Professor Andrew Rice  
Chelsea and Westminster Hospital, London

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Andrew Rice</td>
<td>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</td>
</tr>
</tbody>
</table>

Date: November 2013
BHIVA Best Practice Management Session:
Peripheral Neuropathy

Andrew SC Rice
a.rice@imperial.ac.uk
• Neuropathic pain

• HIV-associated neuropathy
  – Epidemiology
  – (Pathogenesis)
  – Clinical presentation
  – Clinical assessment
  – Treatment
• Neuropathic pain

• HIV-associated neuropathy
  – Epidemiology
  – (Pathogenesis)
  – Clinical presentation
  – Clinical assessment
  – Treatment
Persisted Pain

Nociceptive Pain
• Pain in response to a noxious stimulus
• Nociplastic: sensitivity to stimuli may be enhanced by inflammation

Neuropathic Pain
• Pain as a direct consequence of a lesion or disease affecting the somatosensory system
  • Absence of a noxious stimulus
  • No discernable biological function
  • Disorder of nerve repair/regeneration?

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

- Variably associated with sensory perturbations:
  - Sensory Loss:
    • Pain in areas of sensory loss - *Anaesthesia Dolorosa*

  - Sensory gain:
    • *Alldynia* - pain in response to an innocuous stimulus
    • *Hyperalgesia* - increased response to a painful stimulus
    • *Hyperpathia* - increased response to a repetitive noxious stimulus, often associated with an increased threshold.

- Prevalence UK & France ~ 7%¹

- Usually severe and chronic²:
  - Mean duration 78 months
  - Mean pain intensity 6/10

¹ Torrance et al 2006; Smith et al 2007; Brekenstra et al 2008
² Backonja & Stacey 2004
<table>
<thead>
<tr>
<th>Range of Underlying Diseases Associated with Neuropathic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trauma to nervous system</td>
</tr>
<tr>
<td>• Peripheral neuropathies</td>
</tr>
<tr>
<td>• Metabolic, dietary &amp; toxic</td>
</tr>
<tr>
<td>• Infection</td>
</tr>
<tr>
<td>• CNS disease</td>
</tr>
<tr>
<td>• Tumours</td>
</tr>
<tr>
<td>• Nerve compression</td>
</tr>
<tr>
<td>• Genetic channelopathies</td>
</tr>
</tbody>
</table>
• Neuropathic pain

• HIV-associated neuropathy
  – Epidemiology
  – (Pathogenesis)
  – Clinical presentation
  – Clinical assessment
  – Treatment
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 demyelinating polyradiculopathy
  - Chronic inflammatory demyelinating 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 polyradiculomylitis
  - Lymphomatous polyradiculopathy
  - AIDS cachexia neuropathy

- **All stages**
  - Antiretroviral toxic neuropathy
  - Other drugs (e.g. 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)

<table>
<thead>
<tr>
<th></th>
<th>1993 Pre-CART</th>
<th>N = 94</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-SN Prevalence</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Any Pain</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Pain &gt; 5/10</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Using NRTI</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ever used NRTI</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>
HIV-Sensory Neuropathy Prevalence

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

<table>
<thead>
<tr>
<th></th>
<th>1993 Pre-CART (N = 94)</th>
<th>2001 CART- dNRTI era (N = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-SN Prevalence</td>
<td>13%</td>
<td>44%</td>
</tr>
<tr>
<td>Any Pain</td>
<td>?</td>
<td>74%</td>
</tr>
<tr>
<td>Pain &gt; 5/10</td>
<td>?</td>
<td>37%</td>
</tr>
<tr>
<td>Using NRTI</td>
<td>-</td>
<td>62%</td>
</tr>
<tr>
<td>Ever used NRTI</td>
<td>-</td>
<td>82%</td>
</tr>
</tbody>
</table>
### HIV-Sensory Neuropathy Prevalence

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

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

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

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: Nakasuja et al., 2005; USA: Ellis et al., 2010; Simpson et al., 2006
## Genetic Risk Factors for HIV-SN

<table>
<thead>
<tr>
<th></th>
<th>Australia¹</th>
<th>Indonesia²</th>
<th>USA &amp; Italy³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of</td>
<td>TNFA–1031*2</td>
<td>TNFA–1031*2</td>
<td>MTND2*</td>
</tr>
<tr>
<td>neuropathy</td>
<td></td>
<td></td>
<td>LHON4917G</td>
</tr>
<tr>
<td>Decreased risk of</td>
<td>IL12B(3’UTR)*2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Canter et al *Pharmacogenomics J* 2007; 8:71-72..
### Ethnicity and Genes Associated With HIV-SN Risk

<table>
<thead>
<tr>
<th></th>
<th><strong>TNFA-1031</strong>&lt;sup&gt;+&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt; (increased SN risk)</th>
<th><strong>IL12B(3’UTR)</strong>&lt;sup&gt;+&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt; (reduced SN risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Indonesian (Malay)</strong></td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td><strong>African</strong></td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>


Slide Courtesy of Dr P Kamerman
• Neuropathic pain

• HIV-associated neuropathy
  – Epidemiology
  – (Pathogenesis)
  – Clinical presentation
  – Clinical assessment
  – Treatment
D-NRTI Drugs Induce a Mitochondrial Neuropathy

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

Victoria C. J. Wallace, Julia Blackmond, Andrew R. Segenbahl, Fausto Huerta, Timothy Pheby, Stephen B. McFadden and Andrew S. C. Ross

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

Nino Mantini, Andrew L. Wallace, Fausto A. Huerta, Stephen B. McFadden, Andrew S. C. Ross

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

Brendan A. Byrne, Ian J. Wilson, Charlotte M. Holley, Ravi Horvat, Mauri Savitskaya-Kosoff, David C. Samuels, D. Ashley Pricci, and Patrick F. O’Dwyer
GP120 Hypothesis

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

Macrophage

Schwann Cell

TNF-α & other cytokines

Primary Afferent

Dorsal Root Ganglion

CCR5

CxCR4
Natural History of HIV-1 infection

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

Luzzi, G. A. et al.
• Neuropathic pain

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

<table>
<thead>
<tr>
<th></th>
<th>No HIV-SN n=38</th>
<th>HIV-SN n=28</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age yrs (SD)</td>
<td>47.69 (8.87)</td>
<td>51.32 (8.36)</td>
<td>0.097</td>
</tr>
<tr>
<td>Male (%)</td>
<td>32 (84.21)</td>
<td>25 (89.28)</td>
<td>0.553</td>
</tr>
<tr>
<td>Height cm (SD)</td>
<td>175.08 (8.82)</td>
<td>177.14 (7.76)</td>
<td>0.321</td>
</tr>
<tr>
<td>Weight kg (SD)</td>
<td>77.11(15.08)</td>
<td>80.50(12.19)</td>
<td>0.334</td>
</tr>
<tr>
<td>Years since HIV diagnosis (SD)</td>
<td>14.71(7.79)</td>
<td>17.79 (7.02)</td>
<td>0.094</td>
</tr>
<tr>
<td>Current CD4 cells/mm³ (SD)</td>
<td>536.86 (262.92)</td>
<td>536.78 (235.94)</td>
<td>-</td>
</tr>
<tr>
<td>Viral load &lt; 50 copies/ml number of subjects (%)</td>
<td>32 (84.2)</td>
<td>26 (92.8)</td>
<td>-</td>
</tr>
<tr>
<td>White European (%)</td>
<td>33 (86.84)</td>
<td>24 (85.71)</td>
<td>0.553</td>
</tr>
<tr>
<td>African Origin (%)</td>
<td>4 (10.53)</td>
<td>3 (10.71)</td>
<td>0.553</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>1(2.63)</td>
<td>0</td>
<td>0.553</td>
</tr>
<tr>
<td>Mixed ethnicity (%)</td>
<td>0</td>
<td>1 (3.57)</td>
<td>0.553</td>
</tr>
</tbody>
</table>
## SYMPTOMS

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

<table>
<thead>
<tr>
<th></th>
<th>No HIV-SN n=38</th>
<th>HIV-SN n=28</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>4.56 (1.08)</td>
<td>5.01 (1.07)</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>Triglyceride</strong></td>
<td><strong>1.61 (0.77)</strong></td>
<td><strong>2.18 (1.09)</strong></td>
<td><strong>&lt;0.020</strong></td>
</tr>
<tr>
<td>HDL</td>
<td>1.06 (0.36)</td>
<td>1.24 (0.44)</td>
<td>0.069</td>
</tr>
<tr>
<td>LDL</td>
<td>2.75 (0.93)</td>
<td>2.71 (0.95)</td>
<td>0.860</td>
</tr>
<tr>
<td>Cholesterol : HDL ratio</td>
<td>4.53 (1.57)</td>
<td>4.42 (1.27)</td>
<td>0.769</td>
</tr>
<tr>
<td>Random glucose</td>
<td>5.31 (1.20)</td>
<td>5.31 (1.07)</td>
<td>0.863</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>25.28 (5.34)</td>
<td>25.68 (3.69)</td>
<td>0.223</td>
</tr>
<tr>
<td>Waist-hip circ. ratio (SD)</td>
<td>0.98 (0.09)</td>
<td>0.96 (0.12)</td>
<td>0.739</td>
</tr>
<tr>
<td>Current statin use (%)</td>
<td>9 (23.70)</td>
<td>9 (32.14)</td>
<td>0.446</td>
</tr>
</tbody>
</table>
Co-Morbidities

<table>
<thead>
<tr>
<th></th>
<th>No HIV-SN n=38</th>
<th>HIV-SN n=28</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Insomnia (ISI&gt;15)</td>
<td>7 (22.6%)</td>
<td>13 (68.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression (DAPOS)</td>
<td>8.38 (+/-4.10)</td>
<td>11.21 (+/-4.22)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Anxiety (DAPOS)</td>
<td>5.45 (+/-2.89)</td>
<td>7.47 (+/-2.97)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pain interference (BPI)</td>
<td>15.2 (+/-16.2)</td>
<td>46.1 (+/-13.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## QoL SF-36

<table>
<thead>
<tr>
<th>SF-36 Domain</th>
<th>HIV-No SN (n=38)</th>
<th>SD</th>
<th>HIV-SN with pain (n=21)</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>74.03</td>
<td>24.65</td>
<td>34.47</td>
<td>21.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Role Physical</td>
<td>50.78</td>
<td>43.76</td>
<td>11.84</td>
<td>28.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>69.43</td>
<td>24.47</td>
<td>29.42</td>
<td>18.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>General Health</td>
<td>43.78</td>
<td>26.96</td>
<td>26.58</td>
<td>19.88</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vitality</td>
<td>49.53</td>
<td>24.08</td>
<td>25.79</td>
<td>24.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>67.98</td>
<td>27.31</td>
<td>32.24</td>
<td>24.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>54.17</td>
<td>46.18</td>
<td>15.79</td>
<td>32.14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mental Health</td>
<td>63.25</td>
<td>21.25</td>
<td>47.79</td>
<td>17.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Sensory Profile
## DFNS Quantitative Sensory Testing Protocol

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Fibre type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold Detection Threshold (CDT)</td>
<td>Aδ</td>
</tr>
<tr>
<td>Warm Detection Threshold (WDT)</td>
<td>C</td>
</tr>
<tr>
<td>Thermal Sensory Limen (TSL) &amp; Paradoxical Heat Sensation (PHS)</td>
<td>Aδ &amp; C Pathological response</td>
</tr>
<tr>
<td>Cold Pain Threshold (CPT)</td>
<td>Aδ? C?</td>
</tr>
<tr>
<td>Heat Pain Threshold (HPT)</td>
<td>C</td>
</tr>
<tr>
<td>Mechanical Detection Threshold (MDT)</td>
<td>Aβ</td>
</tr>
<tr>
<td>Mechanical Pain Threshold (MPT)</td>
<td>Aβ</td>
</tr>
<tr>
<td>Mechanical Pain Sensitivity (MPS)</td>
<td>Aδ Stimulus response function</td>
</tr>
<tr>
<td>Dynamic Mechanical Allodynia (DAA)</td>
<td>Aβ Stimulus response function</td>
</tr>
<tr>
<td>Windup Ratio (WUR)</td>
<td>Aδ Temporal Summation - Pathological response</td>
</tr>
<tr>
<td>Vibration Detection Threshold (VDT)</td>
<td>Aβ</td>
</tr>
<tr>
<td>Pressure Pain Threshold (PPT)</td>
<td>Aδ? C?</td>
</tr>
</tbody>
</table>

Non-noxious; noxious

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


<table>
<thead>
<tr>
<th>Intraepidermal Nerve Fibre Density</th>
<th>No HIV-SN n=34</th>
<th>HIV-SN n=26</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibres/mm (median; range)</td>
<td>9.2 (1.7-14.4)</td>
<td>6.3 (0.7-12.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with &lt; 7.63 fibres/mm (%)</td>
<td>8 (21%)</td>
<td>17 (61%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Targeted Prescribing Of Analgesics In Neuropathic Pain According To Individual Profiles

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

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

- NPRS diff to placebo
  - Change from baseline (points 19)
  - * vs placebo
  - vs placebo
  - $p = 0.9$

- punctate hyperalgesia score ≥8 [n=39]
- punctate hyperalgesia score ≤7 [n=260]
• Neuropathic pain

• HIV-associated neuropathy
  – Epidemiology
  – (Pathogenesis)
  – Clinical presentation
  – Clinical assessment
  – Treatment
Diagnosis & Assessment of Neuropathic Pain

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?
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
HIV-SN Diagnostic Sensitivity and Specificity of Individual HIV-PINs Measurands
CHANT – Clinical HIV-associated Neuropathy Tool

<table>
<thead>
<tr>
<th>The purpose of this questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triage for Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following tool has been developed within an algorithm to answer the following four questions systematically:</td>
</tr>
</tbody>
</table>

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?
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 severity 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?

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)

Subjective foot at great toe:
- 0 = normal
- 1 = diminished/absent

Ankle reflex:
- 0 = normal
- 1 = diminished/absent

Total Score
Total Score Both Sides
CHANT – Clinical HIV-associated Neuropathy Tool

**The purpose of this questionnaire**

This questionnaire is designed to assist in 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 cascadingly:

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?

**To address question #2:**

*Is the pain neuropathic?*

**Part 1**

Using the following body map, please ask the patient to shade the area where pain is felt.
CHANT – Clinical HIV-associated Neuropathy Tool

The purpose of this questionnaire

1. The following tool has been developed within an algorithm to answer the following five questions: symptomually.

2. Does the patient have neuropathy?

3. What are the severity and characteristics of the pain?

4. What is the impact of the pain?

Part II

DN4 Interview 1

Interview

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Does the pain have one or more of the following characteristics?

- Burning
- Pinprick
- Electrocutaneous
- Is the pain associated with one or more of the following symptoms in the same area?
- Tingling
- Pin and needles
- Numbers
- Location

Total Score [Yes = 1 point, No = 0 point]

Reference:

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

- 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%

Finnerup et al Pain 2010:150:573-851
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\textsubscript{50} 6.46
  - (NB Simpson et al 2012)
- Smoked cannabis (Abrams 2007; Ellis 2008)
  - NNT\textsubscript{50} 3.6
  - NNT\textsubscript{50} 3.5

**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)

**No Evidence**

- Opioids
**Imperial College**

- Victoria Wallace
- Philippa Moss
- Tudor Phillips
- Wenlong Huang
- Yohannes Woldeamanual

- Klio Maratou
- Fauzia Hasnie
- Julie Blackheard
- Isobel Lever
- Andy Segerdahl
- Ewen Legg
- Matthew Brown
- Tim Pheby

- Sarah Cox
- Kenji Okuse

**External**

- Peter Kamerman – Johannesburg
- Maria Papathanasopoulos – Johannesburg
- Steve McMahon - KCL
- Meirion Davies / Susan Hall - KCL
- Christine Orengo/Jim Perkins – UCL
- Dave Bennett/Juan Ramirez-Rozo/Margarita Calvo – KCL
- Amanda Williams -UCL
- Christoph Maier/Elena Krumova (DFNS)

**Funding**

- The London Pain Consortium
- The Wellcome Trust
- The Derek Butler Trust
- IMI
- Euro Pain
- IASP