

Persisting High Prevalence of HIV Distal Sensory Peripheral Neuropathy in the Era of Combination ART: Correlates in the CHARTER Study

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OBJECTIVE

To assess changes in prevalence, risk factors, and clinical impact of both distal sensory polyneuropathy and neuropathic pain in HIV.

BACKGROUND AND SIGNIFICANCE

- Before combination antiretroviral therapy (CART) was introduced, neuropathic pain due to Distal Sensory Polyneuropathy (DSPN) was the most prevalent neurologic complaint in HIV.
- DSPN symptoms include hyperalgesia, tingling, numbness, and pain.
- CART has resulted in substantial immune reconstitution among the HIV population.
- The use of "d-drugs" (D4T, DDJ), known to be associated with the onset of neuropathic pain, has declined.
- As the HIV population ages and antiretroviral therapy evolves, updated estimates of DSPN and neuropathic pain frequency, associated risk factors and overall impact are needed to guide therapeutic strategies.

METHODS

Design

- 1,539 HIV-infected individuals were enrolled and analyzed in CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research), a prospective, multi-site, observational study.

Subjects

- Inclusion: HIV-infected and on/off ART
- Exclusion: Presence of OIs, schizophrenia, or inability to undergo a full evaluation.

DSPN & Pain

- Evaluations were administered by nurses, nurse practitioners and physicians trained according to a standardized protocol
- DSPN signs included diminished ability to recognize vibration on bilateral great toes, reduced ability to reliably discriminate sharp from dull in the lower legs, feet and toes, and absent or weakened bilateral ankle reflexes compared to knees.
- Neuropathy symptoms assessed in the lower legs, feet and toes included dysesthesias, pain, parasthesias, and reported loss of sensation.
- Neuropathic pain was classified into five severity levels as follows: normal, slight, mild, moderate, and severe (see Figure 3).

Risk Factors / Correlates

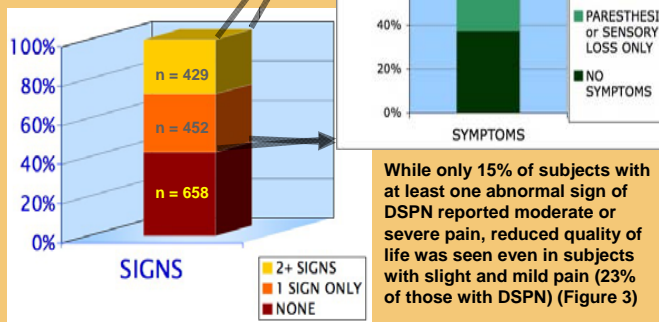
- CART including current and past exposure to d-drugs, markers of HIV disease and progression (plasma viral load and nadir CD4), extent of CD4 recovery with CART, and hepatitis C co-infection.
- History of substance use disorders (specifically alcohol and opiates) was collected using the CIDI – Composite International Diagnostic Interview for DSM IV
- The MOS HIV Health Survey was used to assess overall quality of life, daily functioning, and physical health.

Statistics

- Univariate and mixed stepwise logistic regression were used to determine the unadjusted and adjusted odds of DSPN or neuropathic pain.
- Statistical significance was based on p<0.05.

RESULTS

Figure 1. 57% of HIV+ subjects had at least one sign of neuropathy. Among those with neuropathy signs, symptoms including paresthesias and pain affected 61%.



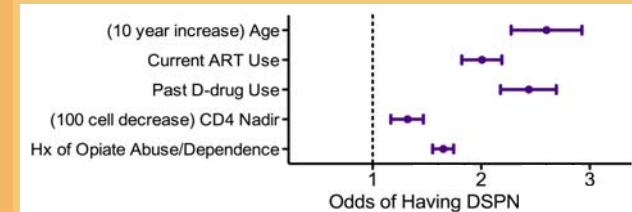
While only 15% of subjects with at least one abnormal sign of DSPN reported moderate or severe pain, reduced quality of life was seen even in subjects with slight and mild pain (23% of those with DSPN) (Figure 3)

Table 1. Selected demographic and clinical characteristics of subjects with and without DSPN defined as at least one sign of neuropathy.

Characteristic	≥1 Sign DSPN (n=881)	No DSPN (n=658)	p value
Age (years)	46 (7.8)	40 (8.3)	<0.0001
Male sex - n (%)	677 (77%)	500 (76%)	0.7044
ART use - n (%)			<0.0001
Current	711 (81%)	384 (58%)	
Past	99 (11%)	111 (17%)	
Naïve	71 (8%)	163 (25%)	
Dideoxynucleoside use - n (%)			<0.0001
Current Use	138 (16%)	72 (11%)	
Past Use	413 (47%)	175 (27%)	
Naïve	330 (37%)	411 (63%)	
CD4 Nadir (cells/μL)	120 (30-246)	231 (106-367)	<0.0001
CD4 Recovery (cells/μL)	229 (87-404)	161 (44-317)	<0.0001
Plasma Viral Load (log ₁₀ copies/mL)	1.9 (1.7-3.7)	2.7 (1.7 - 4.3)	<0.0001
Hepatitis C infection - n (%)	264 (31%)	138 (21%)	<0.0001
Hist. of alcohol abuse/dependence - n (%)	494 (57%)	351 (54%)	0.3188
Hist. of opiate abuse/dependence - n (%)	176 (20%)	91 (14%)	<0.0001

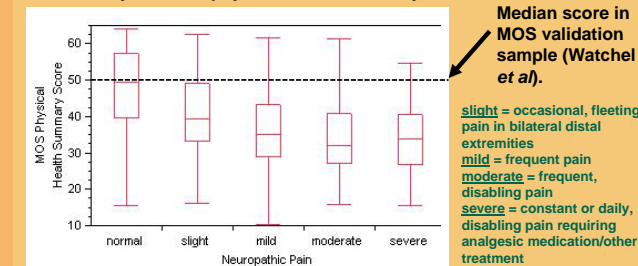
*Values are n (%) or median (interquartile range), as appropriate

Figure 2: Adjusted odds ratios (OR) and 95% confidence intervals (CI) for significant, simultaneous risk factors in multivariate logistic regression*



* Factors not significant in the multivariate regression were gender, current d-drug use, CD4 recovery, plasma viral load, and history of alcohol abuse or dependence

Figure 3. Subjects with neuropathic pain had reduced quality of life as measured by the MOS physical health summary score.



Median score in MOS validation sample (Watchel et al).

slight = occasional, fleeting pain in bilateral distal extremities
mild = frequent pain
moderate = frequent, disabling pain
severe = constant or daily, disabling pain requiring analgesic medication/other treatment

*Boxes represent median and interquartile range; whiskers represent 10th and 90th percentiles

CONCLUSIONS

- DSPN was found to affect more than half of individuals living with HIV, with a particularly high prevalence among those currently taking antiretroviral therapy.
- These findings suggest that the recovery of peripheral nerves with ART, if it occurs, is incomplete.
- Significant risk factors for DSPN in the multivariate regression were lower CD4 nadir, advancing age, current ART use, prior d-drug use and prior opiate abuse/dependence.
- The finding that individuals with higher CD4 nadirs were less likely to have DSPN suggests that earlier ART treatment might prevent the onset of neuropathic pain.
- The effect of current ART use on DSPN was independent of prior d-drug use, consistent with at least two possible explanations: (1) DSPN is promoted by advanced disease requiring ART or (2) ARVs other than d-drugs confer some degree of neurotoxicity.
- The frequent occurrence of DSPN despite CART reinforces the need for novel treatments to manage neuropathic pain and promote neuroregeneration and recovery.

Supported by NIH contract N01 MH22005 (CHARTER; PI: I. Grant). Participating sites include: Johns Hopkins University (J. McArthur); Mt. Sinai School of Medicine (S. Morgello & D. Simpson); University of California, San Diego (J.A. McCutchan); University of Texas Medical Branch, Galveston (B. Gelman); University of Washington, Seattle (A. Collier & C. Marra); Washington University, St. Louis (D. Clifford)