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Neuropathic pain correlates with worsening cognition in people with human immunodeficiency virus

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Neuropathic pain and cognitive impairment are among the HIV-related conditions that have most stubbornly resisted amelioration by virally suppressive antiretroviral therapy. Overlaps between the regional brain substrates and mechanisms of neuropathic pain and cognitive disorders are increasingly recognized, yet no studies have examined the longitudinal relationship between these two disorders.

Participants in the prospective, observational CNS HIV AntiRetroviral Therapy Effects Research (CHARTER) cohort underwent standardized clinical evaluations for clinical examination findings of distal sensory polyneuropathy, reporting distal neuropathic pain and neurocognitive performance at study entry (baseline) and an average of 12 years later. Change in neuropathic pain and neuropathy status from baseline to follow-up was by self-report and repeat examination, and change in neurocognitive performance was assessed using a previously published summary regression-based change score. Relationships between incident or worsened neuropathic pain and neurocognitive change were evaluated using uni- and multivariable regressions, including age at baseline and other relevant covariates.

Participants were 385 people with HIV, 91 (23.6%) females, mean ± standard deviation (SD) age at baseline 43.5 (7.81) years, ethnicity 44.9% African American, 10.6% Hispanic, 42.6% non-Hispanic white and 1.82% other. Baseline median (interquartile range) nadir CD4 was 175 (34 309) cells/μl and current CD4 was 454 (279 639). Incident or worsened distal neuropathic pain occurred in 98 (25.5%) over the follow-up period. People with HIV with incident or worsened distal neuropathic pain had significantly worsened neurocognitive performance at follow-up compared to those without incident or worsened distal neuropathic pain (summary regression-based change score mean ± SD –0.408 ± 0.700 versus –0.228 ± 0.613; $P = 0.0158$). This effect remained significant when considering viral suppression on antiretroviral therapy, incident diabetes and other covariates as predictors. Overall neurocognitive change related to neuropathic pain was driven primarily by changes in the domains of executive function and speed of information processing. Those with incident distal neuropathy signs did not have neurocognitive worsening, nor did individuals who used opioid analgesics or other pain-modulating drugs such as amitriptyline.

Worsened neurocognitive performance in people with HIV was associated with worsened neuropathic pain but not with changes in physical signs of neuropathy, and this was not attributable to therapies for pain or depression or to differences in viral suppression. This finding implies that incident or worsened pain may signal increased risk for neurocognitive impairment, and deserves more investigation, particularly if better pain management might stabilize or improve neurocognitive performance.

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Abbreviations: BDI = Beck Depression Inventory; DNP = distal neuropathic pain; MOS-HIV = Medical Outcomes Study HIV Health Survey; PROCAM = Prospective Cardiovascular Münster; sRBCS = summary regression-based change score

Introduction

Neuropathic pain and cognitive impairment are among the HIV-related conditions that have most stubbornly resisted amelioration by virally suppressive antiretroviral therapy. Distal neuropathic pain (DNP) in people with HIV is often treatment-resistant[1,2]—meaning that it persists despite the use of analgesic medications—and is associated with reduced quality of life,[1,3] greater disability and unemployment[4,5] and other morbidities, including poor balance and falls.[6,7]

Distal sensory polyneuropathy and neurocognitive impairment share multiple risk factors, including diabetes mellitus, abdominal obesity, small vessel disease and arterial stiffness.[8–11] Moreover, neuropathic pain and neurocognitive impairment share some regional brain substrates, such as alterations in the dorsolateral prefrontal cortex and the anterior and posterior cingulate cortices[12,13] and some pathophysiological features, such as microglial activation[14] and abnormal glutamatergic neurotransmission.[15] Together these observations raise the possibility that underlying vascular, inflammatory or neurodegenerative mechanisms contribute to both conditions.

Despite these links, to our knowledge no studies have evaluated the longitudinal evolution of neuropathy, neuropathic pain and neurocognitive impairment. Our goal was to assess whether worsened neuropathic pain and neuropathy were associated with worsened neurocognitive performance in people with HIV.

Materials and methods

Participants

Participants were enrolled in the prospective, observational cohort study, CNS HIV AntiRetroviral Therapy Effects Research (CHARTER), performed at six US sites [Johns Hopkins University (Baltimore), Icahn School of Medicine at Mount Sinai (New York), University of Texas Medical Branch, University of California San Diego, University of Washington (Seattle) and Washington University (St. Louis)]. Eligibility criteria included the ability to provide details of antiretroviral therapy use and during CHARTER assessments of a standardized examination for symptoms and signs of HIV-associated sensory neuropathy. Exclusions were active opportunistic infections or uncontrolled major psychiatric disorders or inability to cooperate with a full day of clinical evaluation. Comorbidities such as hepatitis C infection and substance abuse were permitted. Baseline visits took place between 2003 and 2007, and follow-up assessments approximately 12 years later, between 2016 and 2019. All participants signed local institutional review board-approved written consents.

Clinical assessment of neuropathy and neuropathic pain

Evaluations were conducted by centrally trained clinicians (mid-level practitioners and physicians) and included clinical examination for neuropathy signs (bilateral distal vibration, sharp and touch loss in the legs and feet and reduced ankle reflexes) and self-reported neuropathic pain. Distal sensory polyneuropathy was defined as two or more signs bilaterally. DNP was defined as burning, aching, or shooting symptoms in the distal legs and feet and was classified into five grades of clinician-rated pain severity distal sensory polyneuropathy based on participant report: none, slight (occasional, fleeting), mild (frequent), moderate (frequent, disabling) and severe (constant, daily, disabling, requiring analgesic medication or other pain medication). Worsened DNP was defined as an increase of at least one grade according to the scale above in a participant who had at least mild DNP at baseline.

Neurocognitive testing

Neurocognitive performance at baseline and follow-up both were measured using a comprehensive neuropsychological battery covering seven domains as specified by the Frascati criteria[16] for HIV-associated neurocognitive disorders (HAND). The battery is described in detail in a previous publication, and included tests of executive function, learning, memory, attention, working memory, psychomotor speed and speed of information processing.[17] Raw test scores were converted to standardized T-scores (mean 50, SD 10) that were corrected for age, education, sex and race/ethnicity. Change in neurocognitive performance from baseline to follow-up was measured using practice-corrected, summary regression-based change scores (sRBCS[18]) that correct for baseline performance, practice effect and other statistical artifacts (regression to the mean) and demographics.

Other clinical evaluations

The Medical Outcomes Study HIV Health Survey (MOS-HIV) has been shown to be a reliable and valid tool for assessing overall

quality of life, daily functioning and physical health.[19,20] The MOS-HIV contains 36 questions and includes a pain function subscale. Current mood was assessed by the Beck Depression Inventory (BDI)-II.[21] Dependence in instrumental activities of daily living was assessed with a modified version of the Lawton and Brody scale[16] that asks participants to rate their current and best lifetime levels of independence for 13 major instrumental activities of daily living such as shopping, financial management, transportation and medication management.[22] The Patient's Assessment of Own Functioning Inventory (PAOFI)[23] is a 33-item self-report measure used to measure perceived cognitive symptoms in everyday life. A structured clinical interview administered by trained interviewers was used to collect any history of balance disturbance and its onset over the previous 10 years as previously described.[6] Balance disturbances were classified as not present; occasionally unsteady, no falls; frequently unsteady; some near-falls or rare falls; and must use a cane, walker or other prop. Potential confounds included history of alcohol use disorders, diabetes mellitus (self-report or anti-diabetic medications), hypertension (self-report or antihypertensive medications), hyperlipidaemia (self-report or medications), CD4 measured at baseline, nadir CD4 (self-report) and body mass index and viral suppression at baseline. We also calculated vascular risk (a potential common underlying mechanism) using the Prospective Cardiovascular Münster (PROCAM).[24] Current medications, including opioids, antidepressants and adjunctive pain medications at baseline and follow-up, were collected by self-report.

Laboratory evaluations

HIV infection was diagnosed by enzyme-linked immunosorbent assay with western blot confirmation. HIV RNA in plasma was measured using commercial assays; viral suppression was defined as a level below the lower limit of quantitation of 50 copies/ml. Peripheral blood $CD4^+$ T-cell concentration was measured by flow cytometry.

Statistical analyses

Relationships between incident or worsened neuropathic pain or neuropathy and sRBCS were evaluated using uni- and multivariable regressions, including age at baseline and other relevant covariates. The primary statistical analysis was to test a single hypothesis—that people with HIV with incident or worsened DNP would have worse neurocognitive decline at follow-up than those without incident or worsened DNP. All other analyses, including multivariable models, were secondary, obviating the need to for additional controls for experiment-wide error rate. Secondary analyses were conducted to assess which specific neurocognitive domains were linked to incident or worsened DNP. Domain changes were assessed as regression-based change scores for the tests within each domain. Analyses were conducted using JMP Pro® version 15.0.0 (SAS Institute Inc., Cary, NC, 2018). *Post hoc* follow-up analyses examined regression-based change scores for each domain. Because these were *post hoc* follow-ups, no correction was made for multiple comparisons.

Data availability

Data will be made available upon request to the first author.

Results

Participants

Table 1 shows demographic and clinical characteristics of the study participants, who comprised 385 people with HIV, 91 (23.6%) females, mean ± standard deviation age at baseline 43.5 (7.81) years, ethnicity 44.9% African American, 10.6% Hispanic, 42.6% non-Hispanic white and 1.82% other. Baseline median (interquartile range, IQR) nadir CD4 was 175 (34 309) cells/μl and current CD4 was 454 (279 639). Median (range) of follow-up was 12.4 (9.69–16.2) years. At baseline, 73.6% were on combination antiretroviral therapy and at follow-up 96.3%. Viral suppression rates were 45.8% at baseline and 83.7% at follow-up. Also, as shown in Table 1, at baseline participants with incident or worsening DNP were older, had marginally worse depressed mood, were more likely to be on an opioid medication and had worse MOS pain function, physical health and mental health.

Incident or worsened neuropathic pain

At baseline, 115 participants (29.9%) had DNP. Those with baseline neuropathic pain had much worse overall somatic pain function (MOS pain function scale) at baseline than those without (55.4 ± 21.5 versus 73.3 ± 24.8; $P = 6.10 \times 10^{-11}$). Of 270 (70.1%) who were pain-free at baseline, 65 (24.1%) developed incident neuropathic pain at the 12-year follow-up. Of 117 with DNP at baseline, it worsened in 33 (28.7%) and improved in 55 (47.8%). Thus, incident or worsened DNP occurred in 98 (25.5%). With respect to the clinical significance of worsened pain, those with incident or worsened DNP had much worse pain functioning as indexed by the MOS pain function scale at follow-up than those with no or stable pain (52.7 ± 26.1 versus 68.0 ± 26.5; $P = 1.89 \times 10^{-6}$) and worse reports of poor balance ($P = 0.0002$).

Cross-sectional relationship of DNP to neurocognitive performance

To assess the possibility that neuropathic pain directly affected performance on the neurocognitive tests, we examined the pain-cognition relationship at each visit cross-sectionally. Those with DNP at baseline had global neurocognitive performance no worse than those without DNP (Global deficit scores: 0.477 ± 0.461 versus 0.526 ± 0.499, $P = 0.372$). The same was true for the follow-up visit (0.559 ± 0.562 versus 0.529 ± 0.573, $P = 0.681$). Because manual dexterity in particular might be influenced by pain, we separately evaluated the motor/psychomotor domain of functioning. At baseline, those with DNP performed worse in motor function than those without (domain T-score 44.9 ± 9.94 versus 47.2 ± 10.2. $P = 0.0411$). This relationship was borderline at follow-up (42.9 ± 11.0 versus 45.3 ± 11.4, $P = 0.0530$). Additional findings of interest were whether at baseline participants with sensory paresthesias performed worse with respect to motor function than those without sensory paresthesias (44.9 ± 9.68 versus 47.6 ± 10.3, $P = 0.0118$). Those with reduced ankle reflexes also performed worse on motor testing (44.5 ± 9.48 versus 48.1 ± 10.4, $P = 0.0005$), and those with reduced distal vibratory sensation showed a trend towards worse performance (44.9 ± 9.20 versus 47.2 ± 10.4, $P = 0.051$).

Incident/worsened neuropathic pain and changes in neurocognition

People with HIV with incident or worsened DNP had significantly worsened neurocognitive performance at follow-up compared to those without incident or worsened DNP (sRBCS mean ± SD −0.408 ± 0.700 versus −0.228 ± 0.613; $P = 0.0158$). In a multivariable model adjusting for viral suppression at follow-up, incident or worsened pain remained significant ($P = 0.0323$) while viral suppression was not ($P = 0.923$). In a multivariable regression including incident or

Table 1 Participant demographic and clinical characteristics according to DNP change status

	All	Incident or worsening DNP	Not incident/worsening DNP	P
n	385	98	287	–
Baseline age, years, mean ± SD	43.5 ± 7.81	44.9 ± 7.55	43.0 ± 7.86	0.040
Female sex, *n* (%)	91 (23.6%)	21 (21.4%)	70 (24.3%)	Ns
Ethnicity non-Hispanic white, *n* (%)	164 (42.6%)	46 (46.9%)	118 (41.1%)	Ns
Hispanic/Latino, *n* (%)	41 (10.6%)	9 (9.2%)	32 (11%)	Ns
Black, *n* (%)	173 (44.9%)	40 (40.8%)	133 (46.3%)	Ns
Other, *n* (%)	7 (18.2%)	3 (3.1%)	4 (1.4%)	Ns
Education, years, mean ± SD	13.1 ± 2.62	13.0 ± 2.58	13.1 ± 2.63	Ns
Nadir CD4+ lymphocytes, median (IQR)	175 (34, 309)	193 (47, 326)	168 (30, 306)	Ns
Baseline CD4+ lymphocytes, median (IQR)	454 (279, 639)	436 (267, 643)	475 (328, 616)	Ns
On antiretroviral therapy at baseline, *n* (%)	284 (73.8%)	73 (76.5%)	211 (73.5%)	Ns
On antiretroviral therapy at follow-up, *n* (%)	371 (96.3%)	93 (94.9%)	278 (96.9%)	Ns
Baseline plasma HIV RNA < 50 copies/ml, *n* (%)	174 (45.8%)	48 (50.0%)	126 (44.7%)	Ns
Follow-up plasma HIV RNA < 50 copies/ml, *n* (%)	262 (83.7%)	73 (84.9%)	189 (83.3%)	Ns
Exposed to neurotoxic dideoxynucleoside, *n* (%)	212 (55.1%)	58 (59.2%)	154 (53.7%)	Ns
Years of dideoxynucleoside exposure, mean ± SD	1.83 ± 3.09	2.04 ± 3.31	1.76 ± 3.01	Ns
Follow-up BDI-II, mean ± SD	9.65 ± 9.51	11.3 ± 10.4	9.13 ± 9.14	0.0595
Lifetime substance use disorder, *n* (%)	271 (70.8%)	74 (75.5)	197 (69.1)	Ns
Lifetime alcohol use disorder , *n* (%)	204 (53.3%)	55 (56.1%)	169 (58.9%)	Ns
Current alcohol use disorder, *n* (%)	5 (1.31%)	0 (0.0%)	4 (1.5%)	Ns
Lifetime MDD, *n* (%)	183 (47.8%)	62 (63.3%)	176 (61.3%)	Ns
Current MDD, *n* (%)	49 (12.8%)	7 (7.87%)	21 (7.87%)	Ns
On opioid medication, *n* (%)	53 (13.8%)	19 (19.4%)	34 (11.9%)	0.0697
MOS-HIV pain function, mean ± SD	64.2 ± 27.2	52.7 ± 26.1	68.0 ± 26.5	<0.0001
MOS-HIV physical health summary, mean ± SD	45.0 ± 11.8	40.6 ± 12.1	46.6 ± 11.3	<0.0001
MOS-HIV mental health summary, mean ± SD	50.3 ± 11.2	47.3 ± 12.4	51.3 ± 10.6	0.0036

MDD = major depressive disorder; Ns = not significant.

Table 2 *Post hoc* analysis of neurocognitive domain T-score changes related to incident or worsened DNP (Student's *t*-test)

Neurocognitive domain	Incident/ worse DNP	Not incident/ worse DNP	P
Verbal	−0.285 ± 1.18	−0.120 ± 0.977	0.168
Executive functioning	**−0.499 ± 0.971**	**−0.206 ± 0.966**	**0.0095**
Speed of information processing	**−0.534 ± 1.05**	**−0.122 ± 0.950**	**0.0003**
Learning	−0.216 ± 1.19	−0.243 ± 1.12	0.836
Recall	−0.0561 ± 0.978	0.0331 ± 0.908	0.408
Working Memory	−0.363 ± 1.04	−0.244 ± 0.932	0.286
Motor function	**−1.05 ± 1.14**	**−0.789 ± 1.06**	**0.0414**

worsened DNP, age and their interaction, neuropathic pain remained statistically significantly associated with neurocognitive worsening ($P = 0.0143$), while the other two variables were not significant ($P = 0.516$ and 0.901, respectively).

With regard to the potential clinical significance of the neurocognitive changes, worsened neurocognitive performance correlated with significantly worse depression as indexed by the BDI-II ($r = -0.257$, $P = 3.71 \times 10^{-7}$), more complaints of impaired cognitive functioning (PAOFI; $r = -0.238$, $P = 2.43 \times 10^{-6}$), worse mental ($r = 0.270$, $P = 5.2 \times 10^{-7}$) and physical ($r = 0.266$, $P = 8.10 \times 10^{-7}$) health quality of life as indexed by the HIV-MOS, worse dependence in activities of daily living ($r = -0.174$, $P = 6.54 \times 10^{-4}$) and a greater likelihood of being unemployed [range odds ratio (IQR) 18.3 (3.5, 103)]. In light of the correlations of DNP with both depression and neurocognitive performance and the potential impact of depression on neurocognitive performance, we further examined the interaction of depression and neuropathic pain with respect to neurocognitive performance. Those with DNP had worse depression than those without DNP [BDI-II median 8 (95% CI, 4, 15) versus 7 (2, 15); Wilcoxon $P = 0.0472$] and more severe depressed mood at follow-up correlated with worse neurocognitive change ($r = -0.257$ $P < 0.0001$). The correlation of depression with neurocognitive change was somewhat less strong for those with DNP than for those without ($r = -0.172$, $P = 0.0035$ versus $r = -0.427$ $P < 0.0001$). In a multivariable regression using DNP, BDI-II and their interaction to predict neurocognitive change, the BDI-II was significant ($P < 0.00001$) as was the interaction term ($P = 0.0180$, full model $P = 1.19 \times 10^{-7}$). Removing the interaction from the model, DNP approached significance ($P = 0.0556$, full model $P = 3.98 \times 10^{-7}$).

As shown in Table 2, *post hoc* analyses of neurocognitive domain T-score changes indicated that the relationship of incident DNP to change in neurocognitive performance was principally driven by changes in executive function and speed of information processing. The median change in MOS pain function scores (reflecting overall pain, including neuropathic pain and other sources) was 0 (IQR −22.2, 11.1). Worsened MOS pain was weakly related to worse neurocognitive performance ($r = 0.103$; $P = 0.0482$). Also, those with incident or worsened DNP did not have worsened MOS pain function than those without (−6.69 ± 28.9 versus −2.53 ± 27.3; $P = 0.210$).

Relationships with distal sensory polyneuropathy

At baseline, 101 participants (26.2%) had clinical signs of distal sensory polyneuropathy. Incident distal sensory polyneuropathy occurred in 96 of 284 participants (33.8%). Neurocognitive change as determined by the sRBCS did not differ in those with and without incident distal sensory polyneuropathy (−0.338 ± 0.662 versus −0.228 ± 0.611; $P = 0.163$).

Potential confounds

As shown in Tables 3 and 4, factors not associated with neurocognitive worsening (sRBCS) included sex, race/ethnicity, diabetes at baseline, hyperlipidaemia at baseline, hypertension at baseline, nadir CD4 at baseline, current CD4 at baseline, on antiretroviral therapy at baseline and viral suppression at baseline, body mass index and alcohol use disorder history. Incident diabetes mellitus significantly predicted worse sRBCS (−0.476 ± 0.745 versus −0.245 ± 0.614; $P = 0.0331$), but incident hypertension and hyperlipidaemia did not. Worse depression (higher BDI-II scores) at both baseline and follow-up was associated with worse sRBCS as well ($-r = 0.180$ $P = 0.0004$ and $r = -0.249$, $P = 8.09 \times 10^{-7}$, respectively). A higher value on a composite index of vascular risk, the PROCAM at follow-up, was correlated with worse sRBCS ($r = -0.120$, $P = 0.0330$). Participants taking any opioid medication at the follow-up visit did not show worse sRBCS than those not taking opioids (−0.351 ± 0.679, $n = 53$ versus -0.261 ± 0.633, $n = 332$; $P = 0.3440$). In a multivariable model, neither opioids ($P = 0.901$), nor their interaction with DNP ($P = 0.082$), was significant, while incident/worsened neuropathic pain remained significant ($P = 0.0196$, full model $P = 0.0246$). Similarly, participants taking antidepressant medications did not differ from those not taking them with respect to neurocognitive change (−0.292 ± 0.635, $n = 86$ versus −0.268 ± 0.641, $n = 299$; $P = 0.757$). In a multivariable model, neither antidepressants ($P = 0.898$), nor their interaction with DNP ($P = 0.456$), was significant. In an additional multivariable regression that included opioids, antidepressants and their interaction as predictors of neurocognitive worsening, neither of the main effects nor the interaction term was significant (opioids $P = 0.1252$, antidepressants $P = 0.0598$, interaction $P = 0.0554$; whole model $P = 0.0974$). Adding an additional term to this model, neuropathic pain was the only significant predictor of neurocognitive decline (opioids 0.2071, antidepressants $P = 0.0714$, interaction $P = 0.0848$, neuropathic pain $P = 0.0304$, whole model $P = 0.0265$).

Of the following medications often used as adjunctive treatment for neuropathic pain, none was linked to worse sRBCS, except lamotrigine: duloxetine, pregabalin, gabapentin, amitriptyline, tramadol. Those on lamotrigine ($n = 6$)—used for bipolar affective disorder and seizures as well as neuropathic pain—at follow-up had worse sRBCS than those not on lamotrigine (−0.840 ± 0.339 versus −0.265 ± 0.639, $P = 0.0285$). A composite variable representing being on any one of these medications was not associated with worse sRBCS ($P = 0.566$).

As insulin resistance and diabetes mellitus are risk factors for both DNP and cognitive decline, we examined levels of haemoglobin A1C, which were available at the second visit. Participants with incident or worse DNP had higher HbA1C (5.96 ± 1.48 versus 5.67 ± 1.08, $P = 0.0417$) and those with higher HbA1C had worse global neurocognitive change ($r = -0.106$, $P = 0.0391$). In a multivariable regression including HbA1C, incident or worsening DNP and their interaction, HbA1C and the interaction term were not significant predictors of neurocognitive worsening ($P = 0.112$ and 0.350, respectively), but DNP remained significant ($P = 0.0247$, full model $P = 0.0195$).

Table 3 Correlations (Spearman's *r*) of potential confounds with change in neurocognitive performance (sRBCS)

	r	*P*
Baseline age, years	0.029	0.564
Nadir CD4 cells/μl	−0.078	0.123
Current CD4 cells/μl	−0.058	0.252
Body mass index	−0.061	0.238
Follow-up PROCAM (vascular risk)	0.115	0.0417
Baseline BDI-II score	**−0.181**	**0.0003**
Change in BDI-II	−0.030	0.551

Multivariable models

To account for potential confounds, we performed multivariable regression for those predictors that were statistically significant in the univariable analysis of sRBCS. Incident/worsened DNP ($P = 0.00946$) and incident diabetes ($P = 0.01436$) but not their interaction ($P = 0.06194$) were independently associated with worsened neurocognitive performance (full model $P = 0.0060$), with the interaction trend suggesting that the combination of incident/worsened DNP and incident diabetes was worse than either alone. In a second model evaluating incident/worsened neuropathic pain and PROCAM vascular index as predictors of sRBCS, PROCAM was not significant ($P = 0.0669$), and was therefore removed from the model, leaving only incident/worsened neuropathic pain. In a third model, both worse BDI-II at baseline ($P = 0.00048$) and incident/worsened DNP ($P = 0.0221$) predicted worse neurocognitive change (overall model $P = 0.122 \times 10^{-4}$). Finally, in a model including both lamotrigine and incident/worsened DNP, both variables retained significance (lamotrigine, $P = 0.0316$; incident or worsened DNP, $P = 0.0175$; whole model $P = 0.0054$).

Discussion

Participants with incident or worsened neuropathic pain, but not those with incident findings of neuropathy on exam, experienced worse neurocognitive performance at follow-up. This relationship was not confounded by potential covariates including baseline diabetes mellitus or HIV disease parameters. We were able to assess several other potential explanations for the relationship between incident/worsened DNP and worsened neurocognitive performance, such as depression and medications used to treat neuropathic pain; none of these confounds explained the correlation.

The changes in cognition associated with DNP were clinically significant, being associated with more self-reports of impaired cognitive functioning, worse health-related quality of life, greater dependence in activities of daily living and a greater likelihood of unemployment.

Whether the association of incident/worsened DNP with neurocognitive worsening was due to a direct or indirect causal association or common effects of a shared unobserved variable is uncertain. For example, mitochondrial dysfunction is common in HIV and may influence both brain and peripheral nerves.[25–29] Vascular disease and metabolic syndrome (for example, hyperlipidaemia, hypertension, PROCAM) might separately predispose to both neuropathy and neurocognitive impairment, although we did not find evidence of this in our analysis.

The observation that incident and worsened neuropathic pain, but not incident distal sensory polyneuropathy, was correlated with worsened neurocognitive performance suggests that it is pain, rather than nerve injury, that links the two conditions. While not all of those with neuropathic pain had clinical exam findings of neuropathy, we have shown previously that people with HIV who report neuropathic pain do have abnormal electrophysiological signs consistent with peripheral nerve injury.[30]

In the current study, change in MOS pain function, a measure of global pain that includes neuropathic pain, was not associated with

Table 4 Mean changes in neurocognitive performance (sRBCS) ± SD, according to selected categorical variables

			P
Sex	Female ($n = 91$)	Male ($n = 294$)	
	−0.302 ± 0.638	−0.265 ± 0.641	0.558
Race/ethnicity	Black, Hispanic, other ($n = 221$)	Non-Hispanic white ($n = 164$)	
	−0.256 ± 0.640	0.297 ± 0.639	0.543
Viral suppression at baseline	No ($n = 206$)	Yes ($n = 174$)	
	−0.303 ± 0.622	−0.255 ± 0.660	0.354
On antiretroviral therapy at baseline	No ($n = 101$)	Yes ($n = 284$)	
	−0.237 ± 0.651	−0.286 ± 0.636	0.601
Diabetes at baseline	No ($n = 361$)	Yes ($n = 24$)	
	−0.318 ± 0.579	0.271 ± 0.643	0.731
Hyperlipidaemia at baseline	No ($n = 347$)	Yes ($n = 38$)	
	−0.269 ± 0.640	−0.315 ± 0.634	0.672
Hypertension at baseline	No ($n = 315$)	Yes ($n = 70$)	
	−0.246 ± 0.634	−0.395 ± 0.649	0.0779
Incident diabetes	**No ($n = 305$)**	**Yes ($n = 55$)**	
	−0.241 ± 0.622	**−0.476 ± 0.744**	**0.0127**
Incident hypertension	No ($n = 237$)	Yes ($n = 123$)	
	−0.286 ± 0.638	0.260 ± 0.665	0.712
Incident hyperlipidaemia	No ($n = 249$)	Yes ($n = 111$)	
	−0.260 ± 0.681	−0.315 ± 0.561	0.461
On opioid medication at follow-up	No ($n = 344$)	Yes ($n = 41$)	
	−0.265 ± 0.630	−0.347 ± 0.711	0.435
On antidepressant medication at follow-up	No ($n = 299$)	Yes ($n = 86$)	
	−0.268 ± 0.641	−0.292 ± 0.635	0.757

worse neurocognitive performance. Thus, pain as a predictor of subsequent neurocognitive decline was specific to neuropathic pain, as differentiated from other sources of pain. Of interest, change in neuropathic pain did correlate with change in MOS pain function.[31]

Accumulating observations indicate that chronic neuropathic pain is at least as dependent upon CNS changes as it is upon peripheral nerve injury. Indeed, neuropathic pain and neurocognitive impairment share alterations in specific regional brain substrates, such as the dorsolateral prefrontal cortex and the anterior and posterior cingulate cortices.[13,16] We have observed atrophy in the posterior cingulate cortex in people with HIV with chronic neuropathic pain[32] and other neuropathies are associated with changes in function in the posterior cingulate cortex using functional MRI.[33,34] At the same time, in the healthy brain, the magnitude of reactive changes in posterior cingulate cortex activity is related to cognitive load,[35] and a failure of appropriate deactivation is associated with inefficient cognitive function.[36] Notably, the specific cognitive domains we found to be best correlated with worsening neuropathic pain are those partly mediated by the dorsolateral prefrontal cortex. DNP and neurocognitive impairment also share particular pathophysiological mechanisms, such as microglial activation[16,37,38] and glutamate neurotransmission.[15,16,39,40] These links should be examined in future studies.

The generalizability of this study depends upon the specific cohort characteristics and measurement methods used. For example, relatively few females were included, and most participants had a history of advanced HIV disease. Thus, the results of this study may be less pertinent to women or to people with HIV who never had advanced HIV disease. Another limitation of this study is that it could not determine the causal association between worsened pain and worsened neurocognitive performance. Thus, the presence of pain could interfere with ability to fully concentrate on neurocognitive testing or, conversely, cognitive impairment could adversely impact pain coping. However, if ongoing pain directly affected performance, then one would expect a cross-sectional relationship between the presence of DNP and poorer neurocognitive performance. We showed that those with DNP at baseline performed no worse than those without; the same was true for the follow-up visit. DNP and other sensory disturbances did, however, associate with poor performance on the test of motor functioning, specifically. Future clinical trials to reduce pain and assess the impact of this intervention on neurocognitive performance would provide insight into causality. If an individual reports incident DNP, they may also have or be at increased risk for cognitive difficulties and associated medication nonadherence, virologic failure, reduced independence in instrumental activities of daily living and reduced quality of life. Whether ameliorating neuropathic pain will benefit neurocognitive function is an important future consideration.

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Competing interests

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References

1. Ellis RJ, Rosario D, Clifford DB, *et al*. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: The CHARTER Study. *Arch Neurol*. 2010; 67(5):552–558.
2. Ellis RJ, Toperoff W, Vaida F, *et al*. Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672–680.
3. Mann R, Sadosky A, Schaefer C, *et al*. Burden of HIV-related neuropathic pain in the United States. *J Int Assoc Provid AIDS Care*. 2016;15(2):114–125.
4. Marcus KS, Kerns RD, Rosenfeld B, Breitbart W. HIV/AIDS-related pain as a chronic pain condition: Implications of a biopsychosocial model for comprehensive assessment and effective management. *Pain Med*. 2000;1(3):260–273.
5. Girach A, Julian TH, Varrassi G, Paladini A, Vadalouka A, Zis P. Quality of life in painful peripheral neuropathies: A systematic review. *Pain Res Manag*. 2019;2019:2091960.
6. Sakabumi DZ, Moore RC, Tang B, Delaney PA, Keltner JR, Ellis RJ. Chronic distal sensory polyneuropathy is a major contributor to balance disturbances in persons living with HIV. *J Acquir Immune Defic Syndr*. 2019;80(5):568–573.
7. Erlandson KM, Allshouse AA, Jankowski CM, *et al*. Risk factors for falls in HIV-infected persons. *J Acquir Immune Defic Syndr*. 2012;61(4):484–489.
8. Ding X, Fang C, Li X, *et al*. Type 1 diabetes-associated cognitive impairment and diabetic peripheral neuropathy in Chinese adults: Results from a prospective cross-sectional study. *BMC Endocr Disord*. 2019;19(1):34.
9. Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and Cognitive Impairment. *Curr Diab Rep*. 2016;16(9):87.
10. Tuttolomondo A, Casuccio A, Guercio G, *et al*. Arterial stiffness, endothelial and cognitive function in subjects with type 2 diabetes in accordance with absence or presence of diabetic foot syndrome. *Cardiovasc Diabetol*. 2017;16(1):2.
11. Callaghan BC, Reynolds EL, Banerjee M, *et al*. The prevalence and determinants of cognitive deficits and traditional diabetic complications in the severely obese. *Diabetes Care*. 2020;43(3):683–690.
12. Weizman L, Dayan L, Brill S, *et al*. Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity. *Neurology*. 2018;91(14):e1285–e1294.
13. Kim CE, Kim YK, Chung G, *et al*. Large-scale plastic changes of the brain network in an animal model of neuropathic pain. *Neuroimage*. 2014;98:203–215.
14. Barcelon EE, Cho WH, Jun SB, Lee SJ. Brain microglial activation in chronic pain-associated affective disorder. *Front Neurosci*. 2019;13:213.
15. Palazzo E, Luongo L, Guida F, *et al*. D-Aspartate drinking solution alleviates pain and cognitive impairment in neuropathic mice. *Amino Acids*. 2016;48(7):1553–1567.
16. Antinori A, Arendt G, Becker JT, *et al*. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007; 69(18):1789–1799.
17. Heaton RK, Clifford DB, Franklin DR Jr, *et al*. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010;75(23):2087–2096.
18. Cysique LA, Franklin D Jr, Abramson I, *et al*. Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. *J Clin Exp Neuropsychol*. 2011;33(5):505–522.
19. Wachtel T, Piette J, Mor V, Stein M, Fleishman J, Carpenter C. Quality of life in persons with human immunodeficiency virus infection: Measurement by the Medical Outcomes Study instrument. *Ann Intern Med*. 1992;116(2):129–137.
20. Wu AW, Revicki DA, Jacobson D, Malitz FE. Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). *Qual Life Res*. 1997;6(6):481–493.
21. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 1996;67(3):588–597.
22. Heaton RK, Marcotte TD, Mindt MR, *et al*. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc*. 2004;10(3):317–331.
23. Chelune GJ, Heaton RK, Lehman RAW. Neuropsychological and personality correlates of patients' complaints of disability. *Adv Clin Neuropsychol*. 1986; 3:95–126. Plenum Press.
24. Assmann G, Schulte H. The Prospective Cardiovascular Munster (PROCAM) study: Prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J*. 1988;116(6 Pt 2):1713–1724.
25. Swinton MK, Carson A, Telese F, *et al*. Mitochondrial biogenesis is altered in HIV+ brains exposed to ART: Implications for therapeutic targeting of astroglia. *Neurobiol Dis*. 2019;130:104502.
26. Thangaraj A, Periyasamy P, Liao K, *et al*. HIV-1 TAT-mediated microglial activation: Role of mitochondrial dysfunction and defective mitophagy. *Autophagy*. 2018;14(9):1596–1619.
27. Wang Y, Santerre M, Tempera I, Martin K, Mukerjee R, Sawaya BE. HIV-1 Vpr disrupts mitochondria axonal transport and accelerates neuronal aging. *Neuropharmacology*. 2017;117:364–375.
28. Cotto B, Natarajanseenivasan K, Langford D. HIV-1 infection alters energy metabolism in the brain: Contributions to HIV-associated neurocognitive disorders. *Prog Neurobiol*. 2019;181:101616.
29. Fields JA, Swinton MK, Carson A, *et al*. Tenofovir disoproxil fumarate induces peripheral neuropathy and alters inflammation and mitochondrial biogenesis in the brains of mice. *Sci Rep*. 2019;9(1):17158.
30. Robinson-Papp J, Morgello S, Vaida F, *et al*. Association of self-reported painful symptoms with clinical and neurophysiologic signs in HIV-associated sensory neuropathy. *Pain*. 2010;151(3):732–736.
31. Navis A, Jiao J, George MC, Simpson D, Robinson-Papp J. Comorbid pain syndromes in HIV-associated peripheral neuropathy. *Pain Med*. 2018;19(7):1445–1450.
32. Keltner JR, Connolly CG, Vaida F, *et al*. HIV Distal neuropathic pain is associated with smaller ventral posterior cingulate cortex. *Pain Med*. 2017;18(3):428–440.
33. Boland EG, Selvarajah D, Hunter M, *et al*. Central pain processing in chronic chemotherapy-induced peripheral neuropathy: A

functional magnetic resonance imaging study. *PLoS One*. 2014; 9(5):e96474.
34. Hsieh PC, Tseng MT, Chao CC, *et al*. Imaging signatures of altered brain responses in small-fiber neuropathy: Reduced functional connectivity of the limbic system after peripheral nerve degeneration. *Pain*. 2015;156(5):904–916.
35. Singh KD, Fawcett IP. Transient and linearly graded deactivation of the human default-mode network by a visual detection task. *Neuroimage*. 2008;41(1):100–112.
36. Bonnelle V, Leech R, Kinnunen KM, *et al*. Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. *J Neurosci*. 2011;31(38):13442–13451.
37. Cao S, Fisher DW, Yu T, Dong H. The link between chronic pain and Alzheimer's disease. *J Neuroinflammation*. 2019;16(1): 204.
38. Tyrtyshnaia A, Manzhulo I, Kipryushina Y, Ermolenko E. Neuroinflammation and adult hippocampal neurogenesis in neuropathic pain and alkyl glycerol ethers treatment in aged mice. *Int J Mol Med*. 2019;43(5):2153–2163.
39. Mutso AA, Radzicki D, Baliki MN, *et al*. Abnormalities in hippocampal functioning with persistent pain. *J Neurosci*. 2012;32-(17):5747–5756.
40. Neugebauer V. Amygdala pain mechanisms. *Handb Exp Pharmacol*. 2015;227:261–84.