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Psychological factors associated with painful vs. non-painful HIV-associated sensory neuropathy.

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Informed consent: Written informed consent was obtained from all individual participants included in the study.

Abstract

HIV-associated sensory neuropathy (HIV-SN) is a common, and frequently painful complication of HIV, but factors that determine the presence of pain are unresolved. We investigated: i) if psychological factors associated with painful (n = 125) versus non-painful HIV-SN (n = 72), and ii) if pain and psychological factors affected quality of life (QoL). We assessed anxiety and depression using the Hopkins Symptoms Checklist-25. Pain catastrophizing and QoL were assessed using the Pain Catastrophizing Scale and Euroqol-5D, respectively. Presence of neuropathy was detected using the Brief Neuropathy Screening Tool, and pain was characterised using the Wisconsin Brief Pain Questionnaire. Overall, there was a high burden of pain, depression and anxiety in the cohort. None of the psychological variables associated with having painful HIV-SN. Greater depressive symptoms and presence of pain were independently associated with lower QoL. In those participants with painful HIV-SN, greater depressive symptom scores were associated with increased pain intensity. In conclusion, in a cohort with high background levels of psychological dysfunction, psychological factors do not predict the presence of pain, but both depression and presence of pain are associated with poor quality of life.

Keywords: Depression, Pain intensity, Quality of life, Painful HIV-associated sensory neuropathy

Introduction:

HIV-associated sensory neuropathy (HIV-SN) is a frequent complication of both HIV infection and its treatment, affecting up to 60% of ambulatory people living with HIV/AIDS (PLWHA)¹. Unfortunately, the decrease in incidence and prevalence of the neuropathy that was anticipated with widespread introduction of less neurotoxic antiretroviral drug treatments appears to have been minuscule in Sub-Saharan Africa²⁻⁴, in comparison to the reductions reported by recent US cohorts, which are however, equivocal⁵⁻⁷. Indeed, there are reasons to believe there may be differences between the populations, which include, genetic⁸⁻¹⁰ and behavioural¹¹ differences.

Pain is a common feature of HIV-SN and causes significant physical, psychological, and social dysfunction (e.g., reduced physical independence, increased risk of depression, and increased risk of being unemployed)⁵. But, pain is not a universal symptom of the neuropathy, with 20 - 40% of individuals with HIV-SN being asymptomatic or having symptoms other than pain^{3,5,12,13}. Moreover, in individuals who have a painful neuropathy there is significant heterogeneity in the intensity of pain experienced, with patients reporting intensities anywhere between 'slight pain' and 'worst pain ever experienced'^{5,14-16}. The presence of pain in HIV-SN, and the intensity of that pain have been positively associated with disease-related factors such as greater nadir CD4 T-cell count⁵, past exposure to neurotoxic antiretroviral drugs⁵, and increased viral load¹⁷. However, neither the presence of pain nor the variability in pain intensity is entirely explained by the extent of the neuropathology, as assessed by intraepidermal nerve fibre density¹⁷⁻¹⁹ and somatosensory nerve function^{13,20}.

There is, however, growing evidence that psychological factors, including anxiety, depression and pain catastrophizing, are associated with the presence and intensity of pain, clinical outcomes, and quality of life in individuals with chronic pains such as chronic low back pain and arthritis^{21,22}. Consistent with these findings from other causes of pain, a small study by Lucey and colleagues²³ reported that the intensity of the pain reported by patients with HIV-SN was positively associated with pain catastrophizing. And, in the large, multi-centre CHARTER cohort (<https://www.charternmtc.org>), prevalent and incident painful HIV-SN has been associated with worsening depressive symptoms^{5,24}. The presence and intensity of painful HIV-SN was also positively correlated with worse quality of life^{13,25}, but it appears that the severity of depressive symptoms may be a greater determinant of lower quality of life than is pain intensity²⁵.

Neuropathic pain is typically chronic and PLWHA with access to medical care have a near-normal life expectancy^{26,27}. Therefore, the impact of painful neuropathy on quality of life and long-term well-being of the affected individual, their support network and the healthcare system is substantial. Proven pharmacological agents for the treatment of painful HIV-SN are lacking^{28,29}. It is therefore particularly important that other, potentially modifiable risk factors for the pain and its adverse effects are identified. Consequently, we recruited a cohort of black HIV-positive South Africans with either painful or non-painful HIV-SN to investigate whether i) psychological factors associate with having painful HIV-SN (primary objective 1), and ii) whether pain and psychological factors affect quality of life in this population (primary objective 2). As a secondary objective, we also completed a sub-group analysis of the painful HIV-SN group only to determine whether psychological factors predict the intensity of their neuropathic pain (secondary objective 1).

Methods

One hundred and ninety-seven black African HIV-positive adults on combination antiretroviral therapy (cART) were recruited at Chris Hani Baragwanath Hospital, Johannesburg, South Africa. The Chris Hani Baragwanath Hospital is located in Soweto, Johannesburg. Soweto is a diverse community where multiple African languages are spoken and isiZulu is the predominant language. Thus, most participants in our study spoke isiZulu as their first language [44%, (87/197)], followed by isiXhosa [18%, (36/197)]. Recruitment was conducted at a single site on a convenience sample of outpatients attending a general HIV clinic for collection of treatment and routine care. Recruitment ran from May 2013 to January 2014. The study was approved by the Human Research Ethics committee (Medical) of the University of the Witwatersrand, South Africa (clearance numbers: M121018 and M090671). Written, informed consent was obtained from all participants.

All HIV-positive adults (≥ 18 years of age) with a distal symmetrical polyneuropathy (see *Neuropathy screening*), and with a Mini-Mental State Examination (MMSE) score ≥ 24 ³⁰ (see *Questionnaires*), were eligible for inclusion in the study. We screened 372 HIV-positive adults for the presence of HIV-SN. One hundred and seventy-one participants were excluded (166 participants were HIV-SN free, 4 participants scored < 24 on the MMSE and we were unable to complete a bilateral assessment for HIV-SN in one participant due to a previous limb injury). Of the 372 HIV-adults screened, one hundred and ninety-seven black African HIV-positive adults who presented with HIV-SN were recruited to the study. Thereafter, participants were stratified into painful or non-painful HIV-SN groups (see *Neuropathy screening*). Participants had the following demographic and anthropometric data recorded: sex, age, height, weight, ethnicity, date of HIV diagnosis, years of formal education, other potential causes of neuropathy [diabetes, alcohol consumption (units of alcohol consumed), vitamin B₁₂ deficiency, treatment for current tuberculosis infection and diabetes]. The following haematological data were collected from participants' medical records: initial CD4T-cell count, current CD4 T-cell count, HIV viral load and Hepatitis B status. Participants' medical records were also reviewed to ascertain the type/s and dose/s of analgesic medications and cART regimens prescribed.

Neuropathy screening

A diagnosis of painful HIV-associated sensory neuropathy (HIV-SN) was made based on the bilateral presence of at least two signs (decreased vibration sense in the great toe, absent ankle reflex or decreased pin-prick sensitivity) and pain in the distribution of the neurological deficit in the legs and feet. From the Brief Peripheral Neuropathy Screen (BPNS), only those patients who presented with "pain, aching or burning" in the distribution of the neurological deficit in the legs and feet were classified as having 'pain'. The presence of paraesthesias and numbness were not classified as 'pain'. The diagnosis of non-painful HIV-SN was based on the bilateral presence of at least two signs (decreased vibration sense in the great toe, absent ankle reflex or decreased pin-prick sensitivity) in the feet in the absence of neuropathic pain in the lower limbs.

Vibration sense was assessed using a 128 Hz tuning fork, with a recording of 10 seconds or less deemed abnormal³¹. Pin-prick sensitivity was assessed using a size 4 disposable metal safety pin. We wanted to determine whether patients could differentiate between the blunt and sharp ends of the pin, allowing us to determine the patients' ability to detect a cutaneous pain sensation. Having established that the patient could determine the difference between

sharp and blunt on another part of the body (usually the dorsum of the hand, if sensation was intact), we proceeded with performing the test on the patients' feet. We did not test specific anatomical sites on the foot but focused on assessing the entire foot which encompassed three specific dermatomes: L4, L5 and S1. We gently and alternately placed the 'sharp and blunt' ends of the safety pin on the patients' great toe and asked them to identify the stimulus each time. We then repeated the procedure on the patients middle toes and the smallest toe. Working upwards centripetally from the toe in 2cm intervals up to the ankle region, we performed three repetitions each of the 'sharp' and 'blunt' stimuli on each toe separately. If patients identified all the stimuli correctly, we recorded the result as normal. If the patients identified any of the stimuli incorrectly, we recorded the result as abnormal and mapped out which area of the foot and dermatome were involved in the incorrect responses. The safety pin was then discarded after the test procedure was complete. We did not perform any specific catch tests. We used a similar method of pin-prick sensitivity testing as performed by Singleton and colleagues (2008) in their study on the validation of the Utah Early Neuropathy Scale (UENS)³². When symptoms were present, participants were asked to rate the severity of the symptom(s) on a 10-point numerical pain rating scale (NRS), ranging from 1(mild pain) to 10(most severe pain).

All neuropathy assessments were performed by a single study investigator with six years of experience using the BPNS tool. The study investigator received formal training from Dr. Catherine Cherry (CCL-primary clinician involved in the validation of the BPNS tool for use in clinical studies).

Questionnaires

With the aid of an on-site study interpreter who was fluent in local South African languages, participants were asked to complete a series of questionnaires that assessed pain intensity, pain distribution, cognitive function, coping skills related to pain, pain related anxiety and depression, and health related quality of life. Prior to using these questionnaires, all questionnaires that were not already translated were translated and assessed using the MAPI institute's guidelines for translating and validating questionnaires³³. Briefly, questionnaires were dual forward and back translated into four indigenous South African languages (isiZulu, Setswana, Sesotho and isiXhosa). Thereafter, the questionnaires were pilot tested in a sample of 50 individuals recruited from the same study population used in the present study. All study questionnaires were therefore available in English, isiZulu, Setswana, Sesotho and isiXhosa and all patients were given the option to choose which language version of the questionnaire they preferred to complete.

The Mini-Mental State Examination (MMSE)

The MMSE quantifies cognitive function and screens for cognitive loss³⁰. It tests the participants' orientation, attention, calculation, recall, language and motor skills. The total score for the MMSE is out of 30 and a score of 24 or more is deemed normal. The MMSE has been used in similar populations in South Africa^{34,35}.

Pain Catastrophizing scale (PCS)

The PCS assesses catastrophic thinking related to pain³⁶. It consists of 13 descriptions of thoughts and feelings related to pain. Participants were asked to indicate the level to which they experience these thoughts and feelings on a 5-point rating scale ranging from 0 (not at all) to 4 (always). The questionnaire consists of three subscales: rumination, magnification

and helplessness. The total score for the questionnaire is calculated by adding the scores from each item answered and dividing this value by the total number of items answered (13). Since the PCS questionnaire relates specifically to current pain burden, only participants in the painful HIV-SN group completed this questionnaire. The PCS has not been validated in the population we were using it in. By restricting the use of the PCS to only those people in pain we precluded the completion of an informative factor analysis of the translated questionnaires, however we did assess internal reliability of the translated questionnaires and the English version of the PCS. All scales showed excellent internal consistency as measured by McDonald's coefficient ω (total)³⁷: Nguni translations (isiXhosa and isiZulu, n = 44) $\omega = 0.95$ (95%CI: 0.93 to 0.98), Sotho-Tswana translations (Sesotho and Tswana, n = 21) $\omega = 0.94$ (95%CI: 0.91 to 0.97), and the Original English (as completed by non-first language English speakers, n = 60) $\omega = 0.95$ (95%CI: 0.93 to 0.97). The full analysis script for the internal reliability analysis is provided in supplementary document 1.

EQ-5D-3L

The EQ-5D assesses health related quality of life^{38,39}. It consists of two sections; the first section consists of descriptive questions and the second contains a visual analogue scale (VAS). The first descriptive section is made up of five subscales: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Participants' are asked to rate their own state of health on that particular day for each subscale. The scale ranges from 1 (no problems) to 3 (severe problems). In the second section, participants are asked to rate how good or bad their current state of health is by drawing a line on the VAS where, 0 (worst state of health imaginable) and 100 (best state of health imaginable). The use of the EQ-5D has been validated in a South African population by the EuroQol group who developed the questionnaire³⁹.

The Hopkins Symptoms Checklist-25 (HSCL-25)

The HSCL-25 assesses global psychological function⁴⁰. It consists of two subscales; anxiety and depression. The first scale consists of 10 questions, which assess anxiety related symptoms, and the latter consists of 15 questions, which assess depression related symptoms. Participants are asked to rate how much the symptoms in the two subscales bothered or distressed them using a 4-point rating scale ranging from 1 (not at all) to 4 (extremely). Participants responses are summed and divided by the number of answered items (in each of the two sections) to generate a score for each of the sections. For the anxiety section, the sum of the responses is divided by 10 and for the depression section by 15; the total of the responses is divided by 25. A value >1.75 in each of the sections is considered symptomatic. The HSCL-25 has been used in a South African HIV-positive population previously⁴¹. All patients were given the opportunity to complete the HSCL-25 in the language version of their choice and thus patients completed either the English, isiZulu, Setswana, Sesotho or isiXhosa version of the questionnaire. Although the English version of the HSCL-25 has been used in a South African population⁴¹, it has not been validated in this population. Therefore, we validated the English version of the HSCL-25 (supplementary data 2).

The Wisconsin Brief Pain Questionnaire (WBPQ)-adapted version

The WBPQ assesses pain intensity and interference of pain in the patient's life⁴². Using the WBPQ, patients rate the severity of their pain and the degree to which their pain interferes with common aspects of feelings and function. Pains other than SN-related pains were

determined using the following question from the original WBPQ: “Throughout our lives, most of us have had pain from time to time (such as headaches, muscle aches and tooth aches). Have you had pain other than these everyday kinds of pain during the last month?” For our purposes, we used only two questions from the WBPQ: i) the pain body chart diagram, and ii) the numerical pain rating scale for pain in the past month. In the adapted version of the questionnaire, patients were then specifically asked: i) on the body chart diagram provided, could you please colour in all the places where your pain occurs, and ii) aside from the pain in your ‘feet’, how bad is your ‘other’ pain? Could you please rate this pain on the 10-point numerical pain rating scale from 1 (mild pain) to 10 (most severe). To ensure the patient did not confuse the two types of pain being assessed, during the rating procedure, the onsite translator reminded the patient (in the patient’s home language) that this question was specific to their ‘other body pain’ and not to the pain in their feet (if this symptom was present at this location as well). If patients presented with several additional pain sites (not SN-related), they gave an overall score of the intensity of their pain. The use of the WBPQ for the assessment of pain in ambulatory HIV-positive South Africans has been validated by our laboratory⁴³.

Statistical analysis

Descriptive statistics are presented as mean (SD) for parametric data, median (interquartile range, IQR) for non-parametric data, and percentages for frequency data. Univariate analyses comparing participants with painful HIV-SN and non-painful HIV-SN included: Fisher’s Exact Test (sex, current tuberculosis infection, vitamin B₁₂ deficiency, Hepatitis B infection, Type II Diabetes and number of patients with pains outside the distribution of HIV-SN), Mann-Whitney two-sample statistic (initial CD4 T-cell count, current CD4 T-cell count, time since HIV diagnosis, formal education, units of alcohol consumed, number of pains outside the distribution of HIV-SN, HSCL-25 sub-scales, intensity of non-painful symptoms and EQ-5D-3L VAS), Student’s unpaired t-test (age, height and weight), Chi-squared test (antiretroviral treatment regimen and intensity of pains outside the distribution of HIV-SN) and Chi-squared test for trend (EQ-5D-3L sub-scales).

Variables yielding p-values < 0.1 on univariate analysis, and those previously shown to be associated with painful HIV-SN^{5,17,19,23,44,45}, were included in multivariate regression analyses. The multivariate analyses used differed according to the properties of the data being analysed. All regression modeling was performed using R3.1.2⁴⁶ with the MuMIn⁴⁷ and the rms packages⁴⁸. The analyses were carried out as follows:

Primary objectives 1 and 2

1) Logistic regression analysis was used to examine the relationship between pain status and psychological factors. We also included clinical, demographic, and physical factors in the modelling process. The full model included: time since HIV diagnosis, current CD4 T-cell count, presence of pains outside the distribution of HIV-SN, vitamin B₁₂ deficiency, weight, and height. Model selection was based on step-wise regression, using Akaike information criterion (AIC) as the basis for comparing models.

2) General additive model (GAM) regression modelling was used to assess predictors of health-related quality of life (EQ-5D-3L VAS score) in 1) the full cohort of 197 participants (full model included: age, presence of painful HIV-SN, having other pains, sex, education, HSCL-25 depression score, mean HSCL-25 anxiety score), and 2) within the painful HIV-SN

group only (full model included: age, intensity of neuropathic pain, having other pains, sex, education, HSCL-25 depression score, mean HSCL-25 anxiety score). The modelling assumed an inflated beta distribution of the dependent variable (VAS score expressed as a proportion), which describes [0, 1] bounded continuous probability distributions and thus negates the need to transform the data to stabilize residual variance. Model selection was based on step-wise regression, using Generalized Akaike information criterion (GAIC) as the basis for comparing models.

Secondary objective 1 (painful HIV-SN group only)

3) Ordinal logistic regression was used to assess associations with pain intensity (pain intensity of the neuropathy using the 0-10 NRS) in participants with painful HIV-SN (full model included: number of pain sites outside the distribution of HIV-SN, mean HSCL-25 depression score, mean HSCL-25 anxiety score, total PCS score, and whether currently on treatment for TB).

All data analysed in the multivariate analyses, the analysis scripts, and the outputs from the scripts are hosted on a public GitHub repository (<http://kammermanpr.github.com/painful.HIVSN>), with a back-up hosted in a public Figshare repository⁴⁹.

Results:

One hundred and twenty-five (125/197) patients with painful HIV-SN and seventy-two (72/197) patients with non-painful HIV-SN were recruited. Of the 197 patients, 53% (105/197) completed the English version of the questionnaire set, 25% (49/197) completed the IsiZulu version, 11% (22/197) completed the isiXhosa version, 7% (14/197) completed the Sesotho version and 4% (7/197) completed the Setswana version.

Factors that associated with having painful HIV-SN (primary objective 1)

Univariate analyses

Physical and clinical characteristics of the predominantly female, middle-aged cohort are shown in Table I. All the participants were currently on antiretroviral therapy and had well preserved CD4 T-cell counts. The painful HIV-SN group had, on average, lower median current CD4 T-cell count, a shorter time since HIV diagnosis at their assessment for this study, and a lower prevalence of vitamin B₁₂ deficiency compared with the pain free HIV-SN group. Among participants with painful HIV-SN, 85% (106/125) reported their 'SN-related' pain as "moderate" to "severe" in intensity [11-point Numerical Pain Rating Scale score (NRS): 4 to 10], with a median pain intensity of 7 (IQR 1-10) out of 10. All participants with painful HIV-SN presented with at least one additional pain site (pains outside the distribution of HIV-SN/not SN-related), compared with only a quarter of patients in the non-painful HIV-SN group. Moreover, patients in the painful HIV-SN group were more likely than the non-painful HIV-SN group to report the pain at these other sites (pains outside the distribution of HIV-SN/not SN-related) as "moderate" to "severe". Participants in the painful HIV-SN group were more likely to report experiencing numbness and/or paraesthesias in the distribution of their neuropathy than were individuals in the non-painful HIV-SN group but the severity of these other symptoms, when present, did not differ between the two groups.

Psychological and demographic factors (sex, education, and depressive and anxiety-like symptoms) for the painful and non-painful HIV-SN groups are presented in Table II. There

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were no significant differences between the two groups in the proportion of females (~75%) or years of education completed (~6 years). A similarly high proportion of patients in the painful HIV-SN (88%, 110/125) and non-painful HIV-SN (93%, 67/72) groups reported a clinically relevant burden of depressive and anxiety-like symptoms (>1.75 on each of the HSCL-25 sub-scales). Consistent with this finding, ~60% of participants in both groups reported “moderate” or “severe” depression or anxiety on the EQ-5D-3L (Table III).

Multivariate analyses (Supplementary data 3)

Presence of additional pains outside the distribution of HIV-SN/not SN-related [Odds Ratio (OR)=3.47, 95% Confidence Interval (CI): 6.7×10^{-29} to 1.78, $p=0.63$], time since HIV diagnosis (OR=2.02, 95% CI: 0.08 to 0.49, $p<0.001$) and body mass [OR=1.89, 95% CI: 0.76 to 4.64, $p=0.16$] were retained in the final logistic regression model of predictors for having painful HIV-SN. The model had good predictive value ($R^2=0.76$, Somers D = 0.87, area under the receiver operating characteristic curve = 0.93). However, only time since HIV diagnosis was independently associated with painful HIV-SN. A longer time since HIV diagnosis associated with a reduced likelihood of having pain.

Factors associated with quality of life (primary objective 2)

Univariate analyses

Data from the EQ-5D-3L are reported in Table III. When examining scores from the five subscales of the questionnaire, there was no difference between the painful and non-painful groups for the depression/anxiety subscale, but there were differences for the three remaining EQ-5D-3L items, with a greater proportion of participants with painful HIV-SN reporting having “moderate” or “severe” problems with mobility ($p=0.002$), “moderate” problems with their usual activities ($p=0.03$), and, as anticipated, “moderate” or “severe” pain and discomfort ($p<0.0001$). Consistent with these three EQ-5D-3L items, results from the EQ-5D-3L VAS differed between the two groups; painful HIV-SN participants had a lower median VAS score for their perceived state of health (65 IQR: 0-100 vs. 100 IQR: 50-100). We also measured pain catastrophizing in the patients with painful HIV-SN. The mean PCS score for the painful HIV-SN group was 31.2 with a standard deviation of 13.8, where a score >30 indicates a clinically relevant level of catastrophizing³⁶.

In the full cohort, Hopkins depression mean score ($r=-0.26$, $p<0.002$), Hopkins anxiety mean score ($r=-0.17$, $p=0.01$) and intensity of pains outside the distribution of HIV-SN/not SN-related ($r=-0.54$, $p<0.001$) all correlated with quality of life VAS scores. Other factors considered, including age ($r=0.02$, $p=0.78$), level of education ($r=-0.12$, $p=0.07$) and presence of pains outside the distribution of HIV-SN/not SN-related ($r=-0.23$, $p=0.21$) did not correlate with quality of life VAS scores on univariate analysis.

Within the painful HIV-SN group, Hopkins depression mean score ($r=-0.34$, $p<0.001$), Hopkins anxiety mean score ($r=-0.25$, $p=0.004$), PCS mean score ($r=-0.29$, $p=0.001$), presence of pains outside the distribution of HIV-SN/not SN-related ($r=-0.23$, $p=0.008$) and intensity of other pains ($r=-0.41$, $p<0.001$) all significantly correlated with quality of life VAS scores. Other predictors including age ($r=0.06$, $p=0.47$) and level of education ($r=0.03$, $p=0.72$) did not correlate with quality of life VAS scores on univariate analysis.

Multivariate analyses (Supplementary data 4 and 5)

Using general additive model regression analysis, we identified that having painful HIV-SN (mu coefficient = -0.91, t-value = -4.80, $p < 0.001$) and greater HSCL-25 depression scale scores (mu coefficient = -0.33, t-value = -3.14, $p = 0.002$) predicted lower EQ-5D-3L quality of life VAS score. And in the painful HIV-SN cohort, greater HSCL-25 depression subscale scores were associated with lower EQ-5D-3L VAS scores (mu coefficient = -0.35, t-value = -2.90, $p = 0.004$).

Factors that associated with increased pain intensity (secondary analysis 1)

Univariate analyses

On univariate analysis for associations with pain intensity of the SN, Hopkins depression mean score ($r=0.21$, $p=0.01$), presence of pains outside the distribution of HIV-SN/not SN-related ($r=0.18$, $p=0.04$) and intensity of pains outside the distribution of HIV-SN/not SN-related ($r=0.22$, $p=0.01$) all correlated with intensity of HIV-SN related pain. Other psychological factors, including: sex, education, PCS score, EQ-5D VAS score and Hopkins mean anxiety score did not correlate with pain intensity in this cohort (all $p>0.05$).

Multivariate analyses (Supplementary data 6)

Independent predictors of increasing pain intensity of the SN, included increasing levels of depression (OR=1.95, 95% CI: 1.14 to 3.33, $p=0.01$), additional pains outside the distribution of HIV-SN/not SN-related (OR=1.40, 95% CI: 1.00 to 1.97, $p=0.04$) and being treated for TB infection (OR=0.33, 95% CI: 0.12 to 0.94, $p=0.03$) (supplementary data 6). However, the model had poor predictive value ($R^2=0.09$, Somer's D = 0.25, area under the ROC curve=0.63).

Discussion

We recruited individuals with painful or non-painful HIV-SN to determine: 1) if psychological factors associate with having painful HIV-SN, 2) if pain and psychological factors affect quality of life, and 3) if psychological factors predict the intensity of their pain. We report that in this black, African cohort of PLWHA that: 1) depression, anxiety and pain catastrophizing did not associate with the presence of painful HIV-SN, 2) increased depressive symptoms and presence (but not intensity) of pain independently associated with reduced quality of life, and 3) greater depressive symptoms independently associated with increased pain intensity in patients with painful HIV-SN.

Factors associated with having a painful rather than non-painful HIV-SN

Having additional pains outside the distribution of HIV-SN was retained in the final model of associations with painful HIV-SN, however this was not an independent risk factor ($p=0.63$). As our study was cross-sectional, we cannot comment on the order in which additional pains outside the distribution of HIV-SN and painful SN occurred. However, the data do suggest that those with painful HIV-SN may be predisposed to having pain of any sort. Indeed, it may be that these individuals are generally more sensitive/susceptible to pain and other symptoms, including numbness and paraesthesias. The presence of multiple pain sites could also be indicative of central sensitisation of the central nervous system⁵⁰. Nevertheless, our data provide clear evidence of a high burden of pain among individuals with HIV-SN. Eighty five percent (85%) of those in the painful HIV-SN group reported that the pain of their neuropathy was moderate to severe in intensity. Furthermore, all 125 individuals in the painful

HIV-SN group had at least one additional pain site, and these sites were on average also rated as moderate to severe in intensity. Thus, painful HIV-SN was just one part of a larger pain burden in this group.

Depression and anxiety did not associate with having a painful SN in our cohort, unlike previous studies^{5,13,51}. Indeed, we found a similarly high burden of depressive and anxiety-like symptoms in those with HIV-SN, regardless of whether pain was present. The use of different tools to screen for depression by us (HSCL-25) and other investigators (Becks Depression Inventory^{5,23,25}; and Centre for Epidemiologic Studies Depression Scale [CES-D]⁵¹) prevents direct comparisons of the scores reported across studies. Overall, however, we found 93% of the non-painful and 88% of the painful HIV-SN group had clinically relevant levels of depressive symptoms, compared with 13% of non-painful and 20% of the painful HIV-SN group in the study by Ellis and colleagues⁵. The high level of depressive symptoms in our cohort is not remarkable given the high levels of depression reported in the population from which our study cohort was drawn⁵²⁻⁵⁴. Certainly, only by conducting our research in a unique setting have we been able to demonstrate that high levels of background depression in the community may erode the often reported link between depression and chronic pain⁵⁵⁻⁵⁷.

Effect of pain and psychological factors on quality of life

As in other studies, patients with painful HIV-SN had a lower overall rating of quality of life than SN patients without pain^{5,13,25}. Analysis of subscale data from the EQ-5D-3L also identified that patients with painful HIV-SN were more likely to have problems with their mobility and usual activities, as expected.

In multivariate analyses we found depressive symptoms and presence of pain associated with reduced quality of life. These data fit with reports from other investigators, where coincident pain and depression have associated with reduced quality of life in HIV-positive patients^{58,59}. Of note, we found that the presence of pain, but not its intensity associated with reduced quality of life. Indeed, this is not the first time that factors other than the intensity of pain have associated more strongly with quality of life. In US patients with HIV-SN, depression affected quality of life more than pain intensity²⁵. Neuropathic pain has associated with reduced quality of life in individuals with HIV-SN^{5,13,23,25}. Severe neuropathic pain was associated with reduced quality of life and pain function scores as well as higher pain interference scores^{5,13}. However, Ellis and colleagues also found that mild neuropathic pain associated with a profoundly reduced quality of life⁵. Similarly, high levels of depressive symptoms and the high pain burden (neuropathic pain and the presence of additional pains) observed in our cohort may have made patients more sensitive to any pain, regardless of its intensity. This may explain why we did not find any association between pain intensity and quality of life but rather an association between the presence of pain and reduced quality of life. One of the limitations of using depression instruments in pain studies is that the inclusion of somatic/pain symptoms in various depression instruments makes it quite difficult to ascertain whether there is truly a depressive component or just an artificial inflation due to the confounding from somatic/pain symptoms. One of the most commonly used rating scales for depression in chronic pain patients is the Becks Depression Inventory (BDI). The BDI's factor structure has a strong somatic component which can be very difficult in a chronic pain assessment. We used the HSCL-25 questionnaire that does include a small number of somatic symptoms, which includes 'feeling low in energy', 'difficulty falling asleep, staying asleep', and 'poor appetite'. However, the HSCL-25 does not have a large pain symptom component and only includes a single question on 'headaches' in the anxiety section of the questionnaire.

The use of a depression instrument containing somatic/pain symptoms is a limitation in our study and highlights the need for improved depression tools in the setting of chronic pain patients.

Effect of psychological factors on pain intensity

Although, depressive symptoms did not associate with having a painful SN, they did associate with pain intensity. These data fit with other reports that higher depression scores associate with increased pain intensity in US HIV- positive patients^{59,60}.

Anxiety level did not associate with pain intensity here. Anxiety has not been assessed in relation to intensity of pain in HIV-SN previously, but greater anxiety has been associated with greater pain intensity in arthritis, migraine and back pain in US cohorts²¹.

Having additional pains outside the distribution of HIV-SN was independently associated with greater pain intensity in this cohort. This may be suggestive of a spatial summation effect or may suggest that depression and anxiety (also associated with pain intensity) worsen with an increased load of chronic conditions. Indeed, the observed association between depressive symptom burden and pain burden intimates possible dysfunction in brainstem serotonergic and noradrenergic pathways and/or diffuse noxious inhibitory control system⁶¹.

Catastrophizing has associated with pain intensity in other chronic pain conditions⁶² including intensity of HIV-SN pain^{13,23} but did not associate with pain intensity here. Levels of pain catastrophizing were very high in this cohort: the mean (SD) PCS score was 31.2 (13.8) vs. 19.6 (13.7) in Lucey's U.S cohort²³ and a score >30 indicates a clinically relevant level of catastrophizing³⁶. Thus, similar to our findings for depression, universally high prevalence of pain catastrophizing in this population confounds the detection of an association between catastrophizing and pain.

Conclusion

In this cohort of black African PLWHA attending a public healthcare facility, we found a high pain burden in patients with SN, demonstrated by painful SN being only one of multiple pains experienced by these patients. In this first assessment of psychological factors in a non-US or European cohort with HIV-SN, we found high levels of depression, and depression associated with increased pain intensity and reduced quality of life. Painful HIV-SN is difficult to treat pharmacologically^{29,63} and recent commentary suggests that reducing pain intensity may not be a realistic therapeutic goal for chronic pain conditions⁶⁴ but improving quality of life and function may be more valuable. This suggests that a greater emphasis on assessing and treating depressive symptoms in patients with SN could be advantageous and warrants further investigation.

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Table I: Physical and clinical characteristics of the study cohort.

Characteristic	Entire cohort (n=197)	Painful HIV-SN (n=125)	Non-painful HIV-SN (n=72)	p-value (painful vs. non-painful)
Age (years) ^a	43.2 (12.1)	42.4 (11.3)	44.6 (13.4)	p=0.23 ^d
Initial CD4 T-cell count (cells/mm ³) ^b	142 (94-142)	137.5 (92-231) ⁽ⁿ⁼¹¹⁴⁾	149 (96-221.5) ⁽ⁿ⁼⁶⁴⁾	p=0.59 ^g
Current CD4 T-cell count (cells/mm ³) ^b	424 (256-674)	405 (227-674) ⁽ⁿ⁼¹²⁵⁾	463.5 (352-651) ⁽ⁿ⁼⁷²⁾	p=0.03 ^g
Time since HIV diagnosis (months) ^b	120 (72-162)	108 (60-144) ⁽ⁿ⁼¹⁰⁴⁾	144 (120-186) ⁽ⁿ⁼⁵⁵⁾	p<0.0001 ^g
Height(cm) ^a	163.3 (8.8)	162.4 (8.5) ⁽ⁿ⁼¹¹⁵⁾	164.8 (9.2) ⁽ⁿ⁼⁶⁷⁾	p=0.09 ^d
Weight (kg) ^a	71.7 (19.8)	73.5 (22.0)	68.6 (14.5)	p=0.13 ^d
Current TB infection, n (%)	26 (13)	14 (11)	12 (17)	p=0.28 ^e
Standard units of alcohol consumed ^b	13.5 (2-42)	12.2 (2-29.7) ⁽ⁿ⁼³²⁾	13.5 (6-42) ⁽ⁿ⁼²⁵⁾	p=0.29 ^g
Vitamin B ₁₂ deficiency, n (%)	25 (13)	11 (9)	14 (19)	p=0.04 ^e
Hepatitis B infection, n (%)	15 (7)	9 (7)	6 (8)	p=0.78 ^e
Type II diabetes, n (%)	10 (5)	4 (3)	6 (8)	p=0.17 ^e
Treatment regimen, n (%):				p=0.78 ^f
<i>Non D4T-based</i>	166 (84)	106 (85)	60 (83)	
<i>D4T-based</i>	24 (12)	14 (11)	10 (14)	
<i>Other</i>	7 (3)	5 (4)	2 (3)	
Number of patients with other pain sites, n (%)	143 (73)	125 (100)	18 (25)	p<0.0001 ^e
Number of other pain sites ^b	3 (1-9)	3 (1-9)	2 (1-4)	p=0.02 ^g
Intensity of other pains, n (%)				p=0.02 ^f
<i>Mild</i>	23 (11)	19 (15)	4 (6)	
<i>Moderate</i>	63 (32)	51 (41)	12 (17)	
<i>Severe</i>	57 (29)	55 (44)	2 (3)	
Prevalence of symptoms, n (%):				
<i>Pins and needles</i>	116 (59)	106 (85)	10 (14)	p<0.001 ^e
<i>Numbness</i>	115 (58)	102 (82)	13 (18)	p<0.001 ^e
Intensity of symptoms (0-10 NRS score) ^c				
<i>Pins and needles</i>	5 (1-10) ⁽ⁿ⁼¹⁰⁶⁾	5 (1-10) ⁽ⁿ⁼⁹⁸⁾	4.5 (2-10) ⁽ⁿ⁼⁸⁾	p=0.13 ^g
<i>Numbness</i>	6 (1-10) ⁽ⁿ⁼¹⁰²⁾	6 (1-10) ⁽ⁿ⁼⁹⁰⁾	5 (2-10) ⁽ⁿ⁼¹²⁾	p=0.43 ^g

^aData shown as mean (SD) for parametric data; ^bData shown as median (IQR) for non-parametric data; ^cNumerical pain rating Scale (NRS) scores shown as median (IQR); ^dUnpaired t-test (parametric data); ^eChi-squared test; ^fFishers exact test; ^gMann-Whitney two-sample statistic(non-parametric data);

Table II. Demographic and psychological characteristics of the study cohort.

Characteristic	Entire cohort (n=197)	Painful HIV-SN (n=125)	Non-painful HIV-SN (n=72)	p-value (painful vs. non-painful)
Female sex, n (%)	149 (76)	94(75)	55(76)	p=1.00 ^c
Formal education (years) ^a	6 (0-10)	6 (0-10)	7 (0-10)	p=0.13 ^d
HSCL-25 (average sub-scale score) ^a :				
<i>Anxiety symptoms</i>	2.60 (2.1-3.4)	2.60 (2.1-3.4)	2.60 (1.0-4.0)	p=0.97 ^d
<i>Depressive symptoms</i>	2.53 (2.0-3.1)	2.53 (2.0-3.1)	2.53 (1.0-3.8)	p=0.70 ^d
PCS ^b	-	31.2 (14)	-	-

^aData shown as median (IQR) for nonparametric data; ^bData shown as mean (SD) for parametric data;

^cFishers exact test; ^dMann-Whitney two-sample statistic (nonparametric data)

Table III. Summary of quality of life outcomes from the EQ-5D for painful and non-painful SN.

Characteristic	Entire cohort (n=197)	Painful HIV-SN (n=125)	Non-painful HIV-SN (n=72)	p-value (painful vs. non-painful)
EQ-5D-3L, n (%):				
Mobility (MO):				p=0.0020 ^c
<i>no problems</i>	165 (84)	96 (77)	69 (96)	
<i>moderate problems</i>	27 (14)	24 (19)	3 (4)	
<i>severe problems</i>	5 (2)	5 (4)	0	
Self-Care (SC):				p=0.22 ^c
<i>no problems</i>	183 (93)	114 (92)	69 (96)	
<i>moderate problems</i>	14 (7)	11 (8)	3 (4)	
<i>severe problems</i>	0	0	0	
Usual Activities (UA):				p=0.03 ^c
<i>no problems</i>	170 (86)	102 (82)	68 (94)	
<i>moderate problems</i>	26 (13)	22 (18)	4 (6)	
<i>severe problems</i>	1 (1)	1 (1)	0	
Pain/Discomfort (PD):				p<0.0001 ^c
<i>no problems</i>	89 (45)	31 (25)	58 (81)	
<i>moderate problems</i>	74 (38)	62 (50)	12 (17)	
<i>severe problems</i>	34 (17)	32 (25)	2 (3)	
Anxiety/Depression (AD):				p=0.65 ^c
<i>no problems</i>	79 (40)	51 (41)	28 (39)	
<i>moderate problems</i>	80 (41)	48 (38)	32 (44)	
<i>severe problems</i>	38 (19)	26 (21)	12 (17)	
EQ-5D-3L (VAS) ^a	80 (50-100)	65 (40-80)	100 (50-100)	p<0.0001 ^b

^aData shown as median (IQR) for nonparametric data; ^bMann-Whitney two-sample statistic (nonparametric data); ^cChi-squared test for trend

Assessment of internal consistency for translated versions of the Pain Catastrophizing Scale

Peter Kamerman

23 May 2017

Codebook

Key	Question	Subscale
Q1	I worry all the time about whether the pain will end	Helplessness
Q2	I feel I can't go on	Helplessness
Q3	It's terrible and I think it's never going to get any better	Helplessness
Q4	It's awful and I feel that it overwhelms me	Helplessness
Q5	I feel I can't stand it anymore	Helplessness
Q6	I become afraid that the pain will get worse	Magnification
Q7	I keep thinking of other painful events	Magnification
Q8	I anxiously want the pain to go away	Rumination
Q9	I can't seem to keep it out of my mind	Rumination
Q10	I keep thinking about how much it hurts	Rumination
Q11	I keep thinking about how badly I want the pain to stop	Rumination
Q12	There's nothing I can do to reduce the intensity of the pain	Helplessness
Q13	I wonder whether something serious may happen	Magnification

Import data

```
# Load packages
library(tidyverse)
library(stringr)
library(knitr)
library(boot)
library(psych)

# Read data
pcs <- read_csv('./data/original-data.csv')

# Quick look
dim(pcs)

## [1] 125 15

glimpse(pcs)

## Observations: 125
```

```
## Variables: 15
## $ patient_id <chr> "001", "002", "003", "004", "005", "006", "007", "0...
## $ language <chr> "english", "english", "english", "english", "englis...
## $ Q1 <int> 2, 2, 4, 2, 4, 4, 4, 4, 4, 4, 4, 4, 2, 2, 4, 4, ...
## $ Q2 <int> 2, 2, 4, 1, 3, 3, 2, 2, 4, 3, 2, 1, 4, 3, 4, 2, 4, ...
## $ Q3 <int> 0, 0, 2, 0, 4, 4, 4, 2, 0, 2, 4, 4, 4, 3, 4, 2, 4, ...
## $ Q4 <int> 0, 0, 2, 0, 2, 4, 4, 2, 2, 2, 0, 2, 2, 2, 0, 2, 1, ...
## $ Q5 <int> 0, 1, 4, 0, 4, 4, 4, 2, 2, 4, 4, 4, 4, 2, 4, 4, 4, ...
## $ Q6 <int> 0, 2, 3, 2, 4, 4, 4, 2, 4, 4, 4, 4, 4, 2, 4, 4, 4, ...
## $ Q7 <int> 0, 0, 2, 1, 1, 3, 2, 0, 0, 2, 2, 4, 4, 2, 2, 4, 4, ...
## $ Q8 <int> 2, 1, 2, 1, 4, 4, 4, 1, 4, 4, 4, 4, 4, 2, 4, 4, 4, ...
## $ Q9 <int> 0, 0, 2, 2, 4, 4, 4, 2, 4, 4, 2, 4, 4, 0, 0, 4, 0, ...
## $ Q10 <int> 0, 0, 0, 0, 4, 4, 4, 2, 0, 4, 4, 4, 2, 2, 2, 4, 4, ...
## $ Q11 <int> 2, 2, 4, 2, 4, 4, 4, 4, 4, 2, 4, 4, 4, 2, 2, 4, 4, ...
## $ Q12 <int> 2, 2, 4, 2, 4, 4, 4, 2, 4, 4, 3, 3, 4, 2, 2, 4, 4, ...
## $ Q13 <int> 0, 0, 4, 2, 4, 4, 4, 2, 3, 2, 0, 0, 4, 2, 0, 0, 4, ...
```

Inspect the data

```
pcs %>%
  # Add language grouping
  mutate(`language group` = case_when(
    .$language == 'english' ~ 'english',
    .$language == 'xhosa' | .$language == 'zulu' ~ 'nguni',
    .$language == 'tswana' | .$language == 'sotho' ~ 'sotho-tswana')) %>%
  # Group by language / language group
  group_by(language, `language group`) %>%
  # Summarise data
  summarise(count = n()) %>%
  # Table summary
  kable(caption = 'Number completing each language version of PCS')
```

Table 2: Number completing each language version of PCS

language	language group	count
english	english	60
sotho	sotho-tswana	10
tswana	sotho-tswana	11
xhosa	nguni	7
zulu	nguni	37

Analysis

Our sample size for each of the language-versions of the PCS was well below that required to conduct an informative factor analyses, and therefore we limited our analysis of the questionnaires to the assessment of internal

consistency. Even then, our sample size per language-version was low, and so we grouped the languages by language group. That is, we analysed grouped data from the *Nguni languages* (isiZulu and isiXhosa; n = 44), and *Sotho-Tswana languages* (Sesotho and Tswana; n = 21). We also analysed the original English-language questionnaire, as completed by non-English first language speakers (n = 60). Despite collapsing the data in this manner, our data may still be prone to bias, and therefore we calculated point estimates with bootstrapped 95% confidence interval of the estimate for all outputs (bootstrap resamples with replacement: 800).

Further, we have implemented McDonald's coefficient ω (total) as the measure of the total internal reliability of the test, and not the more common measure, Cronbach α . Cronbach α assumes that each item contributes equally to the underlying construct (τ -equivalence), and that the error variances are not correlated. McDonald's ω does not make these assumptions, and is therefore a more robust test. Because PCS items are assessed on a 5-point Likert scale, we used a polychoric correlation matrix and not the typical Pearson's correlation matrix, which is suited for monotonic interval scales.

Data cleaning

```
# Add grouping variable total and subscales
# (rumification, magnification, helplessness)
pcs_total <- pcs %>%
  # Make into long table
  gather(key = key,
         value = value,
         -patient_id,
         -language) %>%
  # Add language grouping
  mutate(language_group = case_when(
    .$language == 'english' ~ 'english',
    .$language == 'xhosa' |
    .$language == 'zulu' ~ 'nguni',
    .$language == 'tswana' |
    .$language == 'sotho' ~ 'sotho-tswana')) %>%
  # Spread the columns out again
  spread(key = key,
        value = value) %>%
  # Remove patient_id, language, and subscale columns
  dplyr::select(-patient_id,
               -language)
```

Define bootstrap function

```
# Define bootstrap function for total McDonald's omega
omega_func <- function(d, i) {
  # Data sampling using 'index'
  data <- d[i, ]
  # Return total omega value from psych::omega output
  ## Use maximum likelihood method (ml) for factor loadings
```

```

## Use polychoric correlation structure because data are discrete
omega <- psych::omega(m = data,
                      fm = 'ml',
                      poly = TRUE,
                      plot = FALSE)$omega.tot
# Print total omega value
omega
}

```

Internal consistency

```

# Split by language group
## English
total_eng <- pcs_total %>%
  filter(language_group == 'english') %>%
  dplyr::select(-language_group)

## Nguni
total_nguni <- pcs_total %>%
  filter(language_group == 'nguni') %>%
  dplyr::select(-language_group)

## Sotho-Tswana
total_sotho <- pcs_total %>%
  filter(language_group == 'sotho-tswana') %>%
  dplyr::select(-language_group)

# Set seed
set.seed(1234)

# English
foo <- boot(data = total_eng,
            statistic = omega_func,
            R = 800,
            stype = 'i') %>%
  boot.ci(.,
          type = 'basic')

total_eng_w <- round(c(foo$t0, foo$basic[4:5]), 2)

# Set seed
set.seed(1234)

# Nguni
foo <- boot(data = total_nguni,
            statistic = omega_func,
            R = 800,

```

```

        stype = 'i') %>%
boot.ci(.,
        type = 'basic')

total_nguni_w <- round(c(foo$t0, foo$basic[4:5]), 2)

# Set seed
set.seed(1234)

# Sotho-Tswana
foo <- boot(data = total_sothon,
            statistic = omega_func,
            R = 800,
            stype = 'i') %>%
boot.ci(.,
        type = 'basic')

total_sothon_w <- round(c(foo$t0, foo$basic[4:5]), 2)

# Tabulate
tibble(language_group = rep(c('english',
                              'nguni',
                              'sotho-tswana'),
                            each = 3),
        key = rep(c('omega (total)',
                    'l95ci',
                    'u95ci'),
                  times = 3),
        value = c(total_eng_w,
                  total_nguni_w,
                  total_sothon_w)) %>%
group_by(language_group) %>%
spread(key = key,
       value = value) %>%
mutate(`95% CI` = sprintf('[ %.02f - %.02f ]', l95ci, u95ci)) %>%
dplyr::select(language_group, `omega (total)`, `95% CI`) %>%
kable(caption = "McDonald's omega for the full PCS")

```

Table 3: McDonald's omega for the full PCS

language_group	omega (total)	95% CI
english	0.95	[0.93 - 0.97]
nguni	0.95	[0.93 - 0.98]
sotho-tswana	0.94	[0.91 - 0.97]

Within the restriction of our small datasets, we believe we have shown that the overall reliability of the translated versions of the PCS, and the English-language version completed by non-first language English speakers was

good, with narrow confidence intervals.

Session information

```
sessionInfo()
```

```
## R version 3.4.0 (2017-04-21)
## Platform: x86_64-apple-darwin15.6.0 (64-bit)
## Running under: macOS Sierra 10.12.4
##
## Matrix products: default
## BLAS: /Library/Frameworks/R.framework/Versions/3.4/Resources/lib/libRblas.0.dylib
## LAPACK: /Library/Frameworks/R.framework/Versions/3.4/Resources/lib/libRlapack.dylib
##
## locale:
## [1] en_GB.UTF-8/en_GB.UTF-8/en_GB.UTF-8/C/en_GB.UTF-8/en_GB.UTF-8
##
## attached base packages:
## [1] stats      graphics  grDevices  utils      datasets  methods   base
##
## other attached packages:
## [1] coefficientalpha_0.5 rsem_0.4.6          lavaan_0.5-23.1097
## [4] MASS_7.3-47         psych_1.7.5        boot_1.3-19
## [7] knitr_1.15.1        stringr_1.2.0      dplyr_0.5.0
## [10] purrr_0.2.2.2      readr_1.1.0        tidyr_0.6.3
## [13] tibble_1.3.0       ggplot2_2.2.1      tidyverse_1.1.1
##
## loaded via a namespace (and not attached):
## [1] reshape2_1.4.2      haven_1.0.0         lattice_0.20-35
## [4] colorspace_1.3-2    htmltools_0.3.6     stats4_3.4.0
## [7] yaml_2.1.14         foreign_0.8-68      DBI_0.6-1
## [10] modelr_0.1.0        readxl_1.0.0        plyr_1.8.4
## [13] GPArotation_2014.11-1 munsell_0.4.3      gtable_0.2.0
## [16] cellranger_1.1.0    rvest_0.3.2         codetools_0.2-15
## [19] evaluate_0.10       forcats_0.2.0       parallel_3.4.0
## [22] highr_0.6           broom_0.4.2         Rcpp_0.12.10
## [25] scales_0.4.1        backports_1.0.5     jsonlite_1.4
## [28] mnormt_1.5-5        hms_0.3             digest_0.6.12
## [31] stringi_1.1.5       grid_3.4.0          rprojroot_1.2
## [34] quadprog_1.5-5      tools_3.4.0         magrittr_1.5
## [37] lazyeval_0.2.0      pbivnorm_0.6.0     xml2_1.1.1
## [40] lubridate_1.6.0     assertthat_0.2.0    rmarkdown_1.5
## [43] httr_1.2.1          R6_2.2.1            nlme_3.1-131
## [46] compiler_3.4.0
```

Supplementary data 2

Supplementary data 2. Validation of the English version of the Hopkins Symptoms Checklist-25 (HSCL-25).

Reliability and validity of the HSCL-25

The HSCL-25 has been translated and validated in several populations¹⁻³. We performed an exploratory factor analysis of the English version of the HSCL-25 questionnaire in our HIV-positive cohort. The English version of the HSCL-25 questionnaire was completed by 153 participants. One hundred and five participants were from the current cohort and the remaining 48 participants were recruited as part of an additional cohort that was recruited in the same population at the same study site.

Factor loading was assessed using exploratory factor analysis. In particular, we wanted to assess whether the questionnaire items grouped logically under the anxiety and depression factors of the original questionnaire. Throughout the analysis we used apolychoric correlation matrix because each questionnaire item was assessed on an ordinal scale, and Omblin rotation to account for possible correlation between items. To start, parallel analysis of the scree of factors was used to estimate the number of factors to extract. Based on the outcome of the parallel analysis the data were modelled using a two-factor (the structure of the original questionnaire), and a four-factor structure (suggested by parallel analysis). The four-factor analysis produced four 'clean' item groupings; two consisting only of items from the anxiety subscale of the original questionnaire, and two consisting only of items for the depression subscale. Since the HSCL-25 is split into two subscales, that is, anxiety and depression, and the four-factor structure did not offer a significant advantage over the two-factor structure, we chose to retain the two-factor structure. In order to determine how much each factor represented the data, we examined the amount of calculated variance accounted for by the factors. The appropriateness of the grouping of items under each factor was assessed by looking at the factor loadings for each item. If the factor loading for an item under a factor was greater than 0.3, the loading was considered to be significant. Two of the items, which originally assessed anxiety in the HSCL-25 questionnaire, loaded onto the depression factor. These were items number 4: "nervousness or shakiness inside" and number 5: "heart pounding or racing".

To determine the reliability of the questionnaire, we computed Chronbach coefficient alphas for the Anxiety and Depression subscales and for the entire questionnaire. Alpha values ≥ 0.7 are normally considered as evidence of good internal consistency. The coefficient alpha for the anxiety subscale was 0.95 and for the depression subscale was 0.94. The standardised alpha for the entire questionnaire was 0.96. Item whole correlations when

individual items were dropped indicated the internal reliability across the full scale. Our results here provide evidence of the reliability and validity of the HSCL-25 when completed by non-first language English speakers for the assessment of anxiety and depression in a South African HIV-positive population.

Data analysis file may be accessed at: <https://github.com/kamermanpr/painful.HIVSN.git>

References:

1. Lhewa D, Banu S, Rosenfeld B, Keller A. Validation of a Tibetan translation of the Hopkins Symptom Checklist 25 and the Harvard Trauma Questionnaire. *Assessment*. 2007;14(3):223-230. doi:10.1177/1073191106298876.
2. Kaaya SF, Fawzi MCS, Mbwambo JK, Lee B, Msamanga GI, Fawzi W. Validity of the Hopkins Symptom Checklist-25 amongst HIV-positive pregnant women in Tanzania. *Acta Psychiatr Scand*. 2002;106(1):9-19. doi:10.1080/08033260210000205 [pii].
3. Glaesmer H, Braehler E, Grande G, Hinz A, Petermann F, Rompell M. The German Version of the Hopkins Symptoms Checklist-25 (HSCL-25) - Factorial structure, psychometric properties, and population-based norms. *Compr Psychiatry*. 2014;55(2):396-403. doi:10.1016/j.comppsy.2013.08.020.

Supplementary data 3

Supplementary data 3. Final logistic regression model of predictors for having painful versus non-painful HIV-SN

Formula: SN pain status ~ other pain sites + time since HIV diagnosis+ mass

Complete sets of observations: 151 (96 with pain, 55 without pain)

Likelihood ratio test		Discrimination indices		Rank discrimination indices	
<i>LR Chi²</i>	123.52	<i>Nagelkerke R²</i>	0.76	<i>Somer's D</i>	0.87
<i>df</i>	3			<i>ROC AUC</i>	0.93
<i>p</i>	<0.0001				

	Coefficient	Standard error	Wald Z	p
<i>Intercept</i>	-10.66	26.73	-0.40	0.69
<i>Other pain sites (yes)</i>	12.57	26.68	0.47	0.63
<i>Time since HIV diagnosis</i>	-0.017	0.004	-3.52	< 0.001
<i>Mass</i>	0.033	0.023	1.39	0.16

Supplementary data 4

Supplementary table 4. Final general additive model of predictors of quality of life across the full cohort (painful and non-painful HIV-SN)

	Coefficients		t-value	P-value
	Estimate	Standard error		
Mean (μ) subscale				
Intercept	2.02	0.34	5.95	< 0.001
Painful SN (yes)	-0.91	0.19	-4.80	< 0.001
HSCCL-25 depression score	-0.33	0.11	-3.14	0.002
Variance (σ) subscale				
Intercept	-0.32	0.08	-3.93	< 0.001

Supplementary data 5

Supplementary table 5. Final general additive model of predictors of quality of life in patients with painful HIV-SN only

	Coefficients		t-value	P-value
	Estimate	Standard error		
Mean (μ) subscale				
Intercept	1.16	0.34	3.37	< 0.001
HSCCL-25 depression score	-0.35	0.12	-2.90	0.004
Variance (σ) subscale				
Intercept	-0.23	0.09	-2.55	0.01

Supplementary data 6

Supplementary data 6. Final ordinal logistic regression model of predictors of pain intensity in patients with painful HIV-SN

Formula: pain intensity ~ HSCL-25 depression + Additional pain sites + TB treatment

Complete sets of observations: 125

Likelihood ratio test		Discrimination indices		Rank discrimination indices	
<i>LR Chi²</i>	12.79	Nagelkerke <i>R²</i>	0.1	<i>Somer's D</i>	0.27
<i>df</i>	3			<i>ROC AUC</i>	0.64
<i>p</i>	0.005				

	Coefficient	Standard error	Wald Z	p
y≥2	2.3187	0.9708	2.39	0.0169
y≥3	0.6385	0.7365	0.87	0.3860
y≥4	-0.1217	0.7097	-0.17	0.8638
y≥5	-0.4328	0.7080	-0.61	0.5410
y≥6	-1.4878	0.7187	-2.07	0.0384
y≥7	-1.7777	0.7257	-2.45	0.0143
y≥8	-1.9950	0.7332	-2.72	0.0065
y≥9	-2.3548	0.7454	-3.16	0.0016
y≥10	-2.4618	0.7484	-3.29	0.0010
HSCL-25 depression	0.5919	0.2420	2.45	0.0144
Additional pain sites (yes)	0.1711	0.0867	1.97	0.0485
TB treatment (yes)	-1.0802	0.5207	-2.07	0.0380