# Human Immunodeficiency Virus–Associated Distal Sensory Polyneuropathy

## *Still Common After Many Successes*

PERIPHERAL NEUROPATHIES HAVE BEEN ASSOciated with human immunodeficiency virus (HIV) infection since the earliest descriptions of its neurological manifestations. Among several distinct entities (eg, distal sensory polyneuropathy [DSPN], diffuse infiltrative lymphocytosis syndrome, and inflammatory demyelinating polyneuropathy), DSPN is not only the most common but arguably the most difficult to manage because of its chronic course and its painful symptoms. Typically, patients with DSPN report painful distal dysesthesias, burning, pins-and-needles sensations, numbness, and allodynia (painful response to an innocuous stimulus).[1] These symptoms begin in the feet, often on the soles, and, in the more symptomatic cases, progress up the legs.

*See also page 552*

Severe HIV neurocognitive dysfunction (eg, HIV-associated dementia) has decreased dramatically since the widespread use of antiretroviral (ARV) therapy, particularly in the developed countries, where such therapy is readily available. Nevertheless, the prevalence of DSPN has remained high or even increased in recent years. Some of this increase is probably the result of ongoing effects of HIV replication in the peripheral nervous system despite adequate systemic virus suppression. However, a large proportion of DSPN cases are due to the antiviral therapy itself because several ARV drugs can induce neuropathy. Notable among these are the nucleoside reverse transcription inhibitors (or "d-drugs," ie, stavudine [d4T], didanosine [ddI], and zalcitabine [ddC]) and perhaps some of the HIV protease inhibitors such as indinavir sulfate, saquinavir, and ritonavir.[1] The pathophysiologic mechanism of DSPN induced by HIV or ARVs is somewhat obscure, but neuronal mitochondrial injury resulting from mitochondrial DNA (mtDNA) damage through inhibition of the mtDNA gamma polymerase and/or mtDNA intercalation of d-drugs and damage due to mitochondrial stress responses have considerable experimental support.[2] Indeed, increased susceptibility to DSPN has been associated with a specific mtDNA haplogroup that is defined by a combination of mtDNA polymorphisms.[3-5]

A direct role for HIV replication in DSPN remains controversial.[6] Neuropathological studies have shown the presence of HIV sequences in infected peripheral nerves; in some cases these were localized to macrophages,[7-11] and the frequency of this finding roughly correlated with the incidence of neuropathy. In addition, HIV DNA has been identified in the dorsal root ganglia of HIV-infected patients.[12] Although some diagnostic tests, such as biopsies and determinations of specific cerebrospinal fluid metabolites, have been used in attempts to differentiate ARV-induced neuropathies from HIV DSPN, for practical purposes the only definitive way to differentiate between these 2 causes is to alter the ARV regimen, also called combination antiretroviral therapy (cART).

The article by Ellis et al[13] in this issue of the *Archives* is an epidemiological study of the prevalence of HIV DSPN and related painful symptoms at a time when there is widespread use of cART in the developed countries. This study not only confirms several previous smaller studies but also extends the analysis to associate markers for the risk of neuropathic pain within the affected population. This type of investigation is key to beginning to understand the relationship between cART and symptoms of neuropathy and to alert clinicians about what are potentially bothersome and life-altering complications.

Using a cross-sectional design, the investigators assessed the presence of HIV DSPN, the frequency of pain, the performance of activities of daily living, concomitant psychiatric diagnoses, and several markers of the quality of life. Notably, the authors used broad inclusion criteria, ensuring that these individuals represent the population of HIV-infected patients in their geographical area. Within this cohort, 881 (57.2%) had DSPN, defined by the authors as the presence of at least 1 bilateral sign consistent with neuropathy. If the clinical assessment was made additionally stringent by defining neuropathy as the presence of 2 or more signs, a still impressive 27.9% had evidence of DSPN. Furthermore, the investigators found the following highly significant risk factors for DSPN: older age, current cART use (but not current d-drug use), previous d-drug exposure, and lower CD4 nadirs. Among the patients with demonstrable neuropathy, 60.8% reported sensory symptoms, and 38.0% had neuropathic pain.

This study is important for several reasons. First, it confirms the high prevalence of this complication in those who are receiving cART. Second, it links neuropathic pain to effects on the quality of life and employment and, by inference, to a significant societal cost. Finally, the initially paradoxical association between neuropathic pain and a higher CD4 nadir suggests that a functional immune system may contribute to the induction of pain.

The work by Ellis et al also raises the need to consider the risk of HIV DSPN and its associated disability as a factor in determining the decision to begin ARV

therapy in individuals with HIV. The increased risk of neuropathy (although not pain) in individuals with a low CD4 nadir was found to be independent of the suppression of viral load. As the authors point out, this suggests that starting therapy earlier than currently recommended could decrease the risk of developing DSPN. This question could be addressed within the context of a large prospective multicenter trial. Because many of the multiple complications of cART are the subject of intense basic and clinical investigations, opportunities for such a study should be forthcoming.

The study by Ellis et al has considerable strengths. An important one is the sheer number of participants who underwent evaluation (1539 HIV-infected individuals) and the comprehensiveness of the data available regarding them. Because of the cross-sectional design, the authors were able to enroll many participants fairly rapidly, and studying such a large number is invaluable in assessing disease prevalence. In addition, the cohort reflects individuals at different stages of treatment—before and after initiation and maintenance of ARV therapy—and thus may reflect the demographics of the HIV epidemic. The outcomes from well-stratified studies such as this can then focus valuable and costly longitudinal studies in smaller and perhaps more accessible or homogeneous cohorts. Such studies could validate these specific findings, identify additional group-specific risk factors for DSPN with and without pain, and determine applicable treatment intervention outcomes. The reporting of clinically significant associations (ie, quality of life, depression, and employment), although imperfectly measured, presents a context of the cost of HIV DSPN in terms that are increasingly important in judging the value of many medical interventions.

The weaknesses of the study result from the same characteristics of its design that also provide its strengths. Cross-sectional studies cannot provide conclusive cause-and-effect relationships, and studying heterogeneous clinical cohorts could obscure important group-specific associations. Large cohorts such as this must rely principally on clinical data, precluding detailed electrophysiological or even pathological studies. Patient self-reporting of their lowest CD4 nadir raises the issue of the accuracy of this quantified correlate, and this will certainly need further validation in future studies. Again, as a result of the large numbers, the criteria for the diagnosis of DSPN used by Ellis et al ($\geq$1 clinical signs) are greatly simplified and quite subjective, although the authors argue credibly for the sensitivity and specificity of this criterion. However, these are minor limitations in what is an excellent informative study that will help manage HIV and call attention to this important complication.

*Dennis L. Kolson, MD, PhD*
*Francisco González-Scarano, MD*

**Author Affiliations:** Department of Neurology, University of Pennsylvania, Philadelphia.
**Correspondence:** Dr González-Scarano, Department of Neurology, University of Pennsylvania, Hospital of the University of Pennsylvania, 3 W Gates Bldg, 3400 Spruce St, Philadelphia, PA 19104-4283 (scarano@mail.med.upenn.edu).
**Author Contributions:** *Analysis and interpretation of data:* Kolson and González-Scarano. *Drafting of the manuscript:* Kolson and González-Scarano. *Administrative, technical, and material support:* Kolson and González-Scarano.
**Financial Disclosure:** None reported.

## REFERENCES

1. Gonzalez-Duarte A, Robinson-Papp J, Simpson DM. Diagnosis and management of HIV-associated neuropathy. *Neurol Clin*. 2008;26(3):821-832, x.
2. Höschele D. Cell culture models for the investigation of NRTI-induced mitochondrial toxicity: relevance for the prediction of clinical toxicity. *Toxicol In Vitro*. 2006;20(5):535-546.
3. Kallianpur AR, Hulgan T. Pharmacogenetics of nucleoside reverse-transcriptase inhibitor-associated peripheral neuropathy. *Pharmacogenomics*. 2009;10(4):623-637.
4. Canter JA, Haas DW, Kallianpur AR, et al. The mitochondrial pharmacogenomics of haplogroup T: MTND2*LHON4917G and antiretroviral therapy–associated peripheral neuropathy. *Pharmacogenomics J*. 2008;8(1):71-77.
5. Hulgan T, Haas DW, Haines JL, et al. Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: an adult AIDS clinical trials group study. *AIDS*. 2005;19(13):1341-1349.
6. Kolson DL, González-Scarano F. HIV-associated neuropathies: role of HIV-1, CMV, and other viruses. *J Peripher Nerv Syst*. 2001;6(1):2-7.
7. Chaunu MP, Ratinahirana H, Raphael M, et al. The spectrum of changes on 20 nerve biopsies in patients with HIV infection. *Muscle Nerve*. 1989;12(6):452-459.
8. Cornblath DR, McArthur JC. Predominantly sensory neuropathy in patients with AIDS and AIDS-related complex. *Neurology*. 1988;38(5):794-796.
9. de la Monte SM, Gabuzda DH, Ho DD, et al. Peripheral neuropathy in the acquired immunodeficiency syndrome. *Ann Neurol*. 1988;23(5):485-492.
10. Ho DD, Rota TR, Schooley RT, et al. Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *N Engl J Med*. 1985;313(24):1493-1497.
11. Vital A, Beylot M, Vital C, Delors B, Bloch B, Julien J. Morphological findings on peripheral nerve biopsies in 15 patients with human immunodeficiency virus infection. *Acta Neuropathol*. 1992;83(6):618-623.
12. Esiri MM, Morris CS, Millard PR. Sensory and sympathetic ganglia in HIV-1 infection: immunocytochemical demonstration of HIV-1 viral antigens, increased MHC class II antigen expression and mild reactive inflammation. *J Neurol Sci*. 1993;114(2):178-187.
13. Ellis RJ, Rosario D, Clifford DB, et al. Continued high prevalence and adverse clinical impact of human immunodeficiency virus–associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER Study. *Arch Neurol*. 2010;67(5):552-558.