

# New research sets stage for noninvasive monitoring of HIV-induced peripheral neuropathy

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Corneal nerve fiber assessment has great potential as a tool to diagnose and monitor peripheral neuropathy induced by HIV, say scientists at the Johns Hopkins University School of Medicine. The results of their study are published in *The American Journal of Pathology*.

Although corneal nerve assessments have shown increasingly valuable as a replacement for epidermal nerve fiber evaluation in diabetic peripheral neuropathy, the evaluation of corneal alterations in tracking HIV-induced neuropathy has yet to be explored.

"The cornea is the most densely innervated tissue in the body, so corneal nerve assessment is extremely sensitive for detecting small sensory nerve fiber damage as compared to other tests including measurement of intra-epidermal nerve fibers in the skin," notes lead investigator Joseph L. Mankowski, DVM, PhD, who is Professor of Molecular and Comparative Pathobiology, Pathology, and Neurology at the Johns Hopkins University School of Medicine, Baltimore, MD.

Although not life threatening, HIV-induced peripheral neuropathy greatly compromises patient quality of life. Currently, skin biopsy is the accepted standard for measuring the loss of small, unmyelinated C fibers in the epidermis, one of the earliest detectable signs of peripheral nerve damage. However, skin biopsy is an invasive procedure, and ongoing assessment requires repeated surgical procedures. Electrophysiological

testing to measure peripheral nerve conduction properties is not a viable alternative because current methods lack the sensitivity required to detect damage to small, unmyelinated fibers, especially in early stages of disease. Therefore, new sensitive, noninvasive methods of assessing small fiber nerve damage are urgently needed to detect and monitor peripheral neuropathy in HIV-infected individuals.

To study the pathogenesis of HIV-induced PNS disease, Jamie Dorsey, Research Technologist, and the research team led by Dr. Mankowski developed a simian immunodeficiency virus (SIV)-infected macaque model that closely reflects key peripheral nervous system (PNS) alterations seen in HIV patients with peripheral neuropathy. They sought to determine whether SIV infection leads to decreases in corneal nerve fiber density, and whether corneal nerve fiber density correlates with epidermal nerve fiber length counts, thereby setting the stage for follow-up investigation using corneal confocal microscopy.

"Moving to non-invasive and repeatable methods of nerve fiber measurements such as in vivo corneal confocal microscopy would enhance study of peripheral neuropathy by enabling early detection of damage, progression of nerve fiber deterioration, and enable assessment of therapeutic strategies in the SIV/macaque model," explains Dr. Mankowski. "Furthermore, adapting in vivo corneal confocal microscopy for use in tracking HIV-induced PNS damage in patients may be of great value to identify early PNS damage independent of performing skin biopsies."

To determine whether SIV infection leads to corneal nerve fiber loss, the researchers immunostained corneas for the nerve fiber marker  $\beta$ III tubulin. They developed and applied both manual and automated methods developed by Jonathan Oakley, PhD, of Voxeleron to measure nerves in the corneal sub-basal plexus. These counting methods independently demonstrated significantly lower sub-basal corneal nerve

fiber density among SIV-infected animals that rapidly progressed to AIDS as compared to slow progressors. Corneal nerve fiber density was also directly correlated with epidermal nerve fiber length.

Besides decreased corneal nerve fiber density, rapid SIV progressors had increased levels of SIV RNA, CD68-positive macrophages, and GFAP expression by glial satellite cells in the trigeminal ganglia, the location of the neuronal cell bodies of corneal sensory [nerve fibers](#).

Together, these findings demonstrate that emerging noninvasive techniques to measure corneal nerve fiber alterations such as in vivo corneal confocal microscopy may be useful clinical tools to screen for and monitor progression of [peripheral neuropathy](#) in HIV-infected patients.

**More information:** Loss of Corneal Sensory Nerve Fibers in SIV-infected Macaques: An Alternate Approach to Investigate HIV-induced PNS Damage," by Jamie L. Dorsey, Lisa M. Mangus, Jonathan D. Oakley, Sarah E. Beck, Kathleen M. Kelly, Suzanne E. Queen, Kelly A. Metcalf Pate, Robert J. Adams, Carl F. Marfurt, and Joseph L. Mankowski ( [dx.doi.org/10.1016/j.ajpath.2014.02.009](https://doi.org/10.1016/j.ajpath.2014.02.009) ), *The American Journal of Pathology*, Volume 184, Issue 6 (June 2014)

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