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Better Antiretroviral Central Nervous System Penetration is Not Associated with Reduced Chronic Pain in People Living with Human Immunodeficiency Virus

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Abstract

Objective—To determine if better antiretroviral (ARV) central nervous system (CNS) penetration is associated with reduced rates of chronic pain in people living with HIV (PLWH).

Background—Chronic pain remains prevalent in PLWH despite widespread ARV use. Mechanisms underlying this prevalence remain unknown, though neuroinflammation from persistent CNS HIV infection and maladaptive plastic changes in the CNS have been implicated. Here we hypothesize that better CNS ARV penetration, measured using the CNS Penetration-Effectiveness (CPE) score, would decrease rates of chronic pain.

Methods—We interviewed 254 consecutive adults from an HIV clinic in Chiang Mai, Thailand. We collected data on demographics, HIV history, ARV use, and pain characteristics. Patients were evaluated for depression using a Thai two question Patient Health Questionnaire (PHQ-2). Modified CPE score was calculated using established methods and grouped a priori into “low CPE” (7, poor penetration) and “high CPE” (8, good penetration). CPE score was compared with chronic pain scores in SPSS using appropriate statistical tests. A relationship between CPE score and a positive depression screen was tested further using multivariable binary logistic models.

Results—245 of 254 subjects were on ARVs. Complete ARV data was available for 235 patients. 137 of these 235 patients (58.3%) had a CPE score 7, and 98 (41.7%) had a score 8. 49 patients had chronic pain, and 9 had neuropathic pain. Low CPE score was not associated with chronic pain ($p=0.64$), neuropathic pain ($p=0.56$), or frequent pain ($p=0.80$), nor was it associated with the severity of reported “worst pain” or “average pain” in the last 24 hours ($p=0.18$ and 0.48 , respectively). *Post-hoc* analysis revealed that higher CPE score was a significant independent risk

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

factor for depression measured by a positive PHQ-2 screen [OR (95% CI) = 1.29 (1.04–1.61), $p=0.02$]. This relationship was mediated primarily by exposure to zidovudine.

Conclusions—CPE score is not associated with chronic pain in PLWH. *Post-hoc* analysis demonstrated that CPE score, and zidovudine exposure in particular, predicts a positive depression screen. Given the substantial morbidity associated with chronic pain and mood disorders in PLWH, additional studies to determine preventable and treatable factors are imperative.

Keywords

AIDS; antiretroviral agents; depression; HIV; HAART; pain management

INTRODUCTION

Background

Use of combined antiretroviral therapy (cART) has substantially reduced morbidity and mortality from human immunodeficiency virus (HIV) related illnesses and acquired immune deficiency syndrome (AIDS). As HIV transitions from a terminal diagnosis to a chronic illness with the proliferation of cART, quality of life issues will assume greater importance in the care of people living with HIV (PLWH).

Chronic pain is among the world's most costly diseases on both a personal level and a societal level [1]. Chronic pain is particularly problematic in PLWH, since pain remains among the most common symptoms of chronic HIV infection even in the era of widespread antiretroviral (ARV) use [2–7]. Chronic pain is persistently undertreated in PLWH, and this untreated pain substantially and deleteriously impacts quality of life [2, 8–10]. PLWH suffer disproportionately from pain syndromes common to the general population, such as migraines, [11] as well as from other pain syndromes more specific to HIV/AIDS or its treatment, such as painful distal neuropathy [12]. Despite the substantial associated morbidity and cost, to date the underlying causes for this increased prevalence remain unknown, and a significant knowledge gap exists regarding the best ways to prevent and treat chronic pain in PLWH.

Mechanisms Underlying Chronic Pain in PLWH

Substantial accumulated evidence demonstrates that plastic changes in the central nervous system may underlie chronic pain states [13]. Dorsal horn neurons can become sensitized such that normally innocuous stimuli induce pathologic pain [14]. Proinflammatory cytokines released by activated astrocytes can induce plastic changes, enhance excitatory transmission, and suppress inhibitory transmission in dorsal horn neurons and interneurons, [15] and loss of spinal synaptic inhibition has been implicated in the development of chronic pain [16]. In addition, neuroplastic changes in both ascending spinocortical and descending corticospinal connections and in the cortex itself have been shown to play a role in persistent pathologic pain [17].

Though the pathophysiology underlying the increased prevalence of chronic pain in PLWH specifically remains unknown, various mechanisms have been proposed. Viral induced

immune dysregulation, sequelae of opportunistic infections, and toxic effects of therapy have all been implicated, and indeed all may play a role in a multifactorial process [18]. It has been hypothesized that HIV infection of CNS microglia, macrophages, and possibly astrocytes leads to neuronal damage either through direct toxic effects or through local inflammatory phenomena [19]. In animals, intrathecal HIV-1 has been demonstrated to induce enhanced pain states through upregulation of spinal cord proinflammatory cytokines [20]. In humans, these same inflammatory cytokines have been shown to be upregulated in the dorsal horn of pain-positive HIV+ patients, but not HIV+ patients without pain [21].

The central nervous system is a known sanctuary for HIV, and persistent CNS viral infection can be present even when viral load is not detectable in plasma – the so-called “viral escape” phenomenon [22, 23]. HIV’s propensity to chronically infect the CNS and induce the plastic changes mentioned above provides a hypothetical mechanistic framework to explain the observed increased prevalence of pain in PLWH, though the pathophysiologic cascade is not yet understood.

CNS Penetration-Effectiveness score and the Value of Better CNS Penetration

Since the introduction of cART, mortality and quality of life have improved for PLWH. However, recent work highlights the finding that neurologic manifestations of HIV persist even in patient with well-controlled systemic disease on cART. Major disabilities that can persist in the chronic treated phase include gait disorders, cognitive impairment, and various pain syndromes including painful neuropathy and migraine [11, 12, 24–26]. HIV can persist in the CNS, even in the face of cART, partially explaining the persistence of neurologic symptoms, [24, 27] though controversy remains [28]. Furthermore, it has been demonstrated that certain widely used ARV agents do not adequately penetrate the CNS as well as other agents, [29, 30] and that decreased CNS penetration correlates with increased CSF HIV viral load [27].

The CNS Penetration-Effectiveness (CPE) score is a validated tool to quantify the CNS-penetration of ARVs; better penetration has been shown to correlate with reduce HIV CSF viral load independent of the systemic potency of the regimen [31, 32]. In this score, ARVs are ranked according to their ability to penetrate the blood brain barrier and reduce CSF viral load, with higher scores indicating better penetration [31]. This score was updated in 2010 [32]. Using this score, some studies show that the rates and severity of HIV-associated neurocognitive disorders vary with the CNS penetration of the ARV regimen [31, 33].

Like chronic cognitive complaints, chronic pain is predominantly a central phenomenon and therefore susceptible to chronic CNS infection’s deleterious effects on the nervous system. As a corollary, better CNS penetration and reduced CNS viral load may help reduce chronic pain prevalence and severity.

Rationale for the Current Study

Given the evidence reviewed above suggesting that chronic pain in PLWH could result from persistent CNS HIV infection and maladaptive plasticity, we hypothesized that better CNS ARV penetration and an associated decrease in CNS HIV burden would lead to a decreased prevalence of chronic pain in PLWH. Our primary aim was to test if better CNS ARV

penetration, measured using the modified CPE score, was associated with decreased rates of chronic pain in a population of HIV+ Thai adults. Our secondary aims were to investigate if higher CPE scores were associated with decreased severity of pain or decreased rates of chronic neuropathic pain.

METHODS

Subject Recruitment

Consecutive subjects were recruited from an outpatient HIV clinic in a tertiary care hospital in Chiang Mai, Thai-land. Inclusion criteria for the study were age 18 years or older, ability to speak Thai, and known HIV seropositivity. Subjects on cART for whom all agents in the ARV regimen could be identified (either by self-report or in the medical record) were eligible for CPE analyses.

Standard Protocol Approvals, Registrations, and Patient Consent

This study was approved by the Chiang Mai University Faculty of Medicine's Ethical Committee. The data was anonymized by removing personal details, and the master key was kept in a double-locked secured office cabinet and destroyed after study completion. All patients provided informed consent prior to participation.

Survey Methods

After obtaining informed consent, trained interviewers administered standardized surveys in Thai. Surveys were either published previously in Thai or translated into Thai and then back translated into English to ensure accuracy prior to use. The full methods have been published previously [2]. Briefly, the principal 26-item survey questionnaire elicited information on demographics, comorbidities, and HIV clinical information. Continuous data were subdivided into subcategories a priori (e.g., estimated income was recorded as 1999, 2000–4999, 5000–9999, and 10000 Thai baht per month, with 30 Thai baht approximately equal to \$1). Depression and pain were identified with established screening questions (see below). Survey items that could not necessarily be answered by the patient (e.g., CD4 nadir, current medications) were completed by study investigators using the electronic medical records and the historical paper chart as appropriate.

Pain Surveys

To identify pain, all patients were asked the following question (in Thai): “During the past two weeks, have you experienced persistent or frequent pain of any type?” This question has been used before to investigate pain in HIV+ adults in the United States [10]. Patients who answered “yes” to this question were characterized as having frequent pain and were then asked the following question: “Have you had this pain for more than three months?” This question has been previously used in Asia to assess for chronic pain [34]. Patients who answered “yes” to this question were characterized as having chronic pain. Patients with frequent pain were then asked to complete two more surveys related to their pain and medications: the validated Brief Pain Inventory-Short Form (BPI-S) (Thai) [35–37] and the Thai version of the Self-Administered Leeds Assessment of Neuropathic Symptoms and Sign (S-LANSS) [38]. The BPI-S ranks several aspects of pain and the impact of pain on

quality of life using an 11-point ordinal scale (0–10), and the S-LANSS has been widely used to screen for neuropathic pain.

Depression Screening

To screen for depression, patients were asked a “yes/no” Thai form of the two-question Patient Health Questionnaire (PHQ-2) [39]. The Patient Health Questionnaire is widely used around the world to screen for depression, and the full version has been validated in Thai and has good specificity with moderate sensitivity [40]. To increase sensitivity in the current study, patients who answered “yes” to either question of the PHQ-2 were considered to have screened positive for depression. The two-questions asked were as follows: “over the last 2 weeks have you been bothered by little interest or pleasure in doing things,” and “over the last 2 weeks have you been feeling down, depressed, or hopeless.”

CNS Penetration-Effectiveness Score

The CPE score ranks ARVs based on their chemical properties and relative abilities to penetrate the blood-brain barrier, accumulate in cerebrospinal fluid, and reduce CSF viral load [31]. It has been previously validated in the study of HIV-associated neurocognitive disorders, among other conditions [28, 36]. Briefly, the original score used best available evidence to rank ARVs from 0 (low penetration) to 1 (high penetration). A modified CPE score later improved this ranking system, assigning individual ARV CPE scores from 1 (poor penetration) to 4 (best penetration). The CPE numeric values of each drug in the regimen are summed to give the total CPE score for the regimen, such that a regimen of cART can yield an ordinal CPE score that ranges between 3 (three agents with low penetration) and 16 (four agents with high penetration). CNS Penetration-Effectiveness ranks for individuals medications can be seen in (Fig. 1). In the current study, we determined a priori to analyze CPE score as a binary variable (above and below the median), as has been done before in studies examining CPE score [41]. We also analyzed CPE score as an ordinal variable, which more effectively explores the magnitude and directionality of observed effects.

Statistics

Data was analyzed using SPSS v22 (SPSS Inc., Chicago, IL). Bivariate associations between categorical variables were compared using Chi-squared tests. After determining that the data was not normally distributed, the Mann-Whitney *U* test was used to test the associations between low CPE score and ordinal pain severity scores, and between binomial variables and CPE score when CPE score was analyzed as an ordinal variable.

After exploratory analysis demonstrated that high CPE score was significantly associated with a positive depression screen, multivariable binary logistic models were constructed with variables whose bivariate associations with the outcome “PHQ positive” had *p*-values < 0.2. Those variables with multivariable-adjusted *p*-values of < 0.2 were kept in the model. Model fit was assessed with the Hosmer-Lemeshow test. Statistical significance was defined as a *p*-value 0.05.

RESULTS

From March to May 2011 we approached 260 patients, of whom 254 provided consent and were included in the study. See (Fig. 2) for details of subject recruitment. 96.5% (245 subjects) of the total sample was on cART.

Of these 245 subjects, 235 (95.9%) had complete information regarding current ARV and constituted our core sample of patients for whom CPE scores could be calculated. The most commonly used ARVs in the population were as follows: lamivudine (n=229); tenofovir (n=122); nevirapine (n=114); efavirenz (n=98); zidovudine (n=61); stavudine (n=52); lopinavir/ritonavir (n=21); and other (n=8).

For these 235 patients, the median duration on cART was 7.0 years, with an interquartile range (IQ) of 6 years. The median age was 42.0 years (IQ 11). Females represented 56.2% of the sample. The majority of the sample did not finish high school and made less than 350 USD per month, or 10,000 Thai baht. 66 patients (28.1%) screened positive for depression by answering affirmatively to at least one of the PHQ-2 questions. See Table 1 below for baseline demographics of the sample.

Modified CPE scores in this sample ranged from 6 to 10. The median in our sample fell between 7 and 8; 137 patients (58.3%) had CPE score 7 ("low CPE score"), and 98 patients (41.7%) had a score 8 ("high CPE score").

Of note, complete baseline characteristics of the greater study sample, of whom this sample represents the vast majority (235/254), have been published in detail elsewhere [2]. When compared to the 254 patient sample as a whole, this sample of 235 patients did not differ on any of the baseline demographics (all *p*-values > 0.05, results now shown).

Pain Characteristics of the Sample Stratified by CPE Score

Of 235 subjects, 26.4% (n=62) reported persistent or frequent pain of any kind in the last two weeks, and 20.9% (n=49) reported chronic pain of any kind lasting longer than 3 months. Distribution of frequent pain included limb pain (n=18), headache (n=12), back pain (n=14), neck pain (n=3), and other pains (n=21). Of those patients with frequent pain who went on to complete the S-LANSS, 9 patients (3.8%) screened positive for neuropathic pain. Of the patients with frequent pain who completed the BPI-S, the median value for average pain in the last 24 hours (BPI-5) was 3.0, and median worse pain in the last 24 hours (BPI-3) was 4.5. Contrary to our initial hypothesis, CPE score did not predict the presence of chronic pain, acute pain, or neuropathic pain, nor did it predict the severity of average or worst pain (all *p*-values > 0.10). See Table 2 below for bivariate analysis comparing pain variables by CPE score.

To help determine if the non-significant relationship between CPE score and chronic pain was due to lack of statistical power in this sample or a true lack of association, we compared the presence of chronic pain to CPE score analyzed as an ordinal variable with five values (6–10) using the Mann-Whitney *U* test. This analysis also failed to demonstrate an

association (mean rank for chronic pain/no chronic pain = 120.4/117.4, $Z = -0.29$, 2-tailed p -value = 0.77).

CPE score and Depression

After noting a strong relationship between high CPE score and depression, we conducted additional analyses to explore this relationship. In univariate analysis, chronic pain, lack of Thai citizenship, current alcohol use, frequent pain, neuropathic pain, and high CPE score were all associated with a positive depression screen (see Table 3). We then compared CPE score as an ordinal variable to a positive PHQ-2 depression screen and found an even stronger relationship (mean rank of CPE scores compared by PHQ(+)/PHQ(-) = 136.40/110.81, $Z = -2.68$, $p = 0.007$).

To further explore the association between CPE score and a positive depression screen, we constructed binary logistic regression models using covariates identified from the variables listed in Table 3 whose bivariate associations with the outcome “PHQ(+)” had p -values < 0.2. Using logistic regression analysis, high CPE score remained a statistically significant independent risk for a positive depression screen ($p = 0.02$), and each additional increase of one point of CPE score increased the odds of screening positive for depression by 1.29 (95% confidence interval 1.04–1.61). The presence of chronic pain and neuropathic pain were also independent risks for a positive depression screen, as was current alcohol use and belonging to an ethnic group other than Thai. Frequent pain was not significant in regression analysis after controlling for the other factors ($p = 0.84$), likely due to its high correlation with chronic pain ($\phi = 0.86$). Results from logistic regression analysis of factors associated with a positive PHQ-2 screen can be found in Table 4 below. Note that in this table, “Thai citizenship” was transformed to “no-Thai citizenship” to make odds ratios easier to interpret.

To determine if exposure to any individual ARV agent would better explain the relationship between high CPE score and a positive PHQ-2, we tested the relationship between exposure to each individual agent ($n = 15$) and a positive depression screen. While tenofovir use was significantly associated with a negative depression screen in bivariate analysis ($\chi^2 = 5.76$, $n = 126$, $p = 0.02$), only zidovudine remained significantly associated with depression after using a Bonferroni correction to maintain the familywise error rate ($\chi^2 = 9.96$, $n = 59$, $p = 0.002$; corrected $p = 0.03$). To explore this association further, we again constructed logistic regression models as described above but additionally included zidovudine use as a covariate. Including zidovudine use in the model did not change the model’s predictive value (Nagelkerke $R^2 = 0.20$, $p < 0.001$), but CPE score no longer significantly predicted a positive depression screen ($p = 0.71$). Zidovudine use, on the other hand, remained a significant independent risk factor for depression (Exp(B)[95% confidence interval] = 2.40[1.20 – 4.80], $p = 0.01$).

DISCUSSION

In this study, we found no relationship between ARV CNS penetration, as measured by CPE score, and the prevalence of chronic pain in PLWH. We also found no relationship between CPE score and neuropathic pain, frequent pain, and various measures of pain severity. *Post-hoc analysis* revealed that high CPE score, and zidovudine use in particular, is significantly

associated with a positive depression screen, even when accounting for other factors using logistic regression analysis.

As noted in the introduction, several studies have found that chronic pain is more prevalent amongst PLWH. Though we found no effect of higher CPE score on chronic pain prevalence, it is still possible that chronic viral infection itself and/or associated immunologic phenomena could explain the association between chronic HIV infection and chronic pain. Some authors have posited that ARV efficacy against HIV in monocytes/macrophages, a known reservoir for HIV, may be a better metric than ARV penetration into the CSF.³⁷

Alternatively, despite the evidence reviewed above that HIV infection leads to CNS changes known to be associated with chronic pain, it is possible that the viral and immune effects are not directly related to low-grade CNS infection. Damage from HIV may occur at disease onset prior to ARV initiation, so that the ongoing low-grade HIV infection observed even with cART therapy is not clinically relevant.

It is also possible that chronic HIV infection *per se* is not at all related to the increased prevalence of chronic pain in PLWH. Previously we found that several demographic variables, such as low education and low income, were significantly and independently associated with chronic pain in this population [2]. In this study, we again found that social factors such as non-Thai citizenship have significant association with medical conditions such as depression. It is possible that psychosocial factors, rather than chronic HIV infection itself, may instead explain the observed relationship between chronic pain prevalence and HIV infection, and that these factors are not adequately controlled for using cross-sectional study designs. Further research must aim to determine the psychosocial and biologic factors that mediate the robust relationship between chronic HIV infection and chronic pain.

The association between a high CPE score (driven by zidovudine use) and a positive depression screen is novel. Unfortunately, this study was not powered to explore this association in more depth. It is possible that HIV infection or some immune response is playing an as yet undetermined role in preventing depression, such that CNS HIV eradication is deleterious to mood. Alternatively, zidovudine may have direct toxic effects on the nervous system that lead to depression. It is also possible that the relationship between a positive depression screen and CPE score is actually an epiphenomenon. For example, prescribing physicians may choose or avoid certain ARV regimens if a patient has preexisting depression. Finally, while we tried to account for socioeconomic factors through regression analysis, it is possible that some other socioeconomic factor that determines the prescribed ARV regimen may be responsible for the increased depression rates. Future studies will need to replicate this finding and elucidate explanatory factors.

Strengths

This study had several strengths. To our knowledge it is the first study to investigate the relationship between CPE score and chronic pain. Additionally, we were able to add to a growing body of literature on chronic pain and mood disorders in PLWH in non-Western

countries. Given the complex interplay between psychosocial factors, mood disorders, and chronic pain, research in diverse populations is essential.

Limitations

This study had several limitations. The cross-sectional design precluded causal inference. Also, we were not able to collect data on past medication regimens, so our analysis on CPE score was limited to current ARVs. However, most patients in this population had remained on a stable regimen for many years. A second limitation is the relatively small sample size of patients with neuropathic pain in this population, and the limited information collected on the nature of the subjects' pain. It is conceivable that CNS penetration would have more of an impact on certain pains, such as neuropathic pain, rather than chronic pain in general. Finally, as mentioned above, our sample did not have the power to detect factors that may mediate the relationship between CPE score and a positive depression screen, and we collected no additional data on the quality or severity of depression in this population.

CONCLUSIONS

From this study, we conclude that CPE score does not predict the prevalence or severity of chronic pain. There may be a relationship between CPE score, and zidovudine use in particular, and depression, though further work remains to be done. Given the significant detriment to quality of life posed by mood disorders and chronic pain in PLWH, further research aimed at elucidating means for preventing and treating these morbidities is essential.

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Biography

N.M. Robbins

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	4	3	2	1
NRTIs	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PIs	Indinavir-r	Darunavir-r	Atazanavir	Nelfinavir
		Fosamprenavir-r	Atazanavir-r	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir
		Lopinavir-r		Saquinavir-r
				Tipranavir-r
Fusion/Entry Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		
¹ adapted from Letendre <i>et al.</i> , 17th CROI, 2010, Abstract 172 (courtesy of S. Letendre, email communication). NRTIs – nucleoside reverse transcriptase inhibitors. NNRTIs – non-nucleoside reverse transcriptase inhibitors. PIs – protease inhibitors. r – ritonavir boosted.				

Fig. 1.
CNS Penetration-Effectiveness Ranks 2010¹.

Fig. 2.
Flow of participants.

Table 1

Characteristics of the sample.

Variable	Total sample n=235 n (% of total)	CPE score 7 n=137 n (% of CPE 7)	CPE score 8 n=98 n (% of CPE 8)	p-value ¹
Female gender	132 (56.2)	84 (61.3)	48 (36.4)	0.06
Education primary school	78 (33.2)	40 (29.2)	38 (38.8)	0.12
Income <5000 baht * per month	68 (28.9)	36 (26.3)	32 (32.7)	0.29
Ever smoked	66 (28.3)	35 (26.1)	31 (31.3)	0.46
Thai citizen	226 (96.2)	136 (99.3)	90 (91.8)	< 0.01 ²
Current alcohol use	92 (39.1)	49 (35.8)	43 (43.9)	0.21
History of AIDS	120 (51.3)	70 (51.1)	50 (51.5)	0.94
History of stavudine use	52 (22.9)	21 (16.2)	31 (32.0)	< 0.01
PHQ positive	66 (28.1)	31 (22.6)	35 (35.7)	0.03
Ordinal variable	Median (IQR) ^a	Median (IQR)	Median (IQR)	p-value ³
Age in years	42.0 (11)	42.0 (6)	43.0 (16)	0.55
Years since HIV diagnosis ^b	9.0 (8)	10.0 (9)	9.0 (9)	0.28
Years on cART ^a	7.0 (6)	8.0 (5)	7.0 (7)	0.14
Latest CD4 cell count ^b	392.0 (252)	390.0 (261)	386.0 (259)	0.43
Lowest CD4 cell count	70.0 (95)	85.0 (93)	47.0 (93)	0.21

¹ Pearson's Chi-squared,² Fisher Exact test,³ Mann-Whitney *U*.^a IQR = interquartile range,^b n=234;^c n=233,

* in 2011, 1 US dollar = 30 Thai baht

Table 2

Pain comparisons based on CNS Penetration-Effectiveness score.

Variable	Total sample n=235 n (% of total)	CPE score 7 n=137 n (% of CPE 7)	CPE score 8 n=98 n (% of CPE 8)	p-value
Frequent pain in last 2 weeks	62 (26.4)	37 (27.0)	25 (25.5)	0.80 ¹
Chronic pain > 3 months	49 (20.9)	30 (21.9)	19 (19.4)	0.64 ¹
Neuropathic pain on S-LANSS	9 (3.8)	5 (3.6)	4 (4.1)	0.56 ³
	Total chronic pain n=49 median (IQR⁴)	CPE score 7 n=30 median (IQR)	CPE score 8 n=19 median (IQR)	p-value²
Worst pain last 24 hours (BPI-3)	4.0 (4)	4.5 (4)	4.0 (2)	0.18
Average pain last 24 hours (BPI-5)	3.0 (3)	3.0 (2)	3.0 (3)	0.48

¹ Pearson's Chi-squared,² Mann-Whitney *U*,³ Fisher's exact (1-sided),⁴ IQR = interquartile range.

Table 3

Variables associated with a positive depression screen using a modified Thai PHQ-2.

Variable	Total sample n=235	PHQ positive n=66	PHQ negative n=169	
	n (% of total)	n (% of PHQ (+))	n (% of PHQ (-))	p-value ¹
Female gender	132 (56.2)	41 (62.1)	91 (53.8)	0.25
Education primary school	78 (33.2)	26 (39.4)	52 (30.8)	0.21
Income < 5,000 baht per month	68 (28.9)	23 (34.8)	45 (26.6)	0.21
Ever smoked regularly	64 (27.2)	21 (31.8)	43 (25.4)	0.32
Thai citizen	226 (96.2)	59 (89.4)	167 (98.8)	< 0.01 ²
Current alcohol use	92 (39.1)	33 (50.0)	59 (34.9)	0.03
History of AIDS	120 (51.3)	33 (50.0)	87 (51.8)	0.81
Frequent pain	62 (26.4)	26 (39.4)	36 (21.3)	< 0.01
Chronic pain	49 (20.9)	22 (33.3)	27 (16.0)	< 0.01
History of stavudine use	52 (22.9)	13 (20.0)	39 (24.1)	0.51
Low CPE score	137 (58.3)	31 (47.0)	106 (62.7)	0.03
Neuropathic pain	9 (3.8)	7 (10.6)	2 (1.2)	< 0.01 ²
Ordinal variables	Median (IQR)^a	Median (IQR)	Median (IQR)	p-value³
Age in years	42.0 (11)	43.0 (9)	41.0 (11)	0.46
Years since HIV diagnosis ^c	9.0 (8)	10.0 (8)	9.0 (8)	0.52
Years on cART ^b	7.0 (6)	7.0 (7)	6.0 (5)	0.23
Latest CD4 cell count ^c	392.0 (252)	407.0 (186)	382.0 (279)	0.40
Nadir CD4 cell count	70.0 (95)	69.0 (112)	70.0 (92)	0.84

¹ Pearson Chi-Square,² Fisher's Exact test,³ Mann-Whitney *U*.^a IQR = interquartile range,^b n=234;^c n=233.

Table 4

Variables associated with a positive depression screen in logistic regression analysis.

Covariate	Odds ratio (95% confidence interval)	<i>p</i> -value
CPE Score	1.29 (1.04–1.61) ^a	0.02
No Thai citizenship	9.25 (1.67–51.33) ^b	0.01
Current alcohol use	2.18 (1.17–4.09) ^b	0.02
Neuropathic pain	7.53 (1.37–41.37) ^b	0.02
Chronic pain	2.26 (1.09–4.68) ^b	0.03

^a the odds of having an affirmative PHQ-2 screen is 1.29 for each increase of 1 unit of CPE score.

^b the odds of a positive PHQ-2 screen with the listed variable compared to without it.