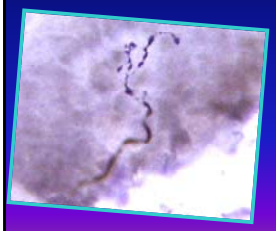
HIV and chemotherapy induced neuropathy



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IMMPACT 2009

Major Neuromuscular Syndromes in HIV Disease

Diagnosis and HIV stage

Sensory neuropathies (DSP, ATN): Variable

Mononeuropathy multiplex: Early (painful); DSP Late (progressive); Hep C

Antiretroviral/toxic neuropathy ATN

Progressive polyradiculopathy: Late, CMV

Inflammatory demyelinating polyneuropathy: Early

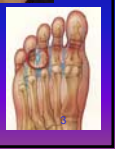
Myopathy: Any (AZT); Early (polymyositis); IBM

ALS-type disorder: Late, rare

HIV-associated neuromuscular weakness syndrome: D4T

Confounding illnesses in the assessment of HIV sensory neuropathies

- Antiretroviral exposure: d4T 8-fold, ddI 4-fold
- Diabetes in 11% of HAART recipients; IGT in ~ 20%
- Alcohol abuse; hepatitis C
- Entrapment neuropathies
- Vitamin deficiencies or overuse
- Morton's neuroma



HOPS: declining incidence of neuropathy Lichtenstein *CID 2005*

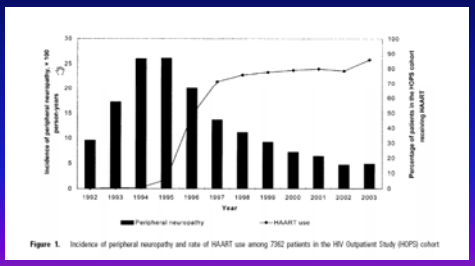


Figure 1. Incidence of peripheral neuropathy and rate of HAART use among 7362 patients in the HIV Outpatient Study (HOPS) cohort

Incidence rates of 15 AIDS-defining events in 5 time periods after initiation of highly active antiretroviral therapy (HAART)

The Antiretroviral Therapy Cohort Collaboration*, Arch Intern Med 2005;165:416-423.

ARCHIVES OF INTERNAL MEDICINE

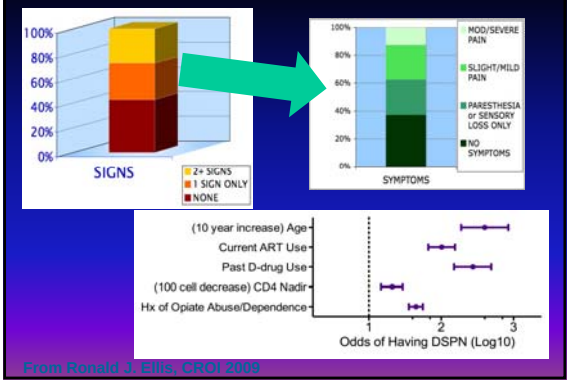
Copyright restrictions may apply.

- CHARTER is a multicenter, observational, NIH contract study designed to assemble a cohort that is similar to the clinic population
  - Overall objective: Determine the effects of antiretroviral therapy on the nervous system
- Study procedures include
  - Comprehensive neuropsychological and neuromedical assessments
  - Phlebotomy and lumbar puncture
  - Neuroimaging
  - Specialized neuropathy assessments

CHARTER — CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

6

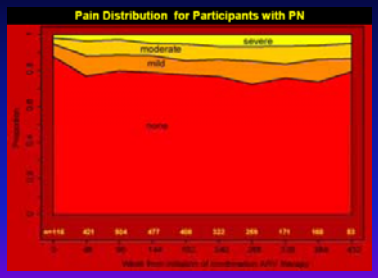
Frequency of neuropathic signs: CHARTER cohort



From Ronald J. Ellis, CROI 2009

Distribution of pain in ALLRT cohort

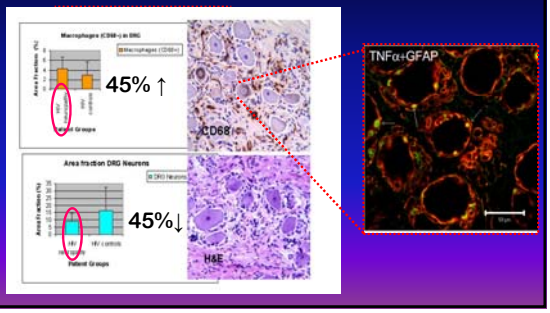
Evans S. CROI 2009



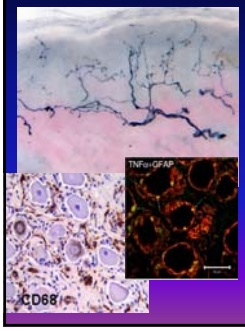
ACTG

9

Macrophage activation and neuronal reduction in DRG correlates with HIV-SN



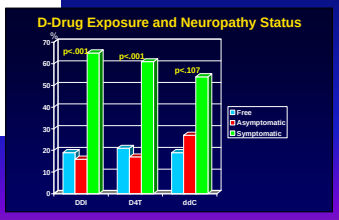
Pathogenesis of sensory neuropathies in HIV/AIDS: summary



- epidermal denervation and prominent *DRG* macrophage activation;
- denervation of Schwann cells and mitochondrial abnormalities *(Ebenezer et al 2007)*
- some NRTI's are toxic to DRG cultures thru' mitochondrial injury *(Keswani, 2003; Hoke + Melli 2005; Zhu, 2008).*
- gp120 causes a dose-dependent axonal degeneration in sensory neurons in DRG cultures, mediated thru' apoptosis *(Hoke, 2005)*

Antiretroviral toxicity

Stavudine



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DOI: 10.1089/aid.2007.0168

Cytokine Genotype Suggests a Role for Inflammation in Nucleoside Analog-Associated Sensory Neuropathy (NRTI-SN) and Predicts an Individual's NRTI-SN Risk

CATHERINE L. CHERRY,[1,2,3] ANN ROSENOW,[4] JACQUITA S. AFFANDI,[3] JUSTIN C. McARTHUR,[4] STEVEN L. WESSELINGH,[1,2,3] and PATRICIA PRICE[4]

B	Odds ratio	95% confidence interval	p value
BAT1 (intron 10)	14.9	1.3–172	0.03
TNFA-1031	10.6	1.1–100	0.04
IL12B (3′ UTR)	0.06	0.003–1.3	0.07
Height (cm)	1.4	1.13–1.8	0.002

Increasing height was associated with toxic neuropathy risk. A model including cytokine genotype and height predicted NRTI-SN status (*p 0.0001, r2 0.54).* Late onset NRTI-SN patients clustered genetically with NRTI-SN-resistant patients, so these patients may be genetically "protected." Cytokine genotype influenced SN risk following dNRTI exposure, suggesting that inflammation contributes to NRTI-SN.

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Skin biopsy: *use in clinical diagnosis of sensory neuropathy*

- **Utility of skin biopsy:**
  - selective for small caliber nerve fibers and can distinguish *neuropathy from radiculopathy from psychogenic*
  - standardization and QC among 10 CLIA-approved labs
  - now accepted as validated outcome measure in clinical trials and for the diagnosis of SFSN

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AAN practice parameters
(*Neurology* 2009;72:1–1)

- "IENF density assessment using PGP 9.5 immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology. Skin biopsy with IENF density assessment is possibly useful to identify DSP which includes SFSN in symptomatic patients with suspected polyneuropathy (Class III)".

Skin biopsy technique

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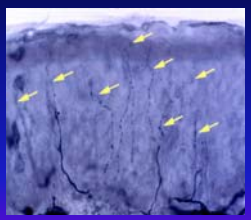
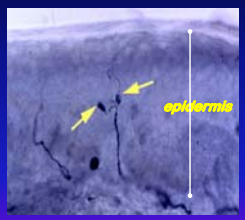
HIV sensory neuropathies
Skin biopsy assesses unmyelinated nerve fibers

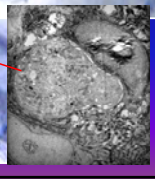


Thigh: normal density



Distal leg: reduced density and nerve fiber swellings

Morphological abnormalities on skin biopsies



Correlates of epidermal nerve fiber densities in HIV-associated distal sensory polyneuropathy

Table 2 Total Neuropathy Score (TNS) neuropathy status by epidermal denervation status

	TNS neuropathy status, n (%)			
Epidermal denervation*	Neuropathy-free	Asymptomatic	Symptomatic	Total, n (%)
No	19 (19.2)	15 (15.2)	27 (27.3)	61 (61.6)
Mild	1 (1.0)	5 (5.1)	9 (9.1)	15 (15.2)
Severe	2 (2.0)	6 (6.1)	15 (15.2)	23 (23.2)
Total	22 (22.2)	26 (26.3)	51 (51.5)	99 (100)

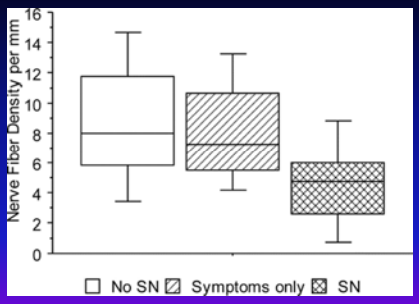
Correlates of epidermal nerve fiber densities in HIV-associated distal sensory polyneuropathy

Table 4 Associations of epidermal nerve fiber density (ENFD) with clinical and electrophysiologic evaluation

	Distal leg ENFD		Proximal leg ENFD	
	Spearman r	p	Spearman r	p
TNS	−0.26	<0.01*	−0.17	0.10
VAS	−0.25	0.01*	−0.18	0.08
GPS	−0.25	0.01*	−0.12	0.25
Sural SNAP amplitudes	0.31	<0.01*	0.18	0.07
Sural velocities	0.18	0.12	0.09	0.42
Toe cooling JND	−0.33	<0.01*	−0.25	0.01*
Toe vibration JND	−0.23	0.02*	−0.03	0.75
Toe heat pain 0.5 JND	0.1	0.37	0.02	0.84
Toe heat pain 5.0 JND	−0.04	0.70	−0.06	0.56

NEUROLOGY 2007;68:2113-2119

Distal calf intraepidermal nerve fiber density (IENFD) measurements by clinical neuropathy and symptom status



Cherry, C. L. et al. Neurology 2005;65:1778-1781

Developing models to study nerve injury in HIV-associated sensory neuropathies…*is there evidence of impaired nerve fiber repair ?*

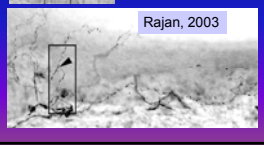
- Punch skin biopsy assessment of epidermal nerve fibers and SCs
- Capsaicin denervation and regenerative regrowth
- Intracutaneous axotomy and collateral sprouting
- Sural nerve biopsy

Mechanisms of nerve fiber repair after cutaneous nerve injury

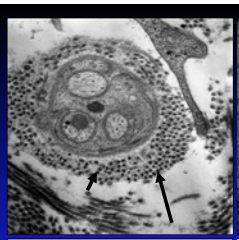
- **Regenerative regrowth ~ from transected nerve fibers along denervated Schwann cell bands**

Cajal, 1913

- **Collateral sprouting from uninjured nerve fibers in neighboring skin**

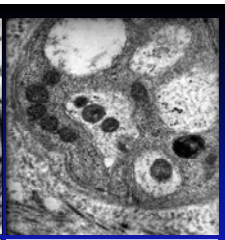


Rajan, 2003



A healthy Remak bundle at the papillary dermis containing 3 axons surrounded by collagen. (x25K)

Healthy control

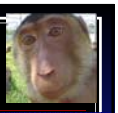


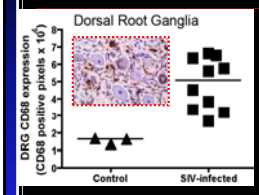
Remak bundle with dilated unmyelinated axons showing watery axoplasm and granular debris.

HIV neuropathy

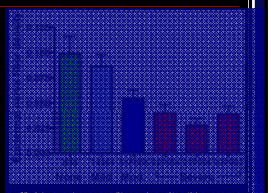
SIV macaque model of HIV DSP

(Mankowski J, Laast V, Zink MC, Clements J)





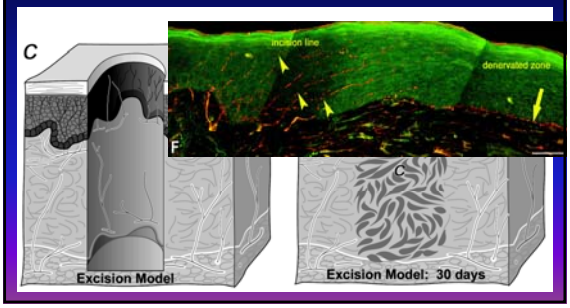
CD68 immunostaining for activated/infiltrating macrophages in DRG of SIV-infected macaques showing significant increase in macrophage staining in DRG



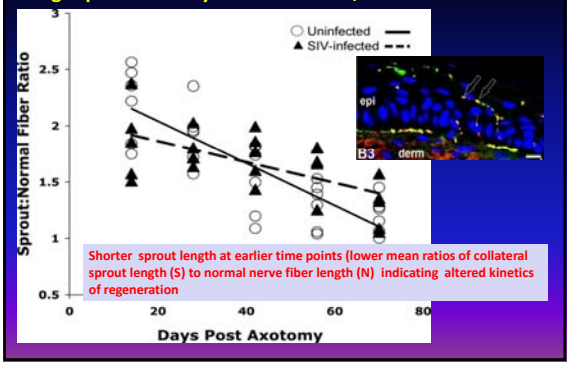
Epidermal nerve fiber density (% volume immunopositive for nerve fiber marker PGP 9.5) decreases with severity of DRG ganglionitis

Excision model to study regeneration in human cutaneous nerve injury: *collateral sprouting*

Rajan B., 2003

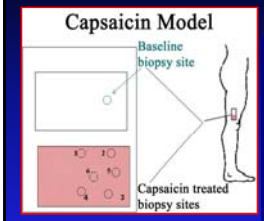


SIV infection alters epidermal nerve fiber length post-axotomy *Ebenezer G., 2009*



Shorter sprout length at earlier time points (lower mean ratios of collateral sprout length (S) to normal nerve fiber length (N) indicating altered kinetics of regeneration

Nerve fiber repair is as impaired in HIV infection as in diabetes



(*unlicensed*) treatments for HIV sensory neuropathies

Lamotrigine: Na channel
Glucuronidation, rash

Topiramate: Glutamate
Renal excretion, wt loss, kidney stones

Gabapentin/pregabalin: A2delta calcium
Renal excretion, edema, sedation

Duloxetine: serotonin/norepinephrine RRI
Nausea, hepatotoxicity

Combination therapies: eg NEJM study of gabapentin + morphine

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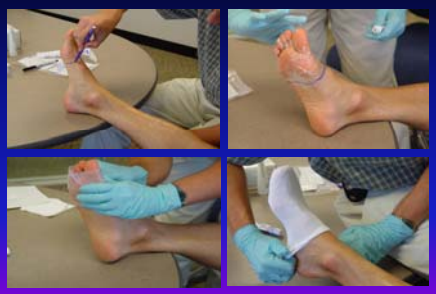
Sampling of controlled trials for HIV-sensory neuropathies

Agent	*Outcome*	*Comments*
Amitriptyline v. acupuncture	No effect	• sham acupuncture used
Topical agents	• Lidocaine *No*	• advantage of intermittent topical therapies compared to oral agents
Amitriptyline v. mexilitene	No effect	• underpowered
Gabapentin	Pain improved	• n = 26
rh NGF	Pain improved	• no effects over 48 weeks on ENF
Lamotrigine	Pain improved	• 2 separate trials • differential placebo effect in ATN

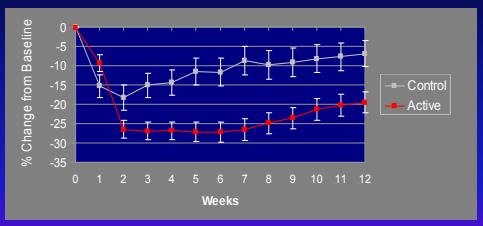
High-Concentration Capsaicin Patch (NGX- 4010)

Application Procedure



C107: Time Course of Pain Change with T NGX- 4010/Qutenza®

Percent Change from Baseline to Weeks 2-12



'Average Pain for Past 24 Hours'
Diary Score
Pooled Control vs. Pooled Active
[mean, SEM]

Simpson et al. Neurology 2008 Jun 10;70(24):2305-13

Potential issues with high dose capsaicin strategy

- Potential dangers of deafferentation
- Does regrowth of fibers occur, with increased excitability ?
- The most common adverse reactions associated were redness, pain, and itching at the application site.

Has the potential for periodic treatment of painful neuropathies without need for continued exposure to agent

Chemotherapy neuropathy: Measuring inches with a yard stick

Table 2. Comparison of Classification Systems for Oxaliplatin-Induced Sensory Neurotoxicity

Grade	NCI-CTC 2.0	Oxaliplatin-Specific Scale
I	Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory symptoms of short duration
II	Objective sensory loss or paresthesia (including tingling), interfering with function, but not with activities of daily living	Sensory symptoms persisting between cycles
III	Sensory loss or paresthesia interfering with activities of daily living	Sensory symptoms causing functional impairment
IV	Permanent sensory loss that interferes with function	—

Abbreviation: NCI-CTC, National Cancer Institute common toxicity criteria.

Ixabepilone— approved despite neurotoxicity

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NCI-CTC vs TNS: which tool is better for grading the severity of chemotherapy-induced peripheral neuropathy?

- The TNS and the TNSc were significantly correlated with the NCI-CTC in scoring CIPN severity
- All patients with a 1-point change on the NCI-CTC scale had a ≥1-point difference in the TNS (94% with a change of ≥2 points).
- "As a research tool for measuring change in clinical trials and as a clinical tool for following change during neurotoxic drug treatment, the TNS and TNSc are clearly an advance on what has gone before."

Predictors of CIPN

- Baseline neuropathy
- Co-morbid conditions (DM)
- Age
- Variation
  - Pharmicogenetics
  - Tumor type (Bortezomib)

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- chemotherapy-induced peripheral neuropathy outcome measures standardization study (CI-Perinoms) where impairment, disability, quality of life, and patient-reported outcome measures will be formally compared using a clinimetric approach—

Epidermal Innervation holds promise

Study Outline: Oxaliplatin toxicity

- Visit 1 (Baseline) prior to starting oxaliplatin
- Visit 2 (1 month)
- Visit 3 (3 months)
- Visit 4 (6 months)--completion of therapy
- Visit 5 (Follow-up, 12 months)--6 months after completion

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Hypotheses

- Baseline nerve fiber density would predict development of neuropathy
- Older patients would develop more severe CIPN
- Patients with co-morbidities (DM) would have more severe CIPN
- Improvement between 6 and 12 months.
- CIPN would be predominantly SFSN

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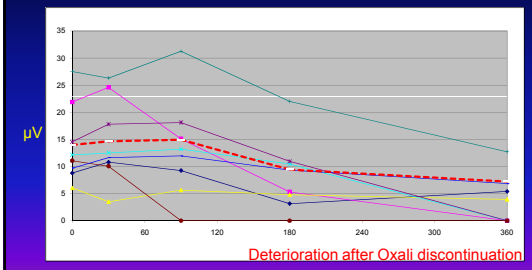
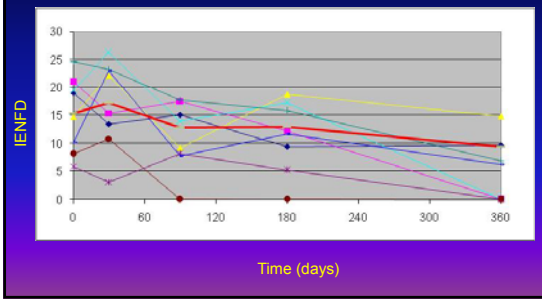
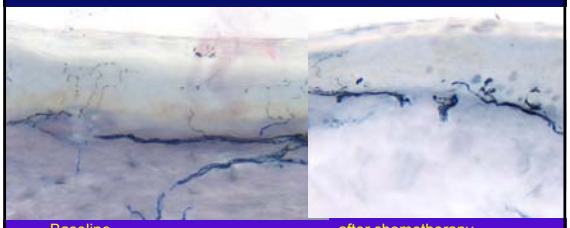
Sural Amplitude



Epidermal Innervation



Skin biopsy: a window into peripheral nerve morphology



Advantages of epidermal innervation

- Truly blinded
- Relatively non-invasive, safe
- Ability to re-sample

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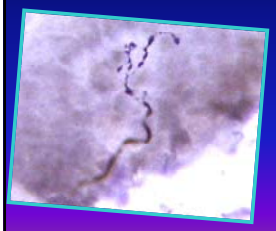
HIV and chemotherapy induced peripheral neuropathy



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