B. Malta, L de S. Lima, M.C. Avellar, Richardson, J.K., and E.A. Hurvitz. 1995. Peripheral neuropathy: a true risk factor for falls. *J Gerontol Series A - Biol Sc & Med Sci*. 50:M211-M215.

Simpson DM, Brown S, Tobias J, and the NGX-4010 C107 Study Group: Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology* 2008; 70 (24): 2305-2313.

Simpson, DM, McArthur JC, Olney R, Clifford D, So Y, Ross D, Baird BJ, Barrett P, Hammer, AE, and the Lamotrigine HIV Neuropathy Study Team: Lamotrigine for HIV-associated painful sensory neuropathies. A placebo-controlled trial *Neurology* 2003; 60 (9): 1508-1514.