British HIV Association
BHIVA

Professor Andrew Rice

Chelsea and Westminster Hospital, London

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Prof Andrew Rice	Professor Rice is a member of the Scientific Advisory Board and owns share options in Spinifex Pharmaceuticals. He also has provided consultancy via Imperial College Consultants (last 36 Months) to Astellas, Asahi Kasei, Servier, Pfizer and Allergan. Professor Rice has also received grant funding (via IMI EUROPAIN) from Pfizer and Astellas
Date	**November 2013**

BHIVA Best Practice Management Session:

Peripheral Neuropathy

Andrew SC Rice
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Imperial College London
Chelsea and Westminster Hospital NHS
NHS Foundation Trust
The Wellcome Trust
The London Pain Consortium

- Neuropathic pain

- HIV-associated neuropathy
  - Epidemiology
  - (Pathogenesis)
  - Clinical presentation
  - Clinical assessment
  - Treatment

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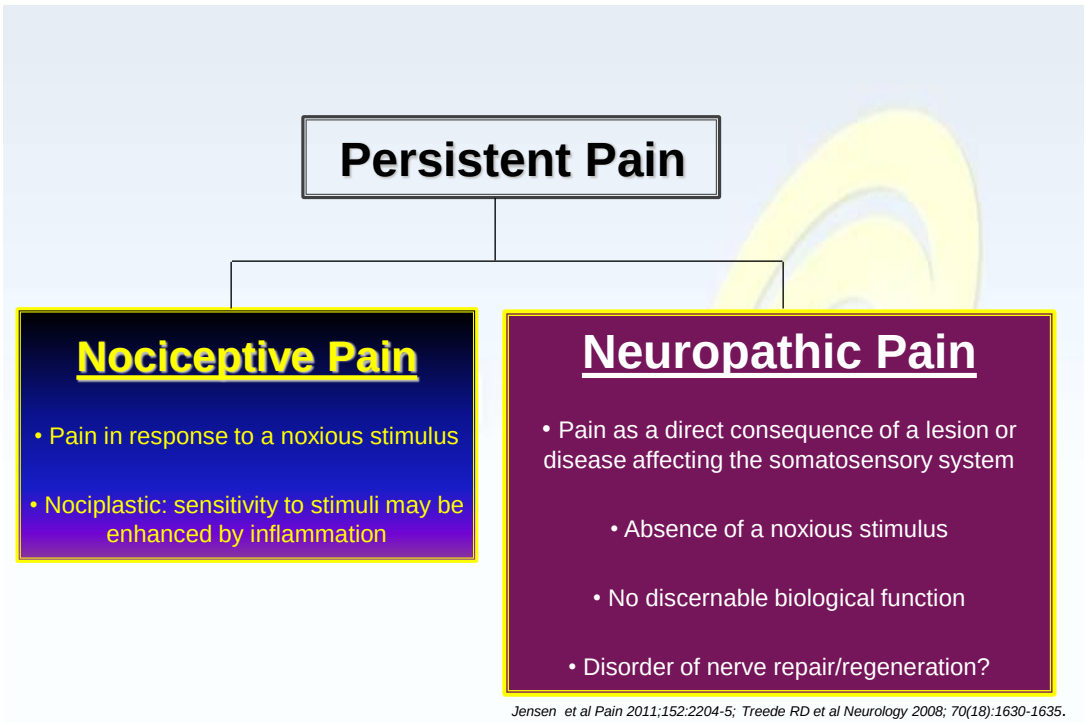

Jensen et al Pain 2011;152:2204-5; Treede RD et al Neurology 2008; 70(18):1630-1635.

Key Features of Neuropathic Pain

- Pain occasionally generated in response to damage to sensory nervous system
- Pain in absence of a noxious stimulus:
  - Spontaneous continuous
  - Spontaneous paroxysmal (lancinating)
  - Evoked (stimulus dependant) pain

- Prevalence UK & France ~ 7%[1]
- Usually severe and chronic[2]:
  - Mean duration 78 months
  - Mean pain intensity 6/10

1 Torrance *et al* 2006; Smith *et al* 2007; Bouhassira *et al* 2008
2. Backonja & Stacey 2004

- Variably associated with sensory perturbations:
  - **Sensory Loss:**
    - Pain in areas of sensory loss - *Anaesthesia Dolorosa*
  - **Sensory gain:**
    - *Allodynia* – pain in response to an innocuous stimulus
    - *Hyperalgesia* – increased response to a painful stimulus
    - *Hyperpathia* - increased response a repetitive noxious stimulus, often associated with an increased threshold.

Range of Underlying Diseases Associated with Neuropathic Pain

- Trauma to nervous system
- Peripheral neuropathies
  - Metabolic, dietary & toxic
- Infection
- CNS disease
- Tumours
- Nerve compression
- Genetic channelopathies

- Neuropathic pain

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Classification of HIV-1 Associated Peripheral Neuropathies

(After Verma J. PNS 2001;6:8-13; Keswani AIDS 2003 16;2105-2117)

- Early stages (immune dysregulation)
  - Acute inflammatory demyleinating polyradiculopathy
  - Chronic inflammatory demyleinating polyradiculopathy
  - Vasculitic neuropathy
  - Brachial plexopathy
  - Cranial mononeuropathy
  - Multiple mononeuropathies
- Mid and late stages (HIV-1 replication driven)
  - HIV-Associated distal sensory polyneuropathy
  - Autonomic neuropathy
- Late stages (opportunistic infection & malignancy)
  - CMV polyradiculopathy
  - CMV mononeuritis multiplex
  - Acute herpes zoster/ post herpetic neuralgia
  - Syphilitic radiculopathy
  - Tuberculosis polyradiculomyelitis
  - Lymphomatous polyradiculopathy
  - AIDS cachexia neuropathy

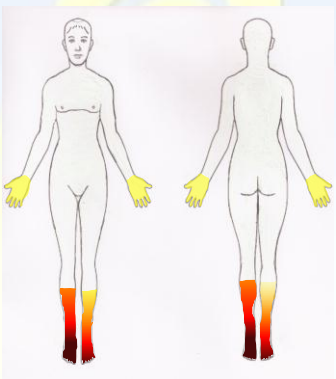
- All stages
  - Antiretroviral toxic neuropathy
  - Other drugs (eg vincristine, ethambutol, thalidomide)
- Other causes e.g.
  - Nutritional (B12, B6)
  - Alcohol, diabetes etc

HIV–Sensory Neuropathy (HIV-SN)

HIV-Sensory Neuropathy

(HIV – Distal Sensory Polyneuropathy & Antiretroviral Toxic Neuropathy)

- Distal symmetrical axonal sensory polyneuropathies
- Length dependant - Distal degeneration “die back” of axons without major loss/apoptosis of DRG cells
- Often associated with neuropathic pain
- Clinically indistinguishable
- High prevalence persists despite modern ARVs



HIV-Sensory Neuropathy Prevalence

(Smyth *et al* HIV Medicine 2007;8:367–373)

	1993 Pre- CART N = 94
HIV-SN Prevalence	13%
Any Pain	?
Pain > 5/10	?
Using NRTI	-
Ever used NRTI	-

HIV-Sensory Neuropathy Prevalence

(Smyth *et al* HIV Medicine 2007;8:367–373)

	1993 Pre-CART N = 94	2001 CART- dNRTI era N = 140
HIV-SN Prevalence	13%	44%
Any Pain	?	74%
Pain > 5/10	?	37%
Using NRTI	-	62%
Ever used NRTI	-	82%

HIV-Sensory Neuropathy Prevalence

(Smyth *et al* HIV Medicine 2007;8:367–373)

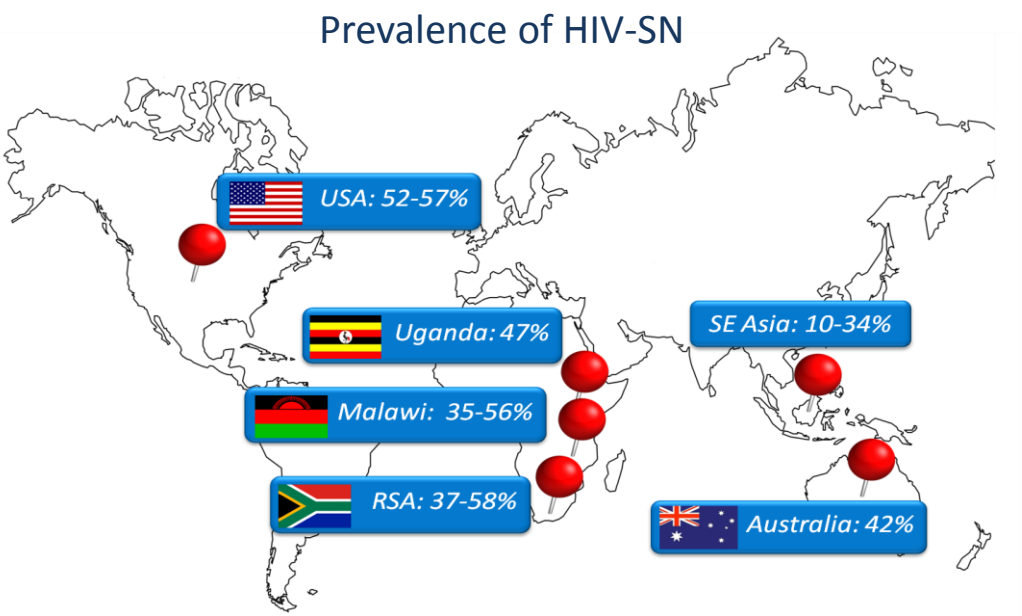
Melbourne outpatient sample, n=100	1993 pre CART N = 94	2001 CART- dNRTI era N = 140	2006 CART – post dNRTI era N = 100
HIV-SN Prevalence	13%	44%	42%
Any Pain	?	74%	93%
Pain > 5/10	?	37%	43%
Using NRTI	-	62%	8%
Ever used NRTI	-	82%	62%

Risk factors for DSP

- Age (Smyth et al 2007; Wright et al 2008)
- Height (Cherry et al 2008; Affandi et al 2008)
- CD4 nadir <200 (Ellis et al 2010; Maritz et al 2010; Banerjee et al 2011)
- Exposure to dNRTIs (Cherry et al 2007; Smyth et al 2007; Wright et al 2008)
- Genetic (Cherry et al 2008; Affandi et al 2008)

HIV-Sensory Neuropathy Prevalence

	Location	n	Evidence of neuropathy	Pain in neuropathy patients	Risk factors
Pettersen et al 2006	Canada	221	**46%**	-	Age, peak viral load, Protease Inhibitors (?hyperglycaemia) & dNRTI exposure
Smyth et al 2007	Australia	100	**42%**	43%	Age, height, dNRTI exposure
Ellis et al 2010 (CHARTER)	USA	1539	**57%**	38%	Age, lower CD4 nadir, current cART use, past dNRTI exposure
Mauritz et al 2010	South Africa	598	**49%**	47%	Age, TB, ART use (esp d4T), CD4 nadir <200
Wadley et al 2011	South Africa	395 (Stavudine treated)	**57% (symptomatic)**	76%	Age, height
Banerjee et al 2011	USA	436	**27%**	?	Age, height, CD4 nadir, elevated triglycerides (statin or protease inhibitor use), type 2 diabetes



Australia: Smyth et al., 2007; **Malawi:** Beadles et al., 2009; van Oosterhout et al., 2005; **South Africa:** Hitchcock et al., 2008; Maritz et al., 2010; Wadley et al., 2011; **SE Asia:** Affandi et al., 2008; Sithinamsuwan et al., 2008; Vivithanaporn et al., 2010; Wright et al., 2008; **Uganda:** Nakasujja et al., 2005; **USA:** Ellis et al., 2010; Simpson et al., 2006

Genetic Risk Factors for HIV-SN

	Australia[1]	Indonesia[2]	USA & Italy[3]
Increased risk of neuropathy	**TNFA–1031*2**	**TNFA–1031*2**	**MTND2* LHON4917G**
Decreased risk of neuropathy	**IL12B(3'UTR)*2**		

The London Pain Consortium

1. Cherry et al., *AIDS Res Hum Retroviruses* 2008;24: 117-123
2. Affandi et al., *AIDS Res Hum Retroviruses* 2008;24: in press
3. Canter et al *Pharmacogenomics J 2007;* 8,:71-72..

Ethnicity and Genes Associated With HIV-SN Risk

	TNFA-1031*2 **(increased SN risk)**	***IL12B(3'UTR)*2*** **(reduced SN risk)**
White	✓	✓
Indonesian (Malay)	✓	✗
African	✗	✗

Affandi et al., *AIDS Res Hum Retroviruses* 24: 1281-1284, 2008; Cherry et al., *AIDS Res Hum Retroviruses* 24: 117-123, 2008; Wadley et al., unpublished data.

Slide Courtesy of Dr P Kamerman

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D–NRTI Drugs Induce a Mitochondrial Neuropathy

doi:10.1093/brain/awm195 *Brain* (2007), 130, 2688–2702

Characterization of rodent models of HIV-gp120 and anti-retroviral-associated neuropathic pain

Victoria C. J. Wallace,[1] Julie Blackbeard,[1] Andrew R. Segerdahl,[1] Fauzia Hasnie,[1] Timothy Pheby,[1] Stephen B. McMahon[2] and Andrew S. C. Rice[1]

IASP PAIN® 154 (2013) 560–575 PAIN®

A clinically relevant rodent model of the HIV antiretroviral drug stavudine induced painful peripheral neuropathy

Wenlong Huang[a,n,1], Margarita Calvo[b,1], Kersti Karu[c], Hans R. Olausen[a], Gabriella Bathgate[a], Kenji Okuse[a], David L.H. Bennett[b,d,1], Andrew S.C. Rice[a,n,1]

The London Pain Consortium

European Journal of Pain 13 (2009) 387–398
Contents lists available at ScienceDirect
European Journal of Pain
journal homepage: www.EuropeanJournalPain.com

Comparison of dorsal root ganglion gene expression in rat models of traumatic and HIV-associated neuropathic pain

Klio Maratou[a,b,1,2], Victoria C.J. Wallace[a,1,2], Fauzia S. Hasnie[a,1], Kenji Okuse[c,1], Ramine Hosseini[d,1], Nipurna Jina[a,1], Julie Blackbeard[a], Timothy Pheby[a,1], Christine Orengo[f,1], Anthony H. Dickenson[b,1], Stephen B. McMahon[b,1], Andrew S.C. Rice[a,*,1]

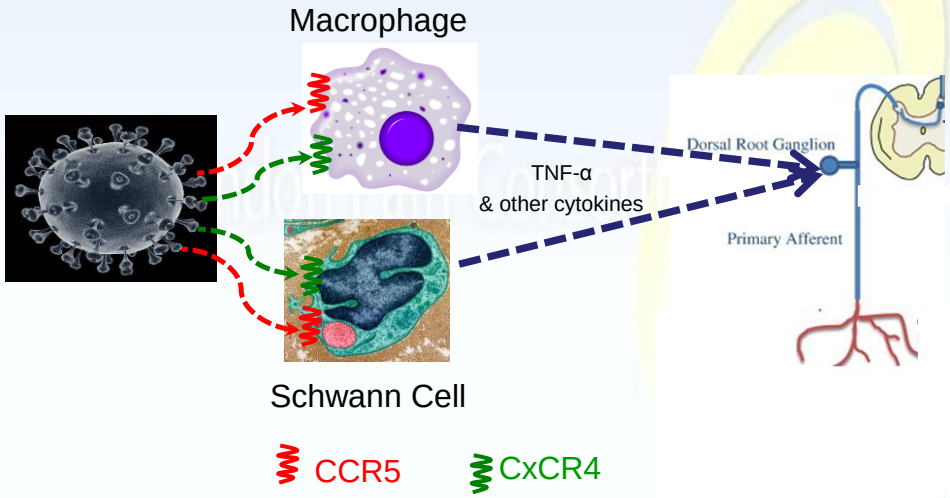
Nat Genet. ; 43(8): 806–810. doi:10.1038/ng.863.

Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations

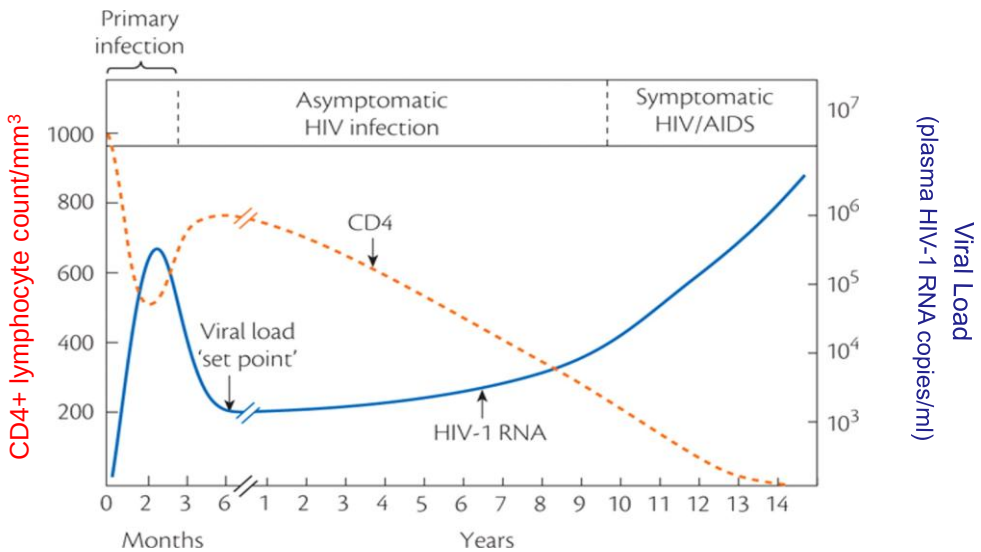
Brendan A I Payne[1,2], Ian J Wilson[1], Charlotte A Hateley[1], Rita Horvath[1], Mauro Santibanez-Koref[1], David C Samuels[3], D Ashley Price[2], and Patrick F Chinnery[1]

GP120 Hypothesis

HIV GP120 interacts with chemokine receptors to induce axonal degeneration of sensory neurones



Natural History of HIV-1 infection



Untreated infection >90% mortality ~8-10 years post infection

Luzzi, G. A. et.al.

Oxford Textbook of Medicine

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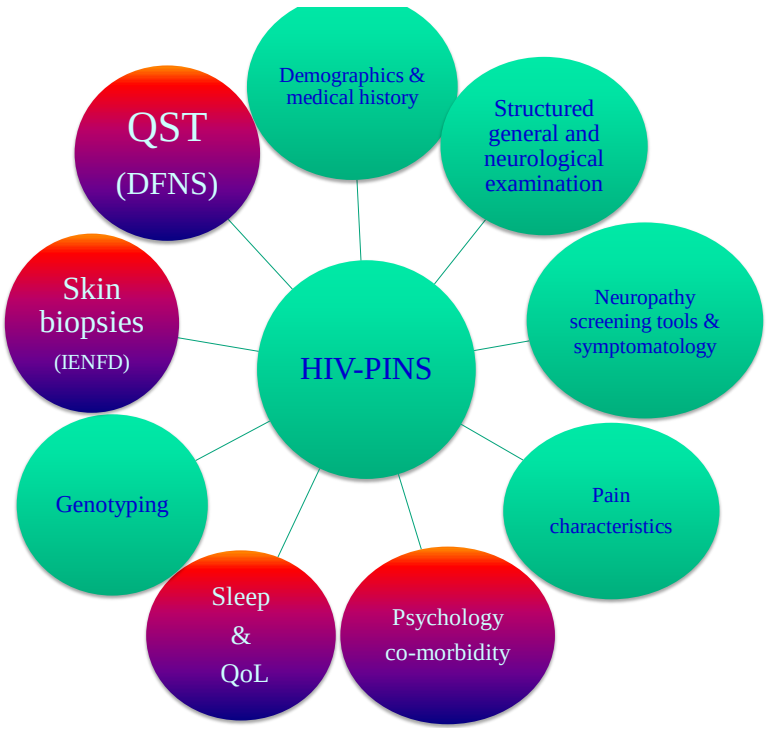

HIV-PINS
Demographics & medical history
Structured general and neurological examination
Neuropathy screening tools & symptomatology
Pain characteristics
Psychology co-morbidity
Sleep & QoL
Genotyping
Skin biopsies (IENFD)
QST (DFNS)

The Majority Of Participants Were White, Middle–Aged Males

~1.75 m tall & 14-17 Years Since HIV Diagnosis with Excellent Antiretroviral Control

	No HIV-SN n=38	HIV-SN n=28	p value
Mean age yrs (SD)	47.69 (8.87)	51.32 (8.36)	0.097
Male (%)	32 (84.21)	25 (89.28)	0.553
Height cm (SD)	175.08 (8.82)	177.14 (7.76)	0.321
Weight kg (SD)	77.11(15.08)	80.50(12.19)	0.334
Years since HIV diagnosis (SD)	14.71(7.79)	17.79 (7.02)	0.094
Current CD4 cells/mm^3 (SD)	536.86 (262.92)	536.78 (235.94)	-
Viral load < 50 copies/ml number of subjects (%)	32 (84.2)	26 (92.8)	-
White European (%)	33 (86.84)	24 (85.71)	0.553
African Origin (%)	4 (10.53)	3 (10.71)	0.553
Asian (%)	1(2.63)	0	0.553
Mixed ethnicity (%)	0	1 (3.57)	0.553

SYMPTOMS

Reported Symptom	**No HIV-SN n=38 (%)**	**HIV-SN n=28 (%)**	p value
Any pain in hands and/or feet.	**11 (28.95)**	**21 (75)**	<0.001
If experiencing pain: 7-day pain diary NRS (0-10)	**2.8 (2.34)**	**5.65 (1.76)**	<0.001
Pain onset yrs after HIV diagnosis	12.29 (5.94)	9.5 (7.59)	0.358
Pain duration years	9.5 (7.59)	8.25 (7.23)	0.811
'Pins and needles' in feet and/or hands	19 (50)	17 (60.71)	0.388
'Numbness' in feet and/or hands	**14 (36.84)**	**21 (75)**	0.002
Perceived 'Weakness' in upper or lower limbs	10 (26.32	10 (35.71	0.412
Postural hypotension	**9 (24.68)**	**14 (50)**	0.015
Urinary dysfunction	**6 (15.79)**	**12 (42.86)**	0.015
Erectile dysfunction	12 (31.58)	14 (50)	0.152
Nocturnal diarrhoea	10 (26.32)	8 (28.57)	0.839

Lipids

	No HIV-SN n=38			HIV-SN n=28		p value
Total cholesterol	4.56	(1.08)		5.01	(1.07)	0.100
Triglyceride	**1.61**	**(0.77)**		**2.18**	**(1.09)**	**<0.020**
HDL	1.06	(0.36)		1.24	(0.44)	0.069
LDL	2.75	(0.93)		2.71	(0.95)	0.860
Cholesterol : HDL ratio	4.53	(1.57)		4.42	(1.27)	0.769
Random glucose	5.31	(1.20)		5.31	(1.07)	0.863
BMI kg/m^{-2}	25.28	(5.34)		25.68	(3.69)	0.223
Waist-hip circ. ratio (SD)	0.98	(0.09)		0.96	(0.12)	0.739
Current statin use (%)	9	(23.70)		9	(32.14)	0.446

Co-Morbidities

	No HIV-SN n=38			HIV-SN n=28		p value
Clinical Insomnia (ISI>15)	7	(22.6%)		13	(68.4%)	<0.001
Depression (DAPOS)	8.38	(+/-4.10)		11.21	(+/-4.22)	<0.05
Anxiety (DAPOS)	5.45	(+/-2.89)		7.47	(+/-2.97)	<0.05
Pain interference (BPI)	15.2	(+/-16.2)		46.1	(+/-13.7)	<0.001

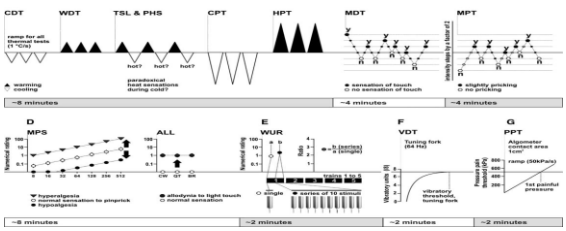
QoL SF-36

SF-36 Domain	HIV-No SN (n=38)	SD		HIV-SN with pain (n=21)	SD	
Physical functioning	**74.03**	24.65		**34.47**	21.74	<0.001
Role Physical	**50.78**	43.76		**11.84**	28.10	<0.001
Bodily Pain	**69.43**	24.47		**29.42**	18.06	<0.001
General Health	**43.78**	26.96		**26.58**	19.88	<0.05
Vitality	**49.53**	24.08		**25.79**	24.45	<0.001
Social Functioning	**67.98**	27.31		**32.24**	24.41	<0.001
Role Emotional	**54.17**	46.18		**15.79**	32.14	<0.05
Mental Health	**63.25**	21.25		**47.79**	17.05	<0.05

Sensory Profile

DFNS Quantitative Sensory Testing Protocol

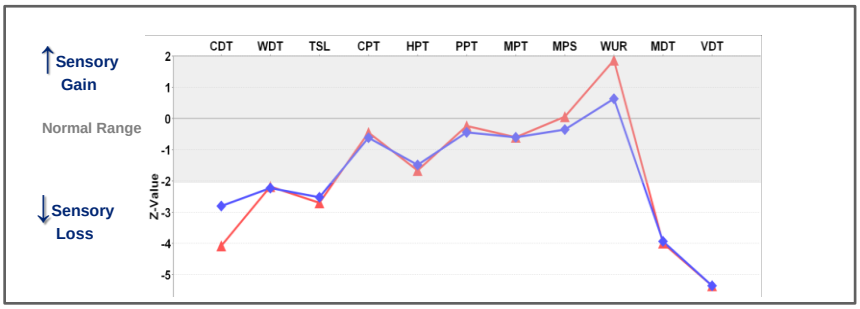
Stimulus	Fibre type
Cold Detection Threshold (CDT)	Aδ
Warm Detection Threshold (WDT)	C
Thermal Sensory Limen (TSL) & Paradoxical Heat Sensation (PHS)	Aδ & C Pathological response
Cold Pain Threshold (CPT)	Aδ? C?
Heat Pain Threshold (HPT)	C
Mechanical Detection Threshold (MDT)	Aβ
Mechanical Pain Threshold (MPT)	Aδ
Mechanical Pain Sensitivity (MPS)	Aδ Stimulus response function
Dynamic Mechanical Allodynia (ALL)	Aβ Stimulus response function
Windup Ratio (WUR)	Aδ Temporal Summation - Pathological respons
Vibration Detection Threshold (VDT)	Aβ
Pressure Pain Threshold (PPT)	Aδ? C?



Non-noxious; noxious

Rolke et al Eur. J. Pain 2006;10:77–88

Sensory Profile in HIV-SN

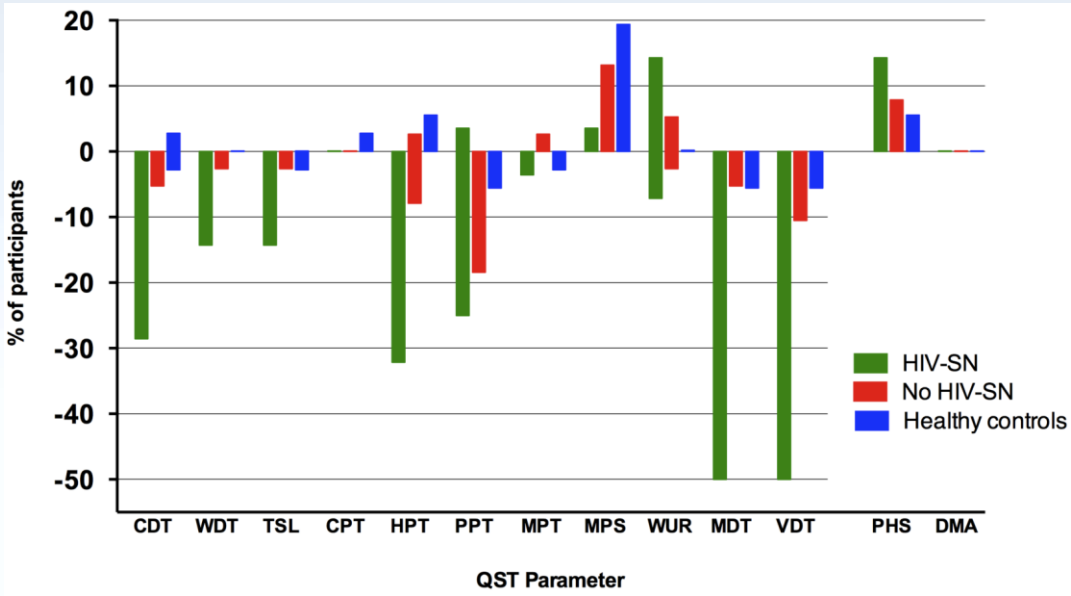


HIV neuropathy (S1)

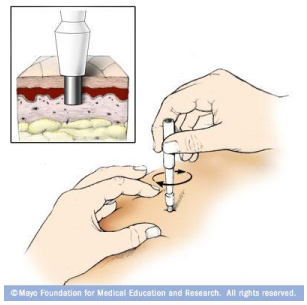
Loss:

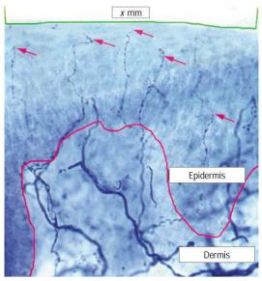
- Cold Detection Threshold (Aδ fibre)
- Warm Detection Threshold (C fibre)
- Thermal Sensory Limen
- Mechanical Detection Threshold (Aβ)
- Vibration Detection Threshold (Aβ)

Gain: Nil


20
10
0
-10
-20
-30
-40
-50
% of participants
CDT
WDT
TSL
CPT
HPT
PPT
MPT
MPS
WUR
MDT
VDT
PHS
DMA
QST Parameter
HIV-SN
No HIV-SN
Healthy controls

HIV-SN “Die Back” Of Sensory Nerve Fibres From Epidermis



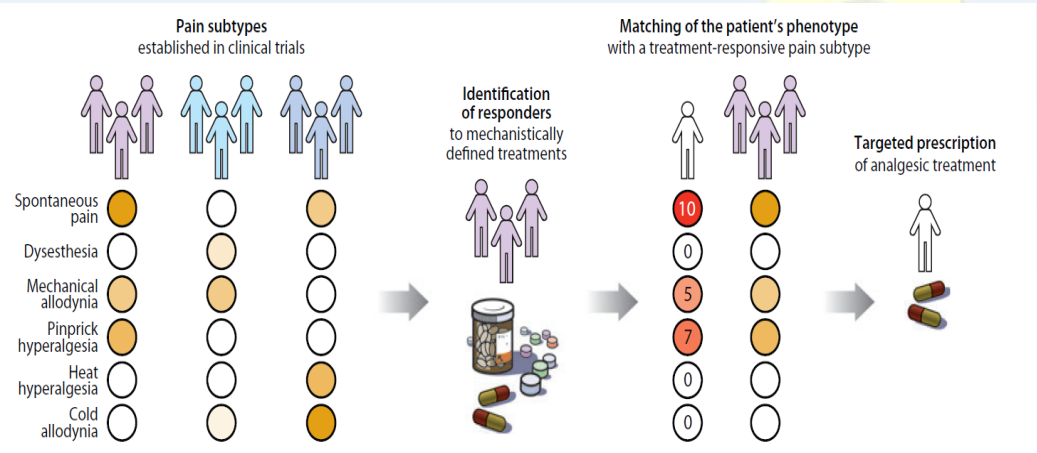


McArthur JC et al Arch. Neurol. 1998;55:1513-20

Intraepidermal Nerve Fibre Density	No HIV-SN n=34	HIV-SN n=26	p
Fibres/mm (median; range)	**9.2** (1.7-14.4)	**6.3** (0.7-12.4)	<0.001
Patients with < 7.63 fibres/mm (%)	**8** (21%)	**17** (61%)	<0.05

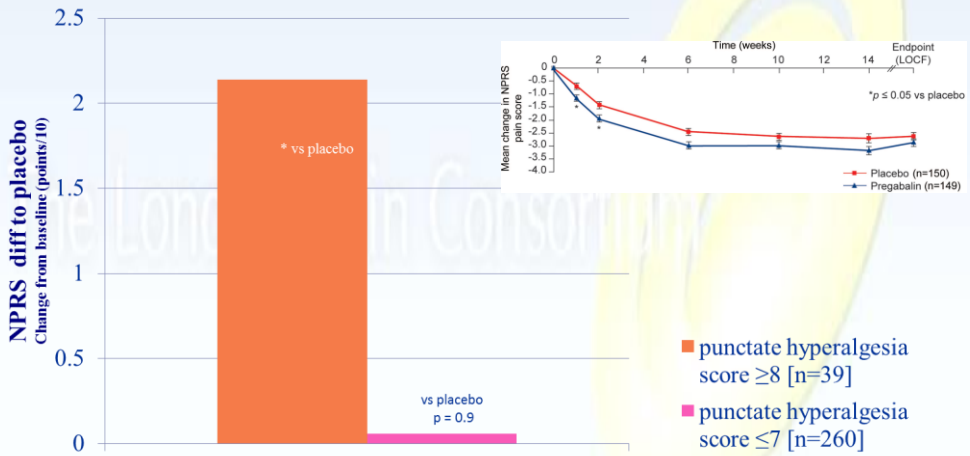
Targeted Prescribing Of Analgesics In Neuropathic Pain According To Individual Profiles

Costigan et al Annu Rev Neurosci 2009; 32:1-32.



Efficacy Of Pregabalin In HIV Neuropathy Patient Subset With Pin Prick Hyperalgesia

Adapted from: Simpson *et al* Neurology 2010;74:413



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Diagnosis & Assessment of Neuropathic Pain

Haanpaa et al. Pain 2011;152:14-27.

1. Investigation of underlying disease.
2. Is there a lesion or disease of the somatosensory system?
3. Is the pain neuropathic?
4. How severe is the pain?
5. What is the impact of the pain?

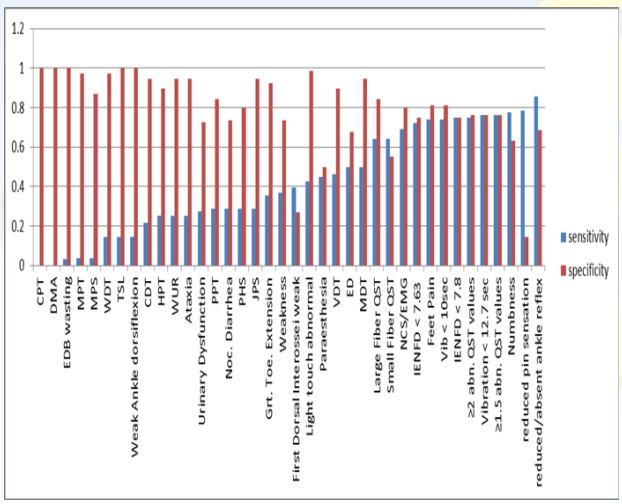
The London Pain Consortium

CHANT – Clinical HIV-associated Neuropathy Tool

- Diagnostic Instrument for Assessment of HIV-SN in:
  - Routine clinical practice, incl. resource-restricted settings
  - Clinical trials
  - Large scale epidemiological/genetics studies

The London Pain Consortium

HIV-SN Diagnostic Sensitivity and Specificity of Individual HIV-PINs Measurands



Yohannes Woldeamanual

Yohannes Woldeamanual

CHANT – Clinical HIV-associated Neuropathy Tool

The purpose of this questionnaire
This questionnaire is designed to assist the diagnosis of HIV-associated peripheral neuropathy, assess the likelihood of any pain being neuropathic in origin, and describe the intensity and characteristics and impact of the neuropathic pain.
Triage for Tools
The following tool has been developed within an algorithm to answer the following four questions systematically.
1. *Does the patient have neuropathy?*
2. *Is the pain neuropathic?*
3. *What are the severity and characteristics of the pain?*
4. *What is the impact of the pain?*

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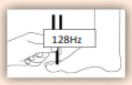
Does the patient have neuropathy?		
	Right	**Left**
Subjective measures (Interview)		
Ask if the patient has foot pain 0 = no foot pain 1 = has foot pain		
Ask if the patient has foot numbness 0 = no foot numbness 1 = has foot numbness		
Objective measures (Examination)		
Vibration test at great toe 0 = normal 1 = diminished/absent 		
Ankle reflex 0 = normal 1 = diminished/absent		
Total Score		
Total Score Both Sides		

Yohannes Woldeamanual

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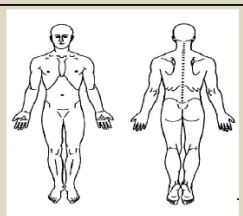
To address question #2

Is the pain neuropathic?

Part I

Using the following body map, please ask the patient to shade the areas where pain is felt.



Yohannes Woldeamanual

CHANT – Clinical HIV-associated Neuropathy Tool

The purpose of this questionnaire

This questionnaire is designed to assist the diagnosis of HIV-associated peripheral neuropathy, assess the likelihood of any pain being neuropathic in origin, and describe the intensity and characteristics and impact of the neuropathic pain.

Triage for Tools

The following tool has been developed within an algorithm to answer the following four questions systematically.

1. *Does the patient have neuropathy?*
2. *Is the pain neuropathic?*
3. *What are the severity and characteristics of the pain?*
4. *What is the impact of the pain?*

Part II

DN4-Interview [1]

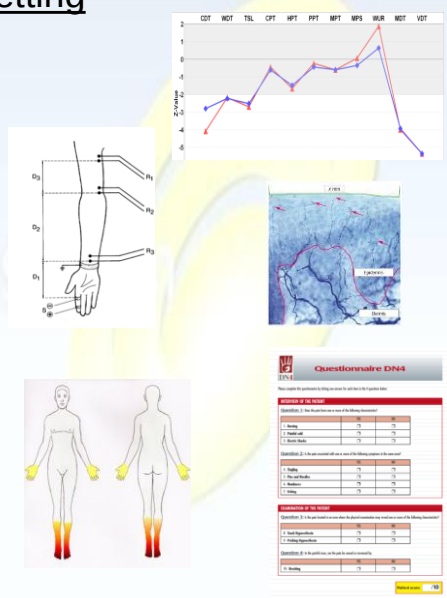
Interview	YES	NO
Does the pain have one or more of the following characteristics?		
Burning		
Painful cold		
Electric shocks		
Is the pain associated with one or more of the following symptoms in the same area?		
Tingling		
Pins and needles		
Numbness		
Itching		
Total Score [Yes = 1 point, No = 0 point]		

Please refer to Appendix II for scoring.

Douleur Neuropathique 4 Questions (DN4)
Bouhassira et al Pain 2005;114:29–36

Clinical Assessment of HIV-SN In High Resourced Specialist Setting

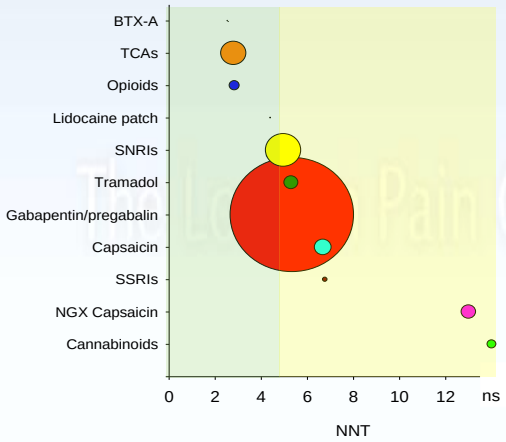
- Evidence of neuropathy?
  - Structured neurological examination
  - Symptom and sensory profiling
  - Diagnostic criteria - 2/3 of:
    - Decreased IENFD on skin biopsy
    - Evidence of axonal neuropathy on NCS
    - > 2 abnormal QST findings
- Exclude other causes of sensory neuropathy
  - Diabetes
  - Chemotherapy
  - Neurology opinion if in doubt
- Is pain neuropathic?
  - Pain drawing
  - DN4 questionnaire



- Neuropathic pain

- HIV-associated neuropathy
  - Epidemiology
  - (Pathogenesis)
  - Clinical presentation
  - Clinical assessment
  - Treatment

Meta-analysis of RCTs in Peripheral Neuropathic Pain



Finnerup et al Pain 2010:150:573-851

- Primary therapy for underlying neuropathy and disease
- Drug therapy for alleviation of pain:
  - Evidence to support use of:
    - Tricyclic antidepressants & duloxetine
    - Gabapentinoids
    - Opioids
    - Topical local anaesthetics
    - Topical capsaicin 0.075% & 8%

Meta-analysis of RCTs for Analgesic Efficacy in HIV-SN

Phillips TJC et al PLoS ONE 2010;5: e14433

Efficacy

- NGF (s.c.) (McArthur 2000)
- Capsaicin 8% (Simpson 2008)
  - ($NNT_{30\%}$ 6.46)
  - (NB Simpson et al 2012)
- Smoked cannabis (Abrams 2007; Ellis 2008)
  - $NNT_{30\%}$ 3.6
  - $NNT_{30\%}$ 3.5

No Evidence

- Opioids

No Efficacy or Minor Effect

- Amitriptyline (Kieburtz 1998; Shlay 1998)
- Mexilitine (Kieburtz 1998)
- Acupuncture (Shlay 1998)
- Peptide T (Simpson 1996)
- Capsaicin 0.075% (Paice 2000)
- Prosaptide (Evans 2007)
- Acetylcarnitine (Youle 2007)
  - Efficacy in EE population
- Lamotrigine (Simpson 2000 & 2003)
  - Efficacy for ATN patients
- Gabapentin (Hahn 2004)
- Pregabalin (Simpson 2010)

Imperial College

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Europain

International Association for the Study of Pain IASP Working together for pain relief