Original Reports

A Comparison of Self-reported Pain Measures Between Sensory Phenotypes in HIV-associated Sensory Neuropathy

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Abstract: Painful HIV-associated neuropathy (HIV-SN) is a prevalent co-morbidity of HIV infection. Sensory phenotyping, using quantitative sensory testing (QST) could allow for improved stratification to guide personalized treatment. However, previous methods of QST interpretation have demonstrated limited association with self-reported pain measures. This study sought to identify differences in self-reported pain measures between composite QST-derived sensory phenotypes, and to examine any differences in participants reporting multi-site, multi-etioloigic chronic pain. In this cross-sectional observational study of participants with HIV (n = 133), individuals were allocated to neuropathy and neuropathic pain groups through clinical assessment and nerve conduction testing. They completed symptom-based questionnaires and underwent standardized QST. Participants were assigned, by pre-determined algorithm, to a QST-derived sensory phenotype. Symptoms were compared between sensory phenotypes. Symptom characteristics and Neuropathic Pain Symptom Inventory scores differed between QST-derived sensory phenotypes: ‘sensory loss’ was associated with more paroxysmal and paraesthetic symptoms compared to ‘thermal hyperalgesia’ and ‘healthy’ phenotypes (P = .023−0.001). Those with painful HIV-SN and additional chronic pain diagnoses were more frequently allocated to the ‘mechanical hyperalgesia’ phenotype compared to those with painful HIV-SN alone (P = .006). This study describes heterogeneous sensory phenotypes in people living with HIV. Differences in self-reported pain outcomes between sensory phenotypes has the potential to guide future stratified trials and eventually more targeted therapy.

Perspective: This article presents quantitative sensory testing derived phenotypes, thought to reflect differing pathophysiological pain mechanisms and relates them to self-reported pain measures in people with HIV infection. This could help clinicians stratify patients to individualize analgesic interventions more effectively.

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https://doi.org/10.1016/j.jpain.2022.09.005
prompt initiation of anti-retroviral therapy (ART) at diagnosis, irrespective of signs of immune compromise \(^1\)\(^{−}\)\(^3\) and improved access to ART \(^4\) has led to HIV becoming a chronic illness in many parts of the world.\(^5\) However, despite viral suppression and overtly preserved immune function, it appears that long-term HIV infection is associated with an increased risk of co-morbidities such as cardiovascular disease, cancer, and chronic pain.\(^6\)\(^−\)\(^8\)

One of the most researched chronic pain conditions in HIV is painful HIV-associated sensory neuropathy (HIV-SN), a consequence of the neurotoxic effects of the virus and its treatment.\(^9\)\(^−\)\(^16\) However, treatment for this condition is still limited with patients often undergoing a cycle of ‘trial and error’ to determine the most appropriate analgesic intervention.\(^12\)\(^,\)\(^17\)\(^−\)\(^21\) In common with other neuropathic syndromes, this issue is thought to be in part due to heterogeneity in symptoms and signs which are hypothesized to reflect distinct underlying pain generating mechanisms with differential response to therapy.\(^22\)\(^,\)\(^23\)

It is hypothesized that determining clusters of such signs and symptoms could lead to an individual being allocated to a specific ‘sensory phenotype’ as a biomarker to guide individualized therapy.\(^23\)\(^−\)\(^27\) Methods for determining phenotypes include symptom-based questionnaires (for example, the neuropathic pain symptom inventory (NPSI), and psychophysical measures such as quantitative sensory testing (QST) and conditioned pain modulation (CPM)).\(^22\)\(^,\)\(^26\)\(^,\)\(^30\)

Previous phenotyping studies have focused on determining differences between clusters of patients rather than allocating an individual to a specific phenotype, which is crucial for its use in clinical or trial settings. Furthermore, allocation, based on a composite sensory profile, rather than a salient sensory modality, potentially provides a more accurate assessment of pathophysiological mechanisms. An algorithm, published by the German Research Network on Neuropathic Pain (DFNS), is now available. It uses all parameters in their standard QST protocol to allocate an individual to 1 of 4 sensory phenotypes: ‘healthy phenotype’, ‘sensory loss’, ‘thermal hyperalgesia’, and ‘mechanical hyperalgesia’.\(^31\)

Another limitation of QST in clinical practice is the apparent lack of association with patient reported measures of pain.\(^32\)\(^,\)\(^33\) Multiple studies have demonstrated its ability to discriminate between those with and without neuropathy but there is limited evidence associating QST findings with the presence or absence of pain, types of painful symptoms or functional measures (both physical and psychological). Very few studies have examined the association between more detailed self-reported pain measures, such as the neuropathic pain symptom inventory (NPSI), and composite sensory phenotypes, which could provide important mechanistic information linking symptoms with pathophysiological processes, ultimately improving precision therapy.

A further complication in determining sensory phenotypes in ‘real world’ populations is the presence of co-existing chronic pain conditions. Commonly patients with ‘secondary conditions’ are excluded from research populations. This limits the generalizability of findings, particularly when very high proportions of patient cohorts are known to have multiple painful conditions. HIV infection is associated with many chronic pain conditions\(^4\)\(^,\)\(^34\)\(^−\)\(^37\) and up to two-thirds of those with HIV-SN report other painful co-morbidities.\(^38\) Multi-etiologic pain, associated with HIV has a high impact on quality of life\(^39\)\(^,\)\(^40\) and can limit the effectiveness of interventions targeted at a specific pain condition, eg HIV-SN. It is therefore important to understand sensory phenotypes and self-reported pain outcomes in the context of other pain as this may reveal differing patterns; for example, those with multi-etiologic pain may demonstrate sensory phenotypes associated with central sensitization.

We hypothesize that individuals with HIV infection can be allocated to one of four different QST-derived composite sensory phenotypes (‘sensory loss’, ‘mechanical hyperalgesia’, ‘thermal hyperalgesia’, and ‘healthy’) and that allocation will be associated with distinct patterns of patient-reported pain symptoms.

We also hypothesize that there is an overlap between painful HIV-SN and other chronic pain conditions and that those with multi-etiologic pain will display differential sensory phenotypes compared to those with isolated HIV-SN.

**Methods**

**Study Design**

The Phenotyping and Genotyping of HIV-SN (POGO)

Study was an observational cross-sectional study approved by the English National Research Ethics Service (14/LO/1574). Study design and documents were reviewed by a patient partner for clarity and acceptability. All participants completed written consent prior to enrolment and were reimbursed for travel expenses.

Participants were recruited pragmatically from outpatient clinics associated with Chelsea & Westminster Hospital NHS Foundation Trust in London, UK and from patient charities in the UK by general advertisement.

For inclusion, participants were required to be aged at least 18 and have a serological diagnosis of HIV infection. Exclusion criteria included limited English language skills that would impair ability to complete

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**Key words:** Neuropathic pain, HIV-associated sensory neuropathy, quantitative sensory testing, sensory phenotype.
sensory testing, pregnancy and co-incident severe neurological condition. Participants with and without HIVSN, and with and without other chronic pain diagnoses were recruited to enable comparison of sensory phenotypes between neuropathy and chronic pain groupings.

Participants attended a single appointment for clinical assessment by one clinical researcher (HIK). Demographic information, including sex, age, and ethnicity were collected and a detailed medical and drug history (including declared illicit drug use) were taken with a focus on HIV and chronic pain diagnoses and medication. Confounding conditions associated with peripheral neuropathy (such as hypothyroidism, hepatitis, diabetes, chemotherapy, and alcohol excess) were recorded. Patient reported data were confirmed and any incomplete responses identified from medical notes where possible.

In a standardized order, participants then underwent a structured neurological examination, sensory phenotyping by quantitative sensory testing (QST) at the foot and point-of-care sural nerve conduction measurement. At the end of the appointment, to reduce the time burden of the study, participants were asked to complete a booklet of questionnaires and to return them by post within 2 weeks. Reminder telephone calls were performed if questionnaires were not returned within 2 weeks.

**Clinical Examination**

A structured, comprehensive neurological examination was performed (protocol previously described in Philips et al	extsuperscript{[34]}) to identify signs of peripheral neuropathy and other neurological signs that may influence QST results. The Clinical HIV-Associated Neuropathy Tool (CHANT) was used as a neuropathy screening tool.

It comprises of a self-report of pain and/or numbness in the feet and lower limbs, and an examination to detect reduced vibration detection at the distal interphalan-geal joint of the great toe, using a 128/64Hz graded Rydel-Seiffer tuning fork, and/or reduced ankle reflexes. The presence of a combination of 1 bilateral sign and 1 bilateral symptom was used to identify participants with neuropathy (see definitions below).

**Quantitative Sensory Testing**

QST was performed to the full protocol designed by the German Research Network for Neuropathic Pain (DFNS)	extsuperscript{[41,42]} by a single investigator (HIK) who underwent formal training with the network and validation by testing on healthy volunteers. All equipment was calibrated prior to study commencement.

Sensory modalities in the DFNS protocol, excepting pressure pain threshold (PPT), were tested in the S1 dermatome of the dorsum of the left foot, unless participants stated the right foot was more painful or if there was evidence of an underlying condition such as previous surgery or trauma which may have confounded results. PPT was tested within the S1 dermatome, but at the sole of the foot.

**Sural Nerve Conduction**

The DPNCheck device (Neurometrix, Waltham, USA) was used to measure sural nerve conduction at the ankle on the same side as QST was conducted. This is a point-of-care nerve conduction device that has been validated in healthy cohorts, by comparison with formal nerve conduction studies, and in diabetic polyneuropathy cohorts, in comparison to electrophysiological and clinical neuropathy gradings. It is a single unit handheld device consisting of a biosensor that is positioned at a static distance from two stimulation probes. Orthodromic stimulation of the sural nerve is achieved with increasing stimuli until depolarization is detected at the sensor. This provides an estimate of sensory nerve action potential (SNAP) and a sensory nerve conduction velocity (SNCV). Individualized normative values based on age and height were calculated for each patient based on the manufacturer’s algorithm.

The DPNCheck became available after the start of study recruitment; therefore in participants where the DPNCheck was not performed, if clinical electrophysiology of the lower limb had been performed with evidence of neuropathy, these data were retrieved from the patient record and used in place of the DPNCheck values as evidence of neuropathy.

**Neuropathic Symptom and Pain Questionnaires**

Participants were asked to complete a booklet of questionnaires. If they reported more than one site of pain, they were asked to complete the pain questionnaires with respect to their feet. The Neuropathic Pain Symptom Inventory (NPSI)	extsuperscript{[50]} was used to characterize neuropathic symptoms and to correlate symptoms with signs elicited on QST. The Brief Pain Inventory (BPI)	extsuperscript{[51]} was used to assess pain severity and pain interference.

**Pain Distribution**

Participants were shown a simplified body map divided into 102 areas (see Supplemental Material 1) and asked to shade all areas where they currently perceived pain. For each painful site, they were asked to...
report the duration of pain and current, average and worst intensity (over the last 7 days) using an 11-point numerical rating scale (NRS). If the diagnostic reason for the pain was known, this was also recorded. The number of discrete areas of pain, as labelled on the body map, was summed to produce a ‘total number of painful sites’. In those with neuropathy, a ‘total number of non-HIV-SN-related painful sites’ was also calculated where the number of sites of pain associated directly with HIV-SN was subtracted from the total number of painful sites. To further assess the spatial burden of pain, painful body sites were also re-categorized to the widespread pain index of the ARC 2010 Fibromyalgia Diagnostic criteria. Those with a widespread pain index (WPI) of ≥3 were categorized into a ‘high pain burden’ group.

Participants were asked to report any previous or current diagnoses of specific chronic pain conditions by checklist (Supplemental Material 1). A ‘total number of non-HIV-SN chronic pain diagnoses’ was calculated for each participant.

**Group Definitions**

It was necessary to define individuals on the basis of 2 definitions. Firstly, the presence of chronic pain at any body site, and secondly, the presence of neuropathy and the likelihood of neuropathic pain.

**Definition of Chronic Pain**

Participants were classified as having chronic pain if they described pain that lasted or recurred for at least 3 months, according to the IASP ICD-11 definition. Those scoring their average pain at least 4 out of 10 on an 11-point numerical rating scale were defined as having ‘at least moderate’ chronic pain, as this is thought to be reflective of ‘clinically meaningful pain’ that interferes with function. Those scoring 3 or less were allocated to no or minimal pain group. This definition was used to define both chronic pain, associated with HIV-SN, and chronic pain at other body sites.

**Definition of Neuropathy and Associated Neuropathic Pain**

Assessment of potential neuropathy was performed as per the updated grading system described in the NeuPSIG guidelines (Fig 1). To be assigned to the painful HIV-SN group, those with pain needed to satisfy the criteria relating to either ‘probable’ or ‘definite’ neuropathic pain:

- **Probable neuropathic pain**: pain associated with sensory signs in the same distribution as pain (participant scored at least one sign and one symptom bilaterally on the Clinical HIV Associated Neuropathy Tool (CHANT)).
- **Definite neuropathic pain**: Demonstration of a lesion of somatosensory system by at least one confirmatory test (sural nerve conduction study or clinical electrophysiological confirmation of neuropathy).

A Comparison of Self-reported Pain Measures Between

If, participants screened positive for neuropathy on CHANT but had normal nerve conduction results, they were still defined as having neuropathy as HIV-SN is known to be a mixed large/small fiber neuropathy, therefore negative nerve conduction studies cannot rule out HIV-SN. Instead, these participants meet only the probable rather than definite criteria for neuropathic pain.

**Group Allocation Based on Criteria for Chronic Pain and Neuropathy**

The process for allocating participants to groups is outlined in Fig 1.

The definitions for both neuropathy and chronic pain were combined to produce three groups to which all participants were allocated; ‘Painful HIV-SN’ (chronic foot pain plus probable or definite evidence of neuropathy), ‘Painless HIV-SN’ (neuropathy with no or minimal pain), or ‘No HIV-SN (no foot pain and no evidence of neuropathy).

Those reporting foot pain but not meeting the criteria for HIV-SN were not included in comparative analyses due to lack of diagnostic clarity.

**Statistical Analysis**

Data were tested for normality visually and by using the Shapiro Wilk test. Normal data are presented as mean (sd) or, for QST z-scores as mean ±95% confidence interval. Comparison of normal data between groups was conducted using ANOVA (LSD post hoc analysis). Data that were not normally distributed are presented as median (IQR) and comparison conducted using Kruskal Wallis tests (Dunn post hoc analysis). Categorical data were compared using chi squared or Fisher’s exact test (for small groups <5). Where multiple comparisons were conducted, the significance level was adjusted using the Benjamini-Hochberg procedure to decrease the false discovery rate. Comparison of demographic and HIV-related data were made between the neuropathy and chronic pain groupings.

Z-scores for all QST parameters from each participant were used to allocate that individual to 1 of 4 QST sensory phenotypes: ‘healthy’, ‘thermal hyperalgesia’, ‘mechanical hyperalgesia’ or ‘sensory loss’, using the previously published sorting algorithm. The algorithm was developed in patients with a diverse etiology of neuropathic pain and validated in human models of neuropathy and neuropathic pain. It should be noted that the sensory phenotyping allocation algorithm is not dependent on individual QST modalities being outside the 95% confidence interval, as traditionally, and conservatively, defined as ‘abnormal’. It is a method that instead assesses similarity across the entire profile allowing for a more nuanced assessment of sensory changes. Demographic and pain characteristics and self-reported pain outcomes were compared between QST-derived sensory phenotype groups. Missing questionnaire data were not imputed.
The number of pain sites and pain diagnoses, pain intensity and WPI were compared between those with painless and painful HIV-SN. The proportion of those with ‘high pain burden’ in each QST-derived sensory phenotype group were determined.

A sample size calculation was not possible to determine a group size sufficient to test differences in pain characteristics between QST sensory phenotype groups as there are no a priori data to base this calculation on. However, to provide some indication of sample size required to correlate QST and patient reported symptoms in a similar population, correlation data between QST parameters and NPSI characteristics from a mixed etiology neuropathic pain cohort (r = .5, \( P < .0001 \)) was used to determine a sample size of 29 per group.28 No imputation was performed for missing questionnaire data and only complete QST profiles were included in analysis. To control for confounding factors in establishing sensory phenotypes, four factors differing between the HIV groups were analyzed in a random-effects model. This decision was made after descriptive statistics were known.

**Results**

One hundred forty-eight participants were recruited and tested (a further 3 were screened but excluded due to diagnoses of recent cerebrovascular accident, chemotherapy administration and Charcot’s foot). As per study definitions, 54 had painful HIV-SN, 36 painless HIV-SN (or minimal pain associated with HIV-SN) and 43 had neither HIV-SN, nor foot pain. Of the 54 participants with painful HIV-SN, 41 had confirmatory nerve conduction studies therefore were described as ‘definite’ neuropathic pain. The remainder could only be classified as ‘probable’ neuropathic pain due to lack of availability of the DPNCheck at the start of the study or inability to gain an appropriate reading. Fifteen participants were not included in the finally analyses as they reported foot pain without signs of neuropathy therefore there was diagnostic uncertainty. Characteristics of this group are displayed in Supplemental Table 1.

**Demographics**

All participants had a diagnosis of HIV-1 infection, and the majority of were male (n = 122, 84%). A large proportion (n = 119, 89%) had an undetectable HIV RNA load and the mean CD4 count was high (672 cells/mm\(^3\)), however 37% (n = 49) had a past or current diagnosis of an AIDS defining illness.9 Only 5 (3%) were not prescribed ART at time of inclusion and of those 4 reported never having taken ART. There was a high rate of previous illicit drug use (n = 78, 59%), but less than a quarter (n = 29, 22%) reported current use. The majority of the cohort was employed (54%).

Those with HIV-SN were significantly older and a longer time had elapsed since HIV diagnosis (Table 1). A
higher proportion of those with HIV-SN reported a history of AIDS defining illnesses. There was, however, no difference in these characteristics between those with painful and non-painful neuropathy. Those with detectable viral load and not currently taking ART were represented in all HIV-SN groups (See Supplemental Table 2).

### Quantitative Sensory Testing

Z-scores for QST parameters are presented in Fig 2. The proportion of participants displaying loss and gain of function in each clinical group in Supplemental Fig 1. The mean z-score values for all groups across all parameters were within the normative data range specified by the DFNS (indicated by dotted lines on Fig 2), although individual values were outside the range for all parameters. Cold detection (CDT: painful HIV-SN vs No HIV-SN -1.04(1.25) vs -0.44 (1.63), P < .001; painless HIV-SN vs No HIV-SN -0.89 (1.37) vs -0.44 (0.63), P < .001) were all increased (loss of function, hypesthesia) in the neuropathy groups compared to those in the No HIV-SN group. Mechanical pain threshold (MPT) was also significantly closer to zero in the neuropathy groups compared to those without neuropathy (painful HIV-SN vs No HIV-SN 0.02 (1.58) vs 1.78 (1.06), P < .001; painless HIV-SN vs No HIV-SN -0.62 (1.48) vs 1.78 (1.06), P < .001), indicating higher thresholds and potentially hypesthesia. The only significant differences between the painful and painless HIV-SN groups were higher warm detection (painful HIV-SN vs painless HIV-SN -1.24(0.82) vs −0.63(1.14), P = .003) and mechanical pain thresholds (painful HIV-SN vs painless HIV-SN .02 (1.58) vs 0.62 (1.48), P = .05) in those with painful symptoms, again indicating greater loss of function in this group.

Brush evoked allodynia was identified in only 8 (6%) participants but was present in all groups (painful HIV-SN n = 4 (7%); painless HIV-SN n = 3 (8%); No HIV-SN n = 4 (7%); painless HIV-SN n = 3 (8%), No HIV-SN

### Table 1. Comparison of Demographic and HIV-associated Features Between Neuropathy Groups.

| Total Cohort | Painful HIV-SN | Painless HIV-SN | No HIV-SN | P Value |
|--------------|----------------|----------------|-----------|---------|
| n = 133      | n = 54         | n = 36         | n = 43    |         |
| Age, years   | 52.9 (9.7)     | 55.6 (7.8)     | 55.1 (10.5) | <.001   |
| Male, n (%)  | 112 (84)       | 42 (78)        | 34 (94)   | .104    |
| Ethnicity    |                |                |           |         |
| White        | 109 (82)       | 41 (76)        | 32 (88)   | .260    |
| Black        | 17 (13)        | 11 (20)        | 2 (6)     | 4 (9)   |
| Other        | 7 (5)          | 2 (4)          | 2 (6)     | 3 (7)   |
| BMI, kg/m²   | 24.7 (3.9)     | 25.5 (4.3)     | 24.3 (3.9) | .105    |
| Height, m    | 1.75 (1)       | 1.75 (1)       | 1.76 (1)  | .666    |
| Years since HIV diagnosis | 17.6 (8.7) | 20.1 (8.6) | 18.7 (8.5) | .001 |
| Years between diagnosis and treatment | 3.8 (4.2) | 4.0 (4.6) | 3.6 (3.7) | .874 |
| CD4 count cells/μm³ | 672 (304) | 630 (277) | 685 (364) | .415 |
| CD4 nadir cells/μm³ | 209 (154) | 184 (159) | 192 (164) | .090 |
| Proportion individuals with undetectable viral load, n (%) | 119 (89) | 48 (89) | 32 (89) | .950 |
| Proportion with history of AIDS defining illness, n (%) | 49 (37) | 23 (43)% | 17 (47)% | .029 |
| Employment   |                |                |           |         |
| Employed     | 72 (54)        | 17 (31)%       | 20 (56)   | 35 (81) | <.001 |
| Sick         | 37 (28)        | 26 (48)%       | 8 (22)    | 3 (7)   |
| Unemployed   | 6 (5)          | 3 (6)          | 1 (3)     | 2 (5)   |
| Retired      | 17 (13)        | 8 (15)         | 7 (19)    | 3 (7)   |
| Current illicit drug use, n (%) | 29 (22) | 11 (20) | 8 (22) | 10 (23) |
| History of illicit drug use, n (%) | 78 (59) | 30 (56) | 22 (61) | 26 (60) |
| Current alcohol use, n (%) | 109 (82) | 40 (74) | 32 (89) | 37 (86) |
| Reported units of alcohol consumed per week, units (sd) | 12.4 (20.3) | 8.7 (12.2) | 12.2 (21.1) | 16.4 (25.6) |
| Exposure to d-type NRTI, n (%) | 57 (43) | 27 (50) | 16 (44) | 14 (33) |
| Diabetes, n (%) | 11 (8) | 8 (15) | 2 (6%) | 1 (2%) |
| Previous (cleared) HCV infection, n (%) | 17 (13) | 8 (15) | 6 (17) | 3 (7) |
| Current HCV infection, n (%) | 6 (5) | 1 (2) | 1 (3) | 4 (9) |

*P < .05 versus Painless HIV-SN group.

**P < .001 versus No HIV-SN group.

†P < .05 versus No HIV-SN group.
Figure 2. Comparison of thermal and mechanical quantitative sensory testing z-scores between painful HIV-SN, painless HIV-SN and No HIV-SN groups. Scatter plot with mean (95% confidence intervals) z-scores indicated. Dashed lines represent the z-score +/- 1.96, outside of which the result is classified as being 'loss of function' or 'gain of function' compared to age and sex adjusted population norms. ANOVA with post hoc LSD tests: **P < .001 *P < .01 P < .05 CDT=Cold detection threshold; WDT=Warm detection threshold; TSL=Thermal sensory limen; CPT=Cold pain threshold; HPT=Heat pain threshold; MDT=mechanical detection threshold; MPT=Mechanical pain threshold; MPS=Mechanical pain sensitivity; WUR=Wind up ratio; VDT=vibration detection threshold; PPT=Pressure pain threshold.
A Comparison of Self-reported Pain Measures Between Different HIV-Related Neurological Disorders

Table 2. Comparison of Demographics and Pain Characteristics Between QST-derived Phenotypes.

|                      | Healthy Phenotype | Thermal Hyperalgesia | Mechanical Hyperalgesia | Sensory Loss |
|----------------------|-------------------|-----------------------|-------------------------|-------------|
| **n**                | 20                | 36                    | 49                      | 28          |
| Age, years           | 44.5 (6.9)        | 49.6 (9.5)            | 55.5 (8.1)              | 59.0 (8.2)  |
|                      |                   |                       |                         | <0.001      |
| Sex male n (%)       | 17 (85)           | 31 (89)               | 39 (80)                 | 25 (89)     |
|                      |                   |                       |                         | 0.063       |
| Years since diagnosis| 14.6 (7.3)        | 14.2 (13.2)           | 18.8 (9.1)              | 22.2 (7.7)  |
|                      |                   |                       |                         | <0.001      |
| No. with d-drug ART exposure n (%) | 4 (20.0) | 11 (30.6) | 22 (44.9) | 22 (71.4) |
|                      |                   |                       |                         | <0.001      |
| No. of non-HIV-SN related painful sites | 1 (0–2.8) | 2 (0–5.0) | 3 (0.0–9.5) | 5.0 (0.25–14.0) |
|                      |                   |                       |                         | 0.003       |
| No. of other chronic pain diagnoses | 0 (0–2.0) | 1 (0–2.0) | 1 (1.0–2.0) | 1.5 (1.0–2.75) |
|                      |                   |                       |                         | <0.001      |
| DN4i                 | 1 (0–4.8)         | 2 (0–4)               | 4 (1.8–5)               | 5 (4–6)     |
|                      |                   |                       |                         | <0.001      |
| BPI Severity         | 8 (0–3.0)         | 9 (0–4.1)             | 4.5 (2.2–5.9)           | 3.9 (2.1–6.1) |
|                      |                   |                       |                         | <0.001      |
| BPI Interference     | 8 (0–2.8)         | 0.9 (7–4.1)           | 2.9 (7–5.2)             | 4.1 (2.0–5.6) |
|                      |                   |                       |                         | <0.001      |

*P<.05 compared to ‘healthy’ phenotype.
**P<.01.
***P<.001.

QST Phenotypes and Self-reported Pain Outcomes

For 17 (12.8%) participants, the questionnaire booklet was not fully completed (7 No HIV-SN; 6 Painless HIV-SN; 4 Painful HIV-SN). When individual QST parameter z-scores were analyzed prior to phenotype allocation, there were no significant correlations between any individual QST parameter z-score and self-reported BPI, DN4i or NPSI scores.

However, there were between phenotype differences in self-reported pain outcomes when participants were allocated to the composite QST-derived phenotypes. Those allocated to the ‘sensory loss’ and ‘mechanical hyperalgesia’ phenotypes reported higher DN4i and BPI severity scores than the ‘healthy’ and ‘thermal hyperalgesia’ phenotypes (Table 2).

Those with a ‘sensory loss’ phenotype reported higher paraesthesia (SL: 6.0 (1.5–7.5) vs H: 0.0 (0–4); P = 0.01; TH: 1.0 (0–4.0); P = 0.006) paroxysmal symptoms (SL: 4.5 (1.0–7.5) vs H: 0.0 (0–1.1); P = 0.002; TH: 0.0 (0–3.0); P = 0.009 and...
overall symptom severity (SL: 3.2 (0.0−7.5) vs H: 0.0 (0.0−0.7); $P = .004$ TH: 3.0 (0.0−2.5); $P = .006$) than those with ‘healthy’ and ‘thermal hyperalgesia’ phenotypes (Fig 4) and the ‘mechanical hyperalgesia’ phenotype showed higher burning (MH: 4.0 (0.0−8.0) vs H: 0.0 (0.0−0.0); $P = .027$) and overall intensity scores (MH: 2.7 (2.5−5.3) vs H: 0.0 (0.0−0.7); $P = .009$) compared to the ‘healthy’ phenotype. However, if the analysis was repeated to solely include those with painful HIV-SN the between phenotype differences were no longer significant.

Characteristics of Non-HIV-SN Chronic Pain

Non-HIV-SN pain diagnoses were prevalent in the cohort, present in 96 (72%). More participants with painful HIV-SN, 87% (n = 47) and painless HIV-SN (78%, n = 28) reported a secondary chronic pain diagnosis, compared to 49% (n = 21) of those without neuropathy ($P < .001$, $X^2 = 16.67$; $P = .011$ × 2 = 6.40). The most commonly reported other chronic pain diagnoses were osteoarthritis (n = 35 (23.6%)), low back pain (n = 50 (33.8%) and migraine (n = 23 (15.5%)). Despite the high prevalence of pain diagnoses, 62 (47%) met the study criteria for current chronic pain on the day of interview.

The median number of pain sites for the total cohort was 5 (1−11). More participants with painful HIV-SN reported at least one other site of chronic pain unrelated to HIV-SN compared to those with painless HIV-SN (80%, n = 43 vs 22%, n = 8; $P < .001$). In general, those with neuropathy had more pain diagnoses and sites than those without (Table 3). The most frequent site of pain unrelated to HIV-SN was the lower back (in 26 (18%)).

Widespread Pain Index

Four individuals (3%) scored at least 7 on the WPI (the criteria for chronic widespread pain (CWP)) and 34 (26%) scored at least 3 (the criteria for CWP if other non-pain symptom severity characteristics are present). Significantly more of the painful neuropathy group 41% (n = 22; $P = .002$) had a WPI of ≥3, this studies definition of ‘high pain burden’ and 9% (n = 5) had a formal diagnosis of fibromyalgia.

Comparison of Characteristics Between Those With and Without a High Pain Burden

Considering the whole cohort, those with a high pain burden had been diagnosed with HIV for a longer length of time (21.9 (7.98) years vs 16.2 (8.51); $P = .001$) but there were no significant differences in age, sex, BMI, ethnicity, CD4 count or nadir, viral load, previous or current substance misuse, exposure to d-type ART or prevalence of history of AIDS-defining illness between those with low and high pain burden in the painful HIV-SN group (Supplemental Table 3). However, high pain burden was associated with a higher rate of being on long-term sickness from work ($P < .001$) and this...
difference was maintained when the analysis was repeated to include only those with painful HIV-SN.

Participants with a high pain burden reported a higher DN4i total score (5.0 (4.0−6.0) vs 3.0 (0−4.0); \(P<.001\)) and this remained significant when tested in just the painful HIV-SN population (6.0 (4.0−6.0) vs 5.0 (4.0−5.0); \(P=.021\)) suggesting the presence of more neuropathic symptoms is associated with a high pain burden.

**High Pain Burden and QST-derived Phenotypes**

There were no differences in individual QST parameter z-scores, including wind up ratio (developed and hypothesized as an indirect measure of central sensitization), between those that had a high pain burden and those that did not.

Although nearly half of those in the high pain burden group (n = 16 (47%)) were allocated to the ‘mechanical hyperalgesia’ phenotype, the proportions allocated to each phenotype was not associated with the presence or absence of the high pain burden classification (\(P=.203\) for whole cohort, \(P=.913\) for painful HIV-SN group) (Fig 5). However, the prevalence of non-HIV-SN chronic pain diagnoses was higher in the ‘mechanical hyperalgesia’ and ‘sensory loss’ phenotypes than the ‘thermal hyperalgesia’ and ‘healthy’ phenotype group (Table 2).

Those with chronic pain as a result of HIV-SN alone were more likely to show a ‘sensory loss’ phenotype compared to those with painful HIV-SN and other chronic pain conditions in which the ‘mechanical hyperalgesia’ phenotype predominated (panflun HIV-SN alone SL: n = 7, 64% MH: n = 9, 26% vs painful HIV-SN plus another diagnosis SL: 9, 21% MH: 22, 51%; \(P=.006\), \(X^2 = 7.66\) (Fig 6).

**Analgesic Use**

Half of the cohort reported analgesic use (n = 66, 50%) (Supplemental Table 4). Nearly a third of those with painful HIV-SN used strong opioids (morphine containing, oxycodone, buprenorphine, fentanyl or methadone) (n = 16, 30%) whereas those with pain unrelated to neuropathy did not. Gabapentinoids were used by 12 (22%) and 20% (n = 11) of those with painful HIV-SN did not use any analgesia. Gabapentinoids were used by 12 (22%) and 20% (n = 11) of those with painful HIV-SN did not use any analgesia. Although numbers were small, those with prior use of capsaicin and lidocaine patches displayed a variety of QST-derived phenotypes (Capsaicin SL n = 1, MH n = 1; Lidocaine SL= n1, TH n = 1, MH n = 2). Of those currently taking strong opioid medication, n = 5 (20.8%) were allocated to the ‘thermal hyperalgesia’ phenotype, 10 to the ‘mechanical hyperalgesia’ (41.7%), 9 to the ‘sensory loss’ (37.5%) and none to the ‘healthy’ phenotype. Those in the high pain burden group (WPI of at least 3) were more likely to be taking current strong opioids than those with a lower WPI (n = 13 (38.2%) vs 11 (11.1%), \(P=.01\)).

**Discussion**

This study highlights the heterogeneity of sensory features and reported symptoms in HIV-SN. Importantly, it identifies associations between QST-derived sensory

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**Table 3. Comparison of Pain Distribution, Chronic Pain Prevalence and Validated Pain Questionnaire Scores. WPI=widespread pain index; BPI=Brief Pain Inventory. Significance value corrected using the Benjamini correction procedure (\(P<.023\)).**

|                      | **TOTAL COHORT** | **PAINFUL HIV-SN** | **PAINLESS HIV-SN** | **NO HIV-SN** | **P VALUE** |
|----------------------|------------------|--------------------|---------------------|---------------|-------------|
|                      | n = 133          | n = 54             | n = 36              | n = 43        |             |
| Median no. of non-HIV-SN-related painful sites | 2 (0−7.5) | 7 (2−18) \(^*\) | 3 (0−5) \(^1\) | 0 (0−2) | <.001 |
| Widespread Pain Index (WPI) | 1 (0−3) | 2 (1−4) \(^1\) | 0.5 (0−2) | 0 (0−1) | <.001 |
| Number of participants with WPI =>3, n (%) | 34 (26) | 22 (41) | 8 (22) | 4 (9) | .002 |
| Median no. other chronic pain diagnoses | 1 (0−2) | 2 (1−3) \(^1\) | 1 (1−2) | 0 (0−1) | <.001 |
| No. participants with other chronic pain diagnosis, n (%) | 96 (72) | 47 (87.0) | 28 (77.8) | 21 (48.8) | <.001 |
| BPI Severity Score | 1.75 (0−5.25) | 5.25 (−6.5) \(^1\) | 0.9 (0−2.2) | 0 (0−0) | <.001 |
| BPI interference score | 2.1 (7−4.8) | 4.2 (2.8−5.6) \(^1\) | 1.6 (7−2.6) | 7 (7−7) | <.001 |

\(^*\)significance versus Painless HIV-SN group.

\(^1\)significance versus No HIV-SN group.

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Figure 5. Allocation of low and high pain burden groups to QST-derived sensory phenotypes. a) Included all participants in the cohort and b) just those in the painful HIV-SN group.
phenotypes and patient-reported pain measures. Those with ‘sensory loss’ reported more paraesthetic and paroxysmal symptoms compared to ‘thermal hyperalgesia’ and ‘healthy’ phenotypes. Previously QST has provided many important insights into the mechanisms of neuropathy, but its association with reported pain is lacking, therefore this study provides evidence for its potential ability to discriminate between patient reported pain measures.

The findings also describe the high prevalence of multisite, multi-etiology pain that is associated with HIV infection. We demonstrated that those with painful, rather than painless neuropathy, reported a higher number of non-HIV-SN painful sites and more chronic pain diagnoses. Participants with multiple pain diagnoses were also more likely to be in the ‘mechanical hyperalgesia’ rather than ‘sensory loss’ groups potentially suggesting a more sensitized profile.

Sensory Profiling in Neuropathic Pain

As reported in other neuropathic pain cohorts, this study showed that participants with painful HIV-SN also demonstrate heterogeneity and differential allocation to sensory phenotypes. Previous sensory profiling studies in HIV-SN using unidimensional QST abnormalities have indicated predominantly sensory loss. Whilst sensory loss was identified in our cohort, a large proportion were allocated to the ‘mechanical hyperalgesia’ sensory phenotype. However, it is important to note that the ‘mechanical hyperalgesia’ phenotype is characterized by thermal hypoesthesic as much as by mechanical hyperalgesic features, therefore it also includes features of sensory loss. The allocation of a relatively high proportion to the ‘mechanical hyperalgesia’ phenotype may also reflect the prevalence of widespread pain that may have skewed the cohort towards a more ‘sensitized’ phenotype.

Identification of a heterogeneity in phenotypes has an impact for prospective trial design as it provides a method of stratification based on phenotype that could identify differential drug responses. If validated, utilizing QST-derived phenotypes as a biomarker of drug response, as suggested by the European Medicines Agency, could allow greater precision in prescribing in the future. Indeed, our ‘mechanical hyperalgesia’ phenotype mirrors a subgroup of trial participants (by post hoc analysis) in a clinical trial of pregabalin in HIV-SN that demonstrated a positive response to pregabalin whilst the overall trial was negative.

Whilst performing QST to a DFNS protocol requires specialized, often expensive equipment, efforts are underway to develop and validate shorter, more clinically relevant ‘bedside’ QST protocols which could allow patients to be assessed and a sensory phenotype determined in a low resource clinic setting. The ultimate goal would be to be able to offer pain interventions targeted at the underlying pain mechanism revealed by such a phenotype.

In the case of pharmacological intervention, it has been suggested that each QST-derived sensory phenotype could be responsive to a particular drug intervention. For example, those exhibiting a ‘sensory loss’ phenotype, potentially representing a deafferentation mechanism with ectopic action potentials being generated at more proximal, uninjured sites, may be more responsive to a centrally acting drug such as an antidepressants or opioid. The ‘thermal hyperalgesia’ profile is hypothesized to represent sensitised nociceptors exhibiting reduced thresholds and spontaneous discharge thereby potentially being more responsive to sodium channel blocking agents. Finally, the ‘mechanical hyperalgesia’ phenotype is thought to reflect a central sensitisation mechanism with similar profiles previously indicating responsiveness to gabapentinoids or N-methyl-D-aspartate antagonists.

Association of Sensory Phenotypes and Patient Reported Outcomes

Previous work has not been able to demonstrate significant individual QST-modality differences between those with painful and painless HIV-SN. This is problematic as association between QST based outcomes...
and patient reported measures is essential to its use as a predictor or biomarker of pain (as opposed to neuropathy) both clinically and in research settings. Weak correlations between NPSI scores and certain QST parameters have been previously identified in neuropathic pain cohorts, but mainly between rarer gain of function signs and symptoms, such as reduced pain thresholds and allodynia/hyperalgesia, not loss of detection, a predominant feature in HIV-SN. Similarly, Forstenpointner et al. and overall intensity than ‘thermal hyperalgesia’ and notype reported the higher spontaneous pain scores with NPSI scores. Participants with the ‘sensory loss’ phenotype reported more loss of function in thermal and mechanical parameters in those with moderate/severe neuropathic pain compared to mild neuropathic pain, suggesting that certain QST features may associate with pain severity.

In our cohort, those with painful HIV-SN demonstrated significantly higher warm detection and mechanical pain thresholds than those with painless neuropathy indicating a greater trend towards hypoesthesia. The recent PiNS study, involving participants with painful diabetic neuropathy, also demonstrated more loss of function in thermal and mechanical parameters in those with moderate/severe neuropathic pain compared to mild neuropathic pain, suggesting that certain QST features may associate with pain severity.

Although there were no significant differences between painless and painful HIV-SN groups in the proportion allocated to QST-derived phenotype, we were able to demonstrate significant differences in NPSI scores based on sensory phenotype that were not evident when individual QST parameters were correlated with NPSI scores. Participants with the ‘sensory loss’ phenotype reported the higher spontaneous pain scores and overall intensity than ‘thermal hyperalgesia’ and ‘healthy’ phenotypes. Similarly, Forstenpointner et al. were unable to discriminate between painful and painless neuropathy based on QST phenotype allocation in a large study of multi-etiologic neuropathy but identified some differences in pain sensitivity.

Although measuring pain through patient report is vital, an objective (or, in the case of QST a semi-objective measure) that can be associated with reported symptoms is important as it can provide insight into mechanistic drivers of different domains of self-report which can then be targeted therapeutically.

It should be highlighted that the association between self-reported pain measures and QST measures were conducted on the whole cohort, including a control group with HIV infection, but without HIV-SN. When only those with painful HIV-SN were considered, between QST-derived sensory phenotypes were not significant. The No HIV-SN group was included, by design, to act as a control group but it highlights an important issue. Although these participants did not meet the clinical criteria for HIV-SN, a proportion demonstrated ‘non healthy’ QST-derived phenotypes. This could be explained by a lack of discrimination of the diagnostic criteria for HIV-SN used, the presence of sub clinical neuropathy or be a consequence of the probabilistic nature of the algorithm used to determine sensory phenotype allocation. We feel it is important to include this group to demonstrate that the range of phenotypes was apparent even in those without overt signs and symptoms of HIV-SN.

Multi-etiologic Pain in HIV-SN

Chronic pain in HIV infection is known to be highly prevalent and a chronic pain diagnosis was described by nearly 3-quarters of this cohort. One chronic pain diagnosis is thought to increase the risk of further pain diagnoses, and, in general, multisite pain is associated with poorer general health, physical function and psychiatric morbidity. Those with a higher pain burden in this cohort were more likely to be outside of the workforce highlighting the vast potential global burden of pain related to HIV infection.

Participants with painful HIV-SN reported a higher number of non-HIV-SN pain sites and diagnoses compared with the painless HIV-SN group. Navis et al. estimated a prevalence of chronic pain co-morbidity in those with HIV-SN of 66%, slightly lower than in our cohort (83%). The Navis cohort did not explicitly describe the proportion of participants with painful neuropathy therefore it might be that our cohort had a higher proportion of participants with painful neuropathy.

Whilst our cohort was likely biased to recruiting those with HIV-SN due to content of recruitment material, it should not have been biased to those with other chronic pain diagnoses as this was not specifically mentioned. The cohort also included a relatively high proportion of those with painless HIV-SN (40% of those with neuropathy) compared to other studies suggesting limited bias towards painful HIV-SN. The study is therefore likely an appropriate estimate of chronic pain in the HIV-SN population. It is therefore unclear how generalizable findings from trials that exclude subjects with multiple pain sites would be to the clinical setting if prevalence of multi-etiologic pain is so high. Since those with the highest spatial burden of pain reported higher pain scores and more neuropathic features, exclusion of such groups from trials may also exclude those with the most severe symptoms.

It may also mean that targeting specific pain etiology, such as HIV-SN, without fully assessing the totality of the chronic pain distribution, mechanisms and impact of widespread pain in the individual, is unlikely to be successful in achieving meaningful symptom relief. The relationship between increased pain severity and a higher spatial burden of pain has also been demonstrated in other neuropathic conditions such as DPN.

The higher incidence of widespread pain in those with HIV-SN suggests an association between the 2 phenomena. A common pathology, such as a diffuse small fiber vulnerability or a persistent inflammatory state leaves some risk of neuroinflammatory pain state and warrants further investigation.

Painful HIV-SN could also predispose to other pain due to sensitization or enhanced global pain facilitation. Indeed, those with painful co-morbidities and painful HIV-SN were more likely to be allocated to the ‘mechanical hyperalgesia’ phenotype. However, wind up ratio, a proxy for central sensitization, could not distinguish between those with differing spatial pain...
burden. Finally, chronic pain conditions may cluster due to common underlying risk factors such as psychiatric comorbidity, genetic risk or socioeconomic variables.70

Limitations

This cohort represents, in general, a population with well-controlled HIV infection. Participants were mostly established on appropriate ART and importantly 60% had not been exposed to d-type nucleoside reverse transcriptase inhibitors, known to be associated with neuropathy. This is in contrast to several other studies of chronic pain in HIV where high proportions of participants show severe immunodeficiency.11,71,72 When comparing results to other studies it should also be noted that this cohort exhibits a high male predominance, and more limited current illicit drug use compared to other similar cohorts.36,38 This study also did not collect data on ART compliance.

Whilst there is no gold standard for the definition of HIV-SN, and difficulty in diagnosis has been previously highlighted, the use of the NeuPSIG grading55 and validated tools for diagnosis of neuropathic pain allowed for a “probable” diagnosis in all and a “definite” diagnosis in the majority of this cohort. Although the DPNCheck nerve conduction system has been validated in healthy, diabetic and chemotherapy induced neuropathy cohorts it has not yet been in HIV44,47 thereby potentially leading to inaccurate group allocation. However, in general the results were corroborated by formal NCS where available. This study design could also not identify those participants with a definite diagnosis of solely small fiber neuropathy as no skin biopsies were taken to provide intra-epidermal nerve fiber density.

The subcohorts differed significantly in relevant factors, like age, years since diagnosis, and history of AIDS-defining illness or use of ‘d’-type ART. In a random effects model including those factors, only age was significantly linked to sensory phenotypes, which has been shown before.22 Nonetheless, it should be noted that our study size was too limited to properly analyze multiple factors and interactions, which may confound these results and can only be uncovered in larger, ideally prospectively planned studies.

This was a cross-sectional study that did not require participants to stop taking analgesic medication prior to performing QST. Patient reported pain scores may have been higher if they had been required to stop their usage. The use of some medications may have had an influence, particularly prior topical application of patches, however, the numbers using these were small and no consistent pattern was seen. With respect to opioids, their use was associated with a higher spatial burden of pain but not a particular QST-derived phenotype, other than being absent in those with a ‘healthy’ phenotype. To our knowledge there is currently no evidence of a pharmacological intervention demonstrating a ‘switch’ between QST-derived phenotypes, although this may be seen in future studies as the use of such phenotyping methods is included longitudinally in clinical trials. Detailed information about illicit drug use was also not recorded but those reporting current use were represented in all QST-derived phenotype groups (7 (24%) to ‘healthy’ phenotype, 7 (24%) to ‘thermal hyperalgesia’, 9 (31%) to ‘mechanical hyperalgesia’ and 6 (21%) to ‘sensory loss’).

Conclusion

In summary this study highlights the ability to identify sensory phenotypes in people living with HIV, based on a QST-derived profile, that are associated with pain and neuropathic symptoms. This has the potential to guide future stratified trials and eventually more targeted therapy in the clinical setting. It demonstrates that painful HIV-SN is associated with an added burden of multi-etiology pain, suggesting some type of common pathology or mechanism that warrants further investigation.

Data Availability

Data will be made available on request.

Acknowledgements

Contributions: HIK and ASCR designed the study. NWSD and GJM contributed to study concept, interpretation and recruitment of participants. HIK performed all participant testing. JV and HIK performed statistical analysis. All authors contributed to writing the manuscript.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2022.09.005.
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