The Association of Chronic Pain and Long-Term Opioid Therapy With HIV Treatment Outcomes

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Background: Chronic pain occurs in up to 85% of persons living with HIV and is commonly treated with long-term opioid therapy (LTOT). We investigated the impact of chronic pain and LTOT on HIV outcomes.

Methods: This was prospective cohort study conducted between July 2015 and July 2016 in 5 HIV primary care clinics. Chronic pain was defined as ≥moderate pain for ≥3 months on the Brief Chronic Pain Questionnaire. Chronic pain and LTOT were assessed at an index visit. Suboptimal retention, defined as at least one "no-show" to primary care, and virologic failure were measured over the subsequent year. Multivariable logistic regression models were built for each outcome adjusting for site.

Results: Among 2334 participants, 25% had chronic pain, 27% had suboptimal retention, 12% had virologic failure, and 19% were prescribed LTOT. Among individuals not on LTOT, chronic pain was associated with increased odds of suboptimal retention [adjusted odds ratio (aOR) 1.46, 95% confidence interval (CI): 1.10 to 1.93, $P = 0.009$] and virologic failure (aOR 1.97, 95% CI: 1.39 to 2.80, $P < 0.001$). Among individuals with chronic pain, there was no association between LTOT and retention, but LTOT was associated with lower rates of virologic failure (aOR 0.56, 95% CI: 0.33 to 0.96, $P = 0.03$).

Conclusions: Chronic pain in participants not on LTOT was associated with virologic failure. This reinforces the need to identify effective chronic pain treatments for persons living with HIV and investigate their impact on HIV outcomes. The apparent protective association between LTOT and virologic failure in those with pain merits further exploration.

Key Words: chronic pain, HIV, opioids, virologic failure, retention in care

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INTRODUCTION

Chronic pain is a common comorbidity in people living with HIV (PLWH). The sources of chronic pain in PLWH are typically either neuropathic, musculoskeletal, or both, and occur in 30%–85% of individuals.[1–3] This wide prevalence range is

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likely due to variations in the populations studied and the methods of pain assessment.[4] Potential reasons for disproportionately high rates of chronic pain in PLWH include: (1) HIV itself causes peripheral neuropathy,[5] (2) exposure to certain older HIV drugs (eg, didanosine) can cause peripheral neuropathy,[6] (3) shared risk factors for chronic pain and HIV, including mental illness and substance use,[4] and (4) biological mechanisms such as chronic inflammation that may contribute to nonneuropathic chronic pain.[7]

The few studies of chronic pain in PLWH suggest that chronic pain is strongly associated with functional impairment[8] and may be associated with suboptimal adherence to antiretroviral therapy (ART),[9] but have not shown a relationship with virologic failure. Recent evidence also suggests a complex relationship between chronic pain and another important HIV care continuum outcome, retention in HIV primary care. We have shown that among PLWH with chronic pain, current illicit substance use is associated with missing fewer scheduled HIV primary care visits ("no-shows"), a measure of retention in care.[1] We hypothesized that this could be due to substance use driving clinic visit attendance to request or obtain prescriptions for opioids, but were unable to examine the role of opioids in that study. Notably, studies in the United States suggest that long-term opioid therapy (LTOT) is prescribed to as many as 17% of PLWH.[10–12]

Therefore, our objective was to investigate the impact of chronic pain on the key HIV care continuum outcomes of retention in HIV primary care and virologic failure. We also sought to understand the interplay between chronic pain and LTOT with respect to these outcomes.

METHODS

We undertook a prospective cohort study between July 2015 and July 2016. We embedded our study in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a national clinic-based cohort of PLWH.[13] This study was conducted at 5 CNICS sites: Fenway Health in Boston, the University of Alabama at Birmingham (UAB), University of California, San Diego (UCSD), University of North Carolina (UNC), and University of Washington (UW). These clinics provide HIV primary care services, and the majority of patients at each clinic are enrolled in the cohort. CNICS collects demographic and clinical data. CNICS participants also complete a clinical assessment of patient-reported measures and outcomes (PROs) using touchscreen tablets every 4–6 months.[14]

Inclusion criteria were initial participation in CNICS at least 1 year before the index visit, regardless of visit attendance during that time, and aged 18 years and older. The "index visit" was defined as the date of the first PRO assessment during the study period. Only PROs from the index visit were included in this study. The study period was defined as the 1-year period after the index visit.

Independent Variables

Based on our qualitative[15] and quantitative[16] investigations, we used the 2-question Brief Chronic Pain Questionnaire (BCPQ) that asks about both pain severity (none to severe) and pain duration.[15,16] Individuals with ≥moderate pain for ≥3 months were considered to have chronic pain and automatically administered the following question as a multiple choice list: "Check everywhere you have had pain for at least 3 months: numbness or tingling in hands and/or feet; headache; abdominal pain; low back pain; hip pain; shoulder pain; knee pain; pain everywhere in your body." Questions in English were translated to Spanish using a professional translation service and back-translated into English to confirm accuracy.

The LTOT variable was developed from medical record data, and defined as opioid prescriptions covering at least 90 consecutive days beginning on the index date.[10]

We hypothesized that LTOT may modify the effect of chronic pain on outcomes. Therefore, as described in the analysis section below, Pain/LTOT groups were entered into the model as independent variables. Because the full interaction term would necessarily include individuals without chronic pain who are prescribed LTOT, we excluded this group with uncertain clinical significance (n = 193 in our cohort). Thus, our independent variable had 3 levels: those with chronic pain on LTOT, those with chronic pain not on LTOT, and those without pain and not on LTOT. We present the 3 pairwise comparisons of this variable.

Outcome Variables

Suboptimal retention in HIV primary care was defined as one no-show to a scheduled visit[17] without another completed visit within the ensuing 31 days (month). We chose this definition to account for participants who may have missed a visit due to pain or logistical impediments but rescheduled within a short time. Virologic failure was defined as plasma HIV RNA >1000 copies per milliliter at any time during the study period, without a repeated test within 30 days that found ≤1000 copies per milliliter.[18] We chose this cut-off, which is higher than those commonly included in clinical guidelines (50 or 200 copies/mL), to maximize the specificity of identifying virologic failure among individuals with "no-shows" who may not return for a confirmatory viral load. Viral loads at the visit closest to the index date were removed to insure that the pain assessment preceded the viral outcome.

Covariates

We included the following covariates potentially related to both chronic pain and outcomes: age, race, sex, depressive symptoms (Patient Health Questionnaire-9 ≥10) and anxiety symptoms (Patient Health Questionnaire anxiety module–anxiety symptoms or panic),[19] self-report of current substance use other than marijuana on the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), and self-report of high-risk alcohol use on the Alcohol Use Disorders Identification Test (AUDIT-C) defined as ≥4 if male and ≥3 if female.[20–22] We did not include marijuana use in our a priori definition of substance use because there is no consistent literature linking it to

TABLE 1. Demographics Across all Sites*

Site†	Fenway Health	UAB	UCSD	UNC	UW	Total	*P*
No. of participants	88	1206	711	39	290	2334	
Age ≥50	35 (39.8%)	501 (41.5%)	340 (47.8%)	22 (56.4%)	124 (42.8%)	1022 (43.8%)	0.034
Female	4 (4.6%)	274 (22.7%)	62 (8.7%)	8 (20.5%)	29 (10%)	377 (16.2%)	<0.0001
Race							<0.0001
Black	11 (12.5%)	723 (60%)	81 (11.4%)	20 (51.3%)	51 (17.6%)	886 (38.0%)	
White	68 (77.3%)	478 (39.6%)	371 (52.2%)	19 (48.7%)	191 (65.9%)	1127 (48.3%)	
Other	9 (10.2%)	5 (0.4%)	259 (36.4%)	0 (0%)	48 (16.6%)	321 (13.8%)	
Hispanic ethnicity	6 (6.8%)	0 (0%)	214 (30.1%)	0 (0%)	28 (9.7%)	248 (10.6%)	<0.0001
$CD4^+$ T-cell count (mean, SD)	640 (473, 802)	614 (401, 830)	557 (374, 745)	656 (445, 775)	572 (373, 842)	590 (390, 803)	0.0027
Anxiety symptoms	23 (26.1%)	254 (21.1%)	167 (23.5%)	12 (30.8%)	79 (27.2%)	535 (22.9%)	0.1149
Depressive symptoms	14 (15.9%)	191 (15.8%)	152 (21.4%)	7 (18%)	62 (21.4%)	426 (18.3%)	0.0206
Substance use within past 3 mo	14 (15.9%)	73 (6.1%)	107 (15.1%)	2 (5.1%)	44 (15.2%)	240 (10.3%)	<0.0001
High-risk alcohol use	19 (22.4%)	135 (11.4%)	123 (17.6%)	5 (15.2%)	63 (22.2%)	345 (12.8%)	<0.0001
Chronic pain	19 (21.6%)	299 (24.8%)	174 (24.5%)	11 (28.2%)	74 (25.5%)	577 (24.7%)	0.9325
Virologic failure	5 (5.7%)	146 (12.1%)	90 (12.7%)	6 (15.4%)	25 (8.6%)	272 (11.7%)	0.1305
Suboptimal retention	28 (31.8%)	265 (22%)	257 (36.2%)	0 (0%)	84 (29.0%)	634 (27.2%)	<0.0001
Long-term opioid therapy	8 (9.1%)	165 (13.7%)	174 (24.5%)	0 (0%)	9 (3.1%)	356 (15.3%)	<0.0001

*Outcome variables values presented refer to their values during the 1-year study period.
†UAB = University of Alabama at Birmingham.
UCSD, University of California, San Diego; UNC, University of North Carolina; UW, University of Washington.

HIV outcomes. All covariates were measured on the index date and were retained in the final model.

Statistical Analyses

Dichotomous and continuous variables were compared across sites using χ^2 and Kruskal–Wallis tests. Multivariable logistic regression models were built for each outcome adjusting for CNICS site.

Two logistic regression models were performed for each outcome: an unadjusted model with only Pain/LTOT group as the independent variable and an adjusted model with all covariates included.

Sensitivity analysis was performed for several changes to our assumptions. Opium and codeine were removed from LTOT because they are used for other indications (eg, codeine for cough), and tramadol was removed because its number of refills that could be provided has been different than other opioids (eg, morphine, oxycodone) due to US federal regulations. In addition, we are unable to determine whether the opioids buprenorphine and methadone were prescribed for chronic pain or opioid use disorder because this is not documented. Therefore, we conducted a sensitivity analysis in which these 2 opioids were excluded. Finally, viremia at the index visit may be associated with viremia at follow-up. Therefore, for the viral load outcome, we conducted a sensitivity analysis in which we excluded participants who were viremic at the index visit.

RESULTS

We enrolled 2334 participants. The largest contributing sites were UAB and UCSD. The CNICS clinical assessment was administered in Spanish to 4% of participants, who were predominantly from UCSD.

Table 1 shows demographic and clinical characteristics across sites. Nearly half were aged 50 years and older. Most were male, white, had high $CD4^+$ T-cell counts, and were virologically suppressed. Of the 577 participants with chronic pain, the most common pain locations were lower back (n = 411), numbness/tingling of hands and/or feet (n = 368), and knee (n = 278); 498 participants reported pain in more than one location. Symptoms of depression and anxiety were common. There were 758 participants with at least one no-show to a primary care visit during the study period; 124 rescheduled, leaving 634 meeting the suboptimal retention outcome criteria.

Table 2 shows bivariate analyses, as well as multivariable analyses of the pain and opioid pairwise comparisons. In the adjusted models, black race, current alcohol use, and illicit drug use were associated with increased risk of suboptimal retention and virologic failure, whereas age greater than or equal to 50 years was protective for both outcomes. Depression [odds ratio (OR): 1.37; confidence interval (CI) = (1.04, 1.82)] and anxiety symptoms [OR: 1.46; CI = (1.13, 1.9)] were associated with increased odds of suboptimal retention. Among individuals not on LTOT, chronic pain was associated with increased odds of suboptimal retention [OR: 1.75; CI = (1.36, 2.25)] and virologic failure [OR: 1.97; CI = (1.39, 2.8)]. Among individuals with chronic pain, LTOT was not associated with suboptimal retention [OR: 0.88; CI = (0.61, 1.27)], but LTOT was associated with lower rates of virologic failure [OR: 0.56; CI = (0.33, 0.66)]. Thus, a PLWH with chronic pain has 97% higher odds of having virologic failure without LTOT than a person without chronic pain without LTOT and has 77% (1 over 0.56) higher odds compared

TABLE 2. Relationship Between Chronic Pain, Long-Term Opioid Therapy (LTOT), and HIV Treatment Outcomes (Virologic Failure and Suboptimal Retention) (n = 2195*)

	Unadjusted OR (CI)	*P*	Adjusted OR (CI)	*P*
Suboptimal retention				
Pain and LTOT vs no Pain and no LTOT	1.55 (1.14 to 2.1)	**0.005**	1.36 (0.97 to 1.92)	0.07
Chronic pain, among patients not on LTOT	1.75 (1.36 to 2.25)	**<0.001**	1.46 (1.1 to 1.93)	**0.009**
LTOT, among patients with chronic pain	0.88 (0.61 to 1.27)	0.51	0.94 (0.64 to 1.38)	0.73
Age ≥50			0.54 (0.44 to 0.67)	**<0.001**
Female			1.1 (0.83 to 1.47)	0.50
Race				
Black			1.67 (1.29 to 2.15)	**<0.001**
Other			0.98 (0.71 to 1.34)	
White			1	
Anxiety symptoms			1.46 (1.13 to 1.9)	**0.004**
Depressive symptoms			1.37 (1.04 to 1.82)	**0.027**
Substance use within past 3 mo			2.55 (1.89 to 3.45)	**<0.001**
High-risk alcohol use			1.2 (0.92 to 1.58)	0.18
Virologic failure				
Pain and LTOT vs no Pain and no LTOT	0.98 (0.62 to 1.55)	0.94	1.11 (0.68 to 1.81)	0.68
Chronic pain, among patients not on LTOT	1.89 (1.34 to 2.59)	**<0.001**	1.97 (1.39 to 2.8)	**<0.001**
LTOT, among patients with chronic pain	0.52 (0.31 to 0.87)	**0.01**	0.56 (0.33 to 0.96)	**0.03**
Age ≥50			0.49 (0.36 to 0.66)	**<0.001**
Female			1.13 (0.79 to 1.62)	0.50
Race				**0.002**
Black			1.79 (1.29 to 2.49)	
Other			0.92 (0.57 to 1.47)	
White			1	
Anxiety symptoms			0.95 (0.66 to 1.37)	0.79
Depressive symptoms			0.92 (0.62 to 1.36)	0.67
Substance use within past 3 mo			2.28 (1.56 to 3.35)	**<0.001**
High-risk alcohol use			0.92 (0.63 to 1.35)	0.68

*Statistically significant *P*-values are bolded.

with someone with chronic pain on LTOT. In the sensitivity analysis excluding opium and codeine, and the analysis excluding participants who were viremic at baseline, there were no clinically or statistically significant changes in the relationships between Pain/LTOT group and outcomes. In the sensitivity analysis excluding buprenorphine and methadone prescriptions in the adjusted model, the *P*-value changed from the original 0.03 to 0.09. However, the point estimates were very similar (OR = 0.56 vs OR = 0.63). We believe that this difference is not sufficient to change our conclusions.

DISCUSSION

We found several associations between chronic pain, LTOT, and key HIV care continuum measures. Specifically, chronic pain in participants not on LTOT was associated with virologic failure and suboptimal retention. Although LTOT among participants with chronic pain was not associated with retention, we also found a previously undescribed protective association between LTOT and virologic failure.

We believe chronic pain is akin to similar comorbidities that are also associated with virologic failure. For example, depression may lead to virologic failure due to both reduced ART adherence and also biological factors such as immune suppression.[23] In addition, our finding is consistent with one previous study that found an association between physical symptoms and virologic failure.[24] If future studies confirm that chronic pain directly contributes to virologic failure, this would reinforce the need to develop chronic pain treatments tailored to PLWH, and if effective, investigate whether they improve HIV-related outcomes. We also found that chronic pain was associated with suboptimal retention. Our analyses controlled for symptoms of depression/anxiety, current alcohol, and current illicit drug use, suggesting that chronic pain itself may have effects on daily life function that are independent of these related comorbidities. Therefore, additional work is needed to further understand these complex relationships.

We found that in those with chronic pain, LTOT was not associated with suboptimal retention but was associated with decreased odds of virologic failure. This runs counter to the hypothesis that we and others have described in the literature: that HIV primary care providers expect that if they prescribe opioids for chronic pain, it will encourage patients to return for refills.[25] If this were an effective strategy, we would expect that LTOT would have been associated with better retention when compared to patients with chronic pain not on LTOT. Furthermore, it invites concerns about unintended opioid-related harms such as misuse, addiction, and overdose. However, it is possible that unmeasured confounders could have obscured a protective association.

We also found an unexpected protective association between being on LTOT and virologic failure among patients with chronic pain. We speculate that several aspects of the patient's lived experience and doctor–patient relationship account for this effect. For example,

it is possible that adherence to LTOT promotes adherence to other medications, including ART, leading to virologic suppression. It is also possible that LTOT is offered or withheld in response to providers' assessment of patient reliability, and that LTOT was a proxy for this personal characteristic. Patients whose pain improves on opioids, or who perceive that their pain is being adequately addressed, may also be more adherent and have lower rates of virologic failure. Also, we are anecdotally aware of HIV providers who tell patients that they will continue to prescribe LTOT as long as the viral load remains suppressed, serving as further motivation for adherence. Finally, the immunologic effects of opioids have been a topic of investigation among PLWH; however, studies to date have yielded few results that guide interpretation of this finding.[26,27] We are cautious in interpreting these findings, given the known risks associated with LTOT in individuals with chronic pain and the lack of evidence supporting the hypothetical explanations for this relationship that we present here.

Our study has limitations. We examined chronic pain and LTOT at one point only. Therefore, we can not draw conclusions about causality or the direction of relationships between chronic pain and virologic failure and retention. Also, this study was conducted in a cohort in which most patients were retained in care and virologically suppressed. Therefore, the findings may not generalize to those with more intermittent care or who are lost entirely to care. Selection bias is also an important consideration: we could only detect no-shows among individuals who had presented for at least some care, and data on individuals completely lost to follow-up before entering this study were not available. Yet, in individuals who have been completely lost to care, it is unlikely that the association between pain and no-shows is reversed such that our findings would be diminished. Regarding the association between pain and viremia, individuals who were completely lost to follow-up are likely to be viremic regardless of whether they have chronic pain.[28] Therefore, it is implausible that there would be an association between chronic pain and viremia in the lost-to-follow-up subset.

Busy clinics may have prevented patients from rescheduling primary care appointments within a month, misclassifying some patients as suboptimally retained in care. In addition, it is unclear why 193 people not meeting chronic pain criteria received LTOT. Potential explanations include wholly effective treatment with opioids resulting in control of chronic pain, but other possibilities include misclassification of patients for reasons that are not clear. Fortunately, this group represents a small proportion of the overall cohort.

Our study underscores the importance of chronic pain as a high-impact comorbidity among PLWH. Next steps include longitudinal studies with repeated measures of pain and opioid prescription that investigate directionality and causality. If studies confirm that chronic pain contributes to virologic failure, future work should include identifying effective chronic pain treatments for PLWH and investigating whether they improve HIV treatment outcomes. In addition, studies that assess potential unmeasured confounders of the association between LTOT and retention are needed.

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