AIDS Behav (2018) 22:1323–1328
https://doi.org/10.1007/s10461-017-1842-2

BRIEF REPORT

Prescription Opioid Use is Associated with Virologic Failure in People Living with HIV

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Published online: 7 July 2017

Abstract Prescription opioid misuse is a rising epidemic in the U.S., and people living with HIV are at increased risk. We assessed the association between prescription opioid use and virologic failure in HIV+ patients in the South Texas HIV Cohort. We found prescription opioid use was significantly associated with virologic failure, after adjustment for age, race, gender, insurance status, years living with HIV, reported HIV risk factor, chronic hepatitis C virus infection, current substance abuse, and care engagement. These findings suggest that opioid analgesic use may have negative consequences beyond misuse in people living with HIV.

Keywords Prescription opioid · HIV · Virologic outcome · Narcotic

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Introduction

While seven percent of adults aged 20 or over in the general population report prescription opioid use, in cohorts of people living with HIV, use ranges from 25 to 57% along with relatively higher doses than those prescribed for patients without HIV infection [1–4]. Despite heavy use, little is known about the consequences of prescription opioid use for people living with HIV. Chronic HIV infection predisposes individuals to opportunistic infections, chronic kidney disease, and other illnesses, and both HIV and the antiretrovirals used for treatment can lead to neuropathy and chronic pain [5].

A high daily Morphine Equivalent Dose of prescribed opioid analgesics (≥100 mg) has been demonstrated to increase the risk of death from drug overdose in diverse populations [6]. Prescription opioid misuse, which has been defined as the use of the prescription opioid in a manner that deviates from the provider's instructions, has been associated with current psychiatric disorders, a past history of substance abuse disorder or physical dependence on opioids, and poor adherence to ART in people living with HIV [7]. Prescription narcotics have drug–drug interactions with many antiretroviral medications that can lead to further misuse and treatment failures [8]. Thus, people living with HIV may have multiple comorbidities, such as neuropathy, concurrent infections, or chronic renal disease, that can result in an increased burden of chronic pain and increased use of prescription opioids. They also may have other conditions, such as mental health disorders, that increase potential negative health consequences of opioid use [9]. The combination of a predisposition for both chronic pain and negative repercussions from opioid use lead to challenges for addressing opioid misuse in people living with HIV.

Primary care providers (PCP) and HIV care providers cite inadequate training in prescription opioid management and little access to pain management experts [9, 10]. Although studies have described adverse consequences of prescription opioid use, to our knowledge, the association between prescription opioid use in persons with HIV infection and HIV treatment outcomes, such as virologic failure, remains unexplored.

Because of the potential negative consequences of opioids for care engagement and adherence, we hypothesized that prescription opioid use would be associated with virologic failure. To test our hypothesis, we used longitudinal, observational data from the South Texas HIV Cohort, a majority minority cohort of over 2000 people living with HIV receiving care in the largest public hospital system in South/Central Texas, to examine the association between prescription opioids and virologic failure, as determined by HIV-1 plasma RNA measurement.

Methods

A retrospective analysis was conducted using existing medical record data extracted from Allscripts Sunrise Clinical Manager, of the University Health System (UHS), the third largest public health system in Texas and the largest HIV treatment center in South Texas. UHS is located in San Antonio, Texas, and affiliated with the University of Texas Health Science Center San Antonio (UTHSCSA). The South Texas HIV Cohort (STHC) includes all patients living with HIV (HIV+) receiving care at UHS. From a total of 1907 patients who visited the Family Focused AIDS Clinical Treatment & Services (FFACTS) clinic during 2013, 1696 HIV+ adults met inclusion criteria of: two or more HIV clinic visits separated by $\geq$3 months in 2013 during calendar year 2013 and at least one HIV-1 plasma RNA measurement.

The outcome, virologic failure, was defined according to the U.S. Department of Health and Human Services guidelines as any HIV-1 plasma RNA measurement $\geq$200 copies/mL in 2013 [11]. The primary explanatory variable was any opioid use, which was a dichotomous variable defined as 'yes' if an individual has an opioid prescription written, as documented in the electronic medication record, between October 1, 2012 and December 31, 2013. Opioid prescriptions included were hydrocodone/ibuprofen, hydromorphone, acetaminophen/hydrocodone, acetaminophen/codeine, acetaminophen/oxycodone, aspirin/oxycodone, codeine, codeine/guaifenesin, codeine/promethazine, fentanyl, methadone, morphine, naloxone/pentazocine and their brand name equivalents.

Age was categorized as 18–24 years, 25–50 years, or >50 years. Gender was categorized as male, female, or transgender. Race and ethnicity were combined into a single variable and categorized as non-Hispanic white, Hispanic, non-Hispanic black, or other. As only 28 patients reported race/ethnicity other than white, black, or Hispanic (1.7% of the cohort), they were excluded from the multiple logistic regression analysis to avoid sparse-data bias. Insurance status categories were insured or uninsured. Uninsured patients received care through medical assistance plans offered by the county government or the Ryan White HIV/AIDS Program.

Active drug use was defined as 'yes' for patient-reported drug use in response to routine screening questions at clinical visits during 2013. Patients were considered to have chronic hepatitis C virus (HCV) infection with either detectable Hepatitis C virus plasma RNA level or two ICD-9 diagnosis codes for chronic Hepatitis C. Patients were considered on antiretroviral therapy (ART) when antiretroviral medications were prescribed between October 2012 and December 2013. Patient-reported HIV transmission risk factor was divided into three groups [heterosexual sex, injection drug use (IDU), and men who have sex with men (MSM)]. Those not falling within these three categories (n = 13) were excluded from analysis when this variable was used. Engagement in care was defined and measured as two provider visits in which weights were measured and BMI calculated separated by at least 90 days in the time frame of 01/01/2013–12/31/13. Median CD4 cell count was calculated for each patient and then categorized as >500, 200–500, or <200 cells/μL.

Analysis

Patients' characteristics were summarized using descriptive statistics, including median and interquartile range (IQR) for continuous variables. Differences in characteristics of patients with and without opioid use were assessed using Fisher's exact test for categorical variables and Mann–Whitney U test for continuous variables, and unadjusted odds ratios are presented for associations between demographic/clinical characteristics and prescription opioid use. To determine whether the observed association between opioid use and virologic failure was robust to adjustment for other factors known to predict failure, a logistic regression model was constructed, adjusting for variables known to be associated with virologic failure in our cohort or other studies: age, race/ethnicity, gender, insurance status, years living with HIV, reported HIV transmission risk factor, HCV infection, substance use, antiretroviral medications, CD4 cell count, and care engagement. A sensitivity analysis also tested a more parsimonious model of the association between opioid use and virologic failure, adjusting only for age, gender, and race/ethnicity. All statistical analysis used SAS Version 9.3 (SAS Institute, Cary,

North Carolina), and were two-sided with a significance cutoff of $p \leq 0.05$.

Funding for this study was provided through the Clinical and Translational Science Award (CTSA), the American Heart Association, and the National Institute of Health (NIH) National Institute for Allergy and Infectious Diseases Career Development Award. The study was approved by the Institutional Review Board of the University of Texas Health Science Center San Antonio. Individual patient consent was waived for this study, as this is a retrospective analysis of existing electronic medical records data.

Results

Cohort Description

Of 1907 patients seen in the clinic in 2013, 1696 met inclusion criteria. The median age for the cohort was 44.8 years (IQR: 34.5, 51.5), 76.3% were men, 61.6% Hispanic, and 17.7% African American. The most common HIV transmission risk factor was men who have sex with men (MSM) (56.4%); and 32.9% of patients had ≥1 HIV-1 plasma RNA level of ≥200 copies/mL in 2013. Hepatitis C (HCV) coinfection was diagnosed in 17.7, 82.6% were receiving ART, and 22.3% had a median CD4 <200 cells/μL. No current drug use was reported by 57.6% of the cohort, but 34.4% of patients were missing data on substance use in 2013. Opioid analgesics were prescribed for 434 patients, or 25.6% of the cohort. Of 1033 total narcotics prescriptions, 87% are acetaminophen-hydrocodone, 1.2% (n = 12) are methadone, and 0.48% (n = 5) are oxycodone.

Predictors of Prescription Opioid Use

In unadjusted, bivariate analysis, prescription opioid use was more likely for older patients (odds ratio [OR] = 1.48; 95% CI 1.16, 1.87 for age >50 vs. 18–50 years) and female (OR = 1.50; 95% CI 1.16, 1.93). Opioid use was also more likely for persons with an HIV transmission risk factor of unprotected heterosexual sex (OR = 1.5; 95% CI 1.2, 1.9 vs. men who have sex with men) or intravenous drug use (OR = 1.7; 95% CI 1.2, 2.5 vs. men who have sex with men), and with HCV coinfection (OR = 1.85; 95% CI 1.42, 2.41). Those prescribed opioids were also more likely to be uninsured, but engaged in care. Having advanced HIV disease with a current CD4+ cell count <200 cells/μL was associated with receipt of prescription opioids (OR = 1.4, 95% CI 1.10, 1.82) versus CD4+ cell count ≥200, and duration of HIV diagnosis (OR = 1.03, 95% CI 1.016, 1.046). The proportion of persons prescribed opioids who also reported active drug use was 8.5% (n = 37), and substance use data were not recorded for an additional 37% of opioid prescriptions (See Table 1, section A for cohort characteristics and breakdown by prescription opioid use; ORs are not presented in table).

Receipt of Opioid Prescription is a Predictor of Virologic Failure

Individuals prescribed opioids had an increased likelihood of virologic failure compared with those who were not prescribed opioids (OR = 1.34; 95% CI 1.01, 1.78), after adjustment for age, gender, race/ethnicity, insurance status, HCV coinfection, drug use, HIV transmission risk factor, duration of HIV infection, care engagement, and CD4+ cell count (see Table 1, Section B). Virologic failure was also associated with age <25 years, female or trans gender, being uninsured, shorter duration of HIV diagnosis, not being engaged in care, and having a CD4 cell count <500 cells/μL. A sensitivity analysis testing for the association between receipt of an opioid prescription and virologic failure, adjusting for only age, race/ethnicity, and gender showed a similar, statistically significant association between opioid prescription and virologic failure.

Discussion

In this majority Hispanic cohort of people living with HIV, over one quarter of patients were prescribed opioid analgesics in 2013. Individuals prescribed opioids were more likely to be: over 50 years of age, female, and uninsured. They were also more likely to report IDU or heterosexual sex as their HIV transmission risk factor, have a longer duration of HIV infection, have a lower CD4+ cell count, and be engaged in care. Our hypothesis that those prescribed opioids would have a higher risk of virologic failure proved correct. Opioid prescription was associated with 34% greater odds having an HIV-1 plasma RNA level >200 copies/mL, after adjustment for key demographic and clinical characteristics as stated above. The association of opioid use with virologic failure was less strong than that of gender, insurance status, engagement in HIV care, and CD4+ T cell count in this cohort, but these are known predictors of virologic failure across many cohorts and settings.

To our knowledge, this is the first study to document an association between prescription opioid use and virologic failure. Prior investigations have focused on opioid misuse, and shown associations between opioid misuse and adverse outcomes for people living with HIV. Prescription opioid misuse, including use of opioids for reasons other than pain relief, was more common in people living with HIV with prior history of substance use in several studies [2, 7, 10].

Table 1 Patients characteristics by (A) presence of an opioid prescription in the electronic medical record and (B) a multiple logistic regression analysis of the association between prescription opioids and virologic failure, adjusted for all other characteristics in the table. Statistically significant differences ($p < 0.05$) are presented in bold for both analyses

Characteristic n (%) or median	All subjects	(A) Opioid prescription		(B) Adjusted multiple logistic reg. of assoc. between rx. opioid and virologic failure	
		Yes	No		
	N = 1696	N = 434	N = 1262	Adjusted OR (95% CI)	P-value
Age category (years)					
18–24	104 (6.1)	12 (2.8)	92 (7.3)	**2.00 (1.21, 3.30)**	**0.007**
25–50	1134 (66.9)	**279 (64.3)**	**855 (67.7)**	Referent	
>50	458 (27.0)	143 (32.9)	315 (25)	0.74 (0.54, 1.01)	0.06
Gender					
Male	1294 (76.3)	**307 (70.7)**	**987 (78.2)**	Referent	
Female	371 (21.9)	118 (27.2)	253 (20)	**1.71 (1.17, 2.49)**	**0.006**
Transgender	31 (1.8)	9 (2.1)	22 (1.7)	**3.05 (1.27, 7.33)**	**0.01**
Race/ethnicity					
White	324 (19.1)	90 (20.7)	234 (18.5)	Referent	
Hispanic	1044 (61.1)	**255 (58.8)**	**789 (63.5)**	0.939 (0.669, 1.32)	0.72
Black	300 (17.7)	**81 (18.7)**	**219 (17.4)**	1.04 (0.681, 1.58)	0.87
Other	28 (1.7)	8 (1.8)	20 (1.6)		
Insurance category					
Insured	902 (53)	274 (63.1)	628 (49.4)	Referent	
Uninsured	794 (47.0)	**160 (36.9)**	**634 (50.6)**	**1.69 (1.28, 2.22)**	**<0.001**
HCV infection[b]					
Yes	300 (17.7)	**108 (24.9)**	**192 (15.2)**	1.14 (0.797, 1.64)	0.47
No	1396 (82.3)	326 (75.1)	1070 (84.8)	Referent	
Active drug use					
Yes	135 (8.0)	37 (8.5)	98 (7.8)	1.28 (0.819, 2.00)	0.28
No	977 (57.6)	**236 (54.4)**	**741 (58.7)**	Referent	
Missing	584 (34.4)	161 (37.1)	423 (33.5)	0.997 (0.766, 1.30)	0.98
HIV risk factor[c]					
Heterosexual	568 (33.7)	169 (39.5)	399 (31.8)	1.03 (0.724, 1.47)	0.86
MSM	956 (56.8)	208 (48.6)	748 (59.6)	Referent	
IDU	159 (9.4)	51 (11.9)	108 (8.60)	1.12 (0.689, 1.82)	0.65
Years living with HIV					
Median [Q1, Q3]	8 [4, 15]	**9 [5, 17]**	**8 [4, 14]**	**0.976 (0.957, 0.995)**	**0.01**
Engaged in care					
Yes	1265 (74.6)	**343 (79.0)**	**922 (73.1)**	Referent	
No	431 (25.4)	91 (21.0)	340 (26.9)	**1.98 (1.51, 2.59)**	**<0.001**
CD4 count category[d]					
<200	378 (22.3)	**117 (27.0)**	**261 (20.7)**	**12.7 (8.62, 18.6)**	**<0.001**
200–500	576 (34.0)	133 (30.6)	443 (35.1)	**2.41 (1.84, 3.15)**	**<0.001**
>500	742 (43.8)	184 (42.4)	558 (44.2)	Referent	
Receives prescription opioids					
Yes				**1.34 (1.01, 1.78)**	**0.04**
No				Referent	

Table 1 continued

Characteristic n (%) or median	All subjects	(A) Opioid prescription		(B) Adjusted multiple logistic reg. of assoc. between rx. opioid and virologic failure	
		Yes	No		
	N = 1696	N = 434	N = 1262	Adjusted OR (95% CI)	P-value
Virologically suppressed[a]					
Yes	1026 (67.1)	**250 (57.6)**	**776 (61.5)**		
No	504 (32.9)	149 (34.3)	355 (28.1)		

Bold characters represent statistically significant differences

MSM = men who have sex with men, IDU = intravenous drug user

[a] Any HIV-1 plasma RNA measurement ≥200 copies/mL in 2013, based off of denominator of N = 1530

[b] HCV: detectable Hepatitis C antibody or 2 HCV ICD9 codes, 2007–2013

[c] Percentages are based off of denominator N = 1683

[d] CD4 count units of 'cells/μL'

Data from a longitudinal cohort of people with advanced HIV disease (CD4+ cell count <50 cells/μL) or chronic, therapy-refractory illnesses such as end stage liver disease demonstrated a correlation between prescription opioid misuse and current psychiatric disorders, past substance use, and poor adherence to ART [7]. Opioid analgesic misuse was associated with decreased adherence to ART in a cohort of adults living with HIV in San Francisco from the Research on Access to Care in the Homeless study (REACH) [1].

Our data may suggest that the association between opioid use and decreased adherence, documented in prior investigations, may lead to the increased risk of virologic failure seen in our cohort. There are also mechanisms by which opioids could be associated with virologic failure, including overlapping medication toxicities or interactions, and the known impact of opioids on gut homeostasis and other inflammatory pathways [12].

These data also raise concerns regarding opioid prescribing practices in this cohort. Over 8% of patients with an opioid prescription were documented to be currently using illicit substances, and substance use data were not recorded for an additional 37% of those receiving prescription opioids. These findings represent deviations from current guidelines regarding appropriate monitoring of prescription opioid use, and prior studies demonstrate that this is not uncommon for HIV providers. A survey of HIV providers across the United States demonstrated that lack of knowledge about pain management and limited access to pain management experts. Providers expressed concerns about potential substance use or addiction, which limited their ability to follow guidelines for opioid prescribing and monitoring [10, 11]. Medical providers' impressions of misuse were often discordant with patient self-reports of opioid analgesic misuse [9]. Finally, the origins of chronic pain in people living with HIV are heterogeneous, and conditions such as HIV-associated neuropathy may not be most effectively addressed with opioids [9]. Our findings, which may be relevant to other HIV treatment centers, highlight the need for improved processes and provider education to enhance compliance with opioid use guidelines and better support people living with HIV who receive prescription opioids.

This investigation has several limitations. It is a cross-sectional, single site study, so it may be limited in its applicability to other settings and not reflective of associations over time. Data on opioid total daily dose, fill rate, or morphine equivalent use over time is unavailable for this cohort because of limitations of the electronic health record (EHR) data. We also lack data on indications for opioid therapy, which could be relevant as the impact of opioid use for substitution therapy, chronic pain, or acute pain, may vary. Further investigation would be useful to determine whether or not the quantity, or chronicity, or indication for opioid use is associated with virologic failure [6]. The analysis is limited to 2013, and opioid prescribing may have shifted significantly in the past three years. We hope this study will serve as a baseline for future assessment of changes in prescribing patterns within the cohort. Finally, we are missing data on substance use in 2013 for 34% of the clinic population. Despite these limitations, we believe that our findings contribute to a growing body of literature suggesting potential hazards associated with the use of prescription opioids by people living with HIV.

Our data demonstrate a significant association between prescription opioid use and virologic failure, which is robust to adjustment for other factors known to predict virologic failure in people living with HIV. The overlap between those reporting active substance use and those receiving prescription opioids and the missing data on substance use screening, suggest that processes within the clinic for prescription opioid use and misuse screening should be strengthened. Providers also may benefit from further education regarding opioid use risk, safety monitoring, and the

limited utility of opioids in management of HIV-associated neuropathy. These findings suggest that patients receiving prescription opioids may be at higher risk for antiretroviral treatment failure, and are worthy of increased support and scrutiny. Further research is needed to determine if opioid use is a marker of other factors that place patients at risk for poor treatment outcomes, or if opioids themselves play a role in the processes leading to virologic failure.

Acknowledgements We gratefully acknowledge the faculty and staff at the FFACTS HIV outpatient clinic of University Health System. We also gratefully acknowledge the faculty and staff at the University of Texas Health Science Center at San Antonio. We would like to thank the Clinical and Translational Science Award program for their Pilot Funding Award CTSA 1 UL1 RR025767, and the National Institutes of Health K23 Career Development Award 7K23AI081538.

Funding The study was funded by the CTSA Pilot funding award CTSA1 UL1 RR025767 and NIH K23 Career Development Award 7K23AI081538.

Compliance with Ethical Standards

Conflict of interest The authors of this manuscript declare no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The University of Texas Health Science Center San Antonio Institutional Review Board determined that individual patient consent could be waived for this study, as this is a retrospective analysis of existing electronic medical records data."

Research Involving Human Participants and/or Animals Human subjects activities under this study was approved by the University of Texas Health Science Center San Antonio Institutional Review Board.

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