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ORIGINAL PAPER

Factors Associated with Prescription of Opioids and Co-prescription of Sedating Medications in Individuals with HIV

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Abstract Opioids are often prescribed for chronic pain, and opioid risks such as overdose and death are heightened when opioids are co-prescribed with other sedating medications. We investigated factors associated with chronic opioid prescription, alone and in combination with benzodiazepines and muscle relaxants, in a clinical cohort of individuals with HIV. We used multivariable logistic regression models to determine participant clinical and demographic characteristics that are associated with chronic prescription of opioids or chronic co-prescription of opioids with sedating medications. Among 1474 participants, chronic prescription of opioids occurred in 253 individuals (17.2 %), and chronic co-prescription occurred in 90 individuals (6.1 %). Age >50, public insurance as compared to private insurance, and symptoms of depression and anxiety were significantly associated with chronic opioid prescription and chronic co-prescription. Our findings raise concern that opioid prescription and co-prescription of sedating medications occurs disproportionately in patients for whom use is riskier.

Keywords HIV · Chronic pain · Opioid · Benzodiazepine · Muscle relaxant

Introduction

Owing to highly effective and tolerable antiretroviral therapies, HIV has been transformed into a chronic disease with a near-normal life expectancy [1]. In the past 10 years, investigators have highlighted numerous comorbidities that are more common among individuals with HIV than among uninfected individuals, including cardiovascular disease and certain non-AIDS-defining malignancies [2]. This has also led to concerns about polypharmacy, which is common in this medically complex population [3]. Polypharmacy has been associated with adverse outcomes in the general population, with emerging data among individuals with HIV [3].

One important aspect of polypharmacy has been understudied among individuals with HIV: prescribing of opioids, alone and in combination with other sedating medications. This is of particular concern because of the dramatic rise in long-term opioid prescribing for chronic non-malignant pain in the population at large. Data from the National Ambulatory Medical Care Survey suggests that among individuals seeking care primarily for pain, the number of opioids prescribed almost doubled from 2000 to 2009 [4]. Additionally, chronic pain among individuals with HIV is reported more commonly than in the general population, with prevalence

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estimates ranging from 39 to 85 % [5–10]. Long-term opioids are prescribed at least as often [11] if not more often [12] in individuals with HIV than in individuals without HIV. This is problematic as there is little evidence of opioids' long-term efficacy [13], yet evidence as to the risk of overdose and death has been well-established [14–18].

Additionally, knowledge of the risks of chronic opioid therapy in combination with other commonly prescribed sedating medications is mounting. Dunn and colleagues found that among individuals on chronic opioid therapy, individuals who were co-prescribed sedative-hypnotic medications had nearly four times the risk of overdose [15]. These findings have been corroborated by several other groups [19–23]. Concurrent use of opioids and benzodiazepines is particularly dangerous because both cause glutamate and gamma amino butyric acid (GABA)-mediated respiratory depression [24].

Given the limited utility and high risk of chronic opioid therapy, especially in combination with sedating medications, it is important to understand the factors that contribute to these patterns of prescribing. Few studies have examined this phenomenon in the general population, and it has not been systematically investigated among individuals with HIV in the modern HIV treatment and opioid prescribing era. We believe that it is critical to investigate this specifically among a contemporary cohort of individuals with HIV, as factors affecting opioid prescribing and sedative co-prescription may be different in this population. First, as chronic pain is more common in this population, opioid prescribing is likely to be more common. Given the burden of medical comorbidity in this population, however, it could be more risky. Additionally, HIV providers in the 1980s and 1990s who operated in a palliative care model where comfort is the primary goal may continue to be liberal prescribers of opioids [25]. Additionally, there is some evidence that HIV prescribers may be hesitant to taper patients on chronic opioid therapy for fear that the patients may stop coming to them for HIV care [26].

Therefore, our objective was to investigate patient demographic and clinical characteristics associated with chronic prescriptions for opioids, alone and in combination with other sedating medications, among individuals with HIV. We believe this study will be an important first step towards developing strategies to improve the safety of opioid prescribing in HIV care.

Methods

This cross-sectional study was conducted using the University of Alabama at Birmingham (UAB) 1917 Clinic Cohort. This is a cohort of HIV-infected individuals receiving care at UAB's HIV Clinic. This clinic includes approximately 3000 patients, and draws from 63 of the 67 counties in Alabama, as well as the four surrounding states (Mississippi, Tennessee, Georgia, and Florida). Primary care providers are mostly infectious diseases-trained physicians and nurse practitioners. The majority (75 % according to a recent study from our clinic) receive primary care at 1917 [27]. Additionally, this clinic is a patient-centered medical home, and includes subspecialty care (e.g., nephrology, dermatology), social services, addiction counseling, a pharmacy, and a laboratory on-site.

Cohort participants who were at least 19 years of age, and who had Patient Reported Outcome (PRO) data within the year prior to July 29, 2012, were included in the analysis. This study was approved by UAB's Institutional Review Board.

Data Collection

The 1917 Clinic Cohort routinely collects data on a variety of participant characteristics electronically at the point of care every 4–6 months. Demographic characteristics include age, gender, race, and insurance status. HIV clinical markers include CD4+ T cell count, HIV viral load, HIV transmission risk factor, and mortality. Other participant characteristics are assessed using PRO measures, which include validated assessments of depression and anxiety symptoms, and alcohol and other substance use. Prescribed medications are recorded in the electronic medical record. PRO data and prescription data are described in more detail below.

Outcome Variables: Chronic Prescription of Opioids or Other Sedating Medications

Prescription data was obtained from the 1917 Clinic's electronic medical record. While medications written outside the clinic are not systematically included, providers are trained and encouraged to manually enter outside prescriptions into the electronic medical record. A comprehensive list of medications in each class was generated using the Drug Facts and Comparisons database (see Tables, Supplemental Electronic Content 1–3). We defined an opioid as any short or long-acting opioid, including combination pills (e.g., hydrocodone-acetaminophen) and tramadol. Methadone or buprenorphine for treatment of opioid dependence were not prescribed within the clinic during the study timeframe, and would only be included if the primary care provider specifically added them to the participant's medication list. Methadone prescribed for pain is not distinguished from methadone prescribed for opioid dependence, but the clinic does not have a methadone maintenance program for opioid dependence. We defined other sedating medications as any benzodiazepine

or muscle relaxant. Chronic prescription of any of these substances was defined as prescription covering 90 or more consecutive days immediately prior to July 29, 2012. We defined chronic co-prescription as chronic prescription of an opioid plus chronic prescription of another sedating medication (benzodiazepine and/or a muscle relaxant) during the same period.

Clinical and Demographic Characteristics

The nearest PRO prior to July 29, 2012 was used in the analyses. All PRO measures were dichotomized as follows. Depressive symptoms were defined by a score of ≥10 on the PHQ-9, and anxiety symptoms were defined by anxiety/panic on the PHQ anxiety module [28]. Given the high degree of clinical overlap between depression and anxiety, we also constructed a four-level variable consisting of both depression and anxiety; depression alone; anxiety alone; and neither. Pain was defined by moderate or severe pain "today" as reported on the EuroQOL [29]. Current substance use was defined by current use of any illicit drug other than marijuana on the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) [30]. At-risk alcohol use was defined by a score of ≥5 for men or ≥4 for women on the Alcohol Use Disorders Identification Test (AUDIT-C) [31].

Analysis

To describe use of opioids and sedating medications, we first conducted descriptive analysis with continuous variables presented as means and standard deviations (SDs), and categorical variables presented as frequencies and percentages. To determine whether participant characteristics were associated with the outcomes (chronic prescription of opioids or co-prescription of sedating medications), we conducted univariate and multivariable logistic regression analyses. Associations were expressed in terms of odds ratios (ORs) and corresponding 95 % confidence intervals (CIs). In multivariable analyses, the final model included the following clinically significant variables: demographics, HIV transmission risk factor, depression-anxiety, pain, alcohol (AUDIT-C) use, and current substance use (Alcohol, Smoking, and Substance Involvement Screening Test [30]). Model performance was examined using c-statistics, max-rescaled r-square and Hosmer–Lemeshow test for model fit. Multicollinearity of the independent factors was examined with variance inflation factor (VIF) by adjusting the linear combinations by the weight matrix used in the maximum likelihood algorithm; the VIF for all the factors was <3.4, indicating no multicollinearity [32]. Analyses were conducted using SAS statistical software (Cary, NC), version 9.3.

Results

Among 1474 participants, approximately one-third were over the age of 50 with a mean of 45.2 years (SD = 10.8). Most were male, nearly half were white, more than half were publicly insured or uninsured, and the vast majority had CD4+ T-cell counts ≥200 cells/μL and an undetectable viral load (Table 1). Most (66.5 %) did not exceed the thresholds for significant symptoms of depression and/or anxiety. Common comorbid medical conditions included diabetes (149, 10.1 %), cancer (148, 10.0 %), and cardiovascular disease other than myocardial infarction or stroke (74, 5.0 %), and a history of myocardial infarction (23, 1.6 %).

Chronic prescription of opioids occurred in 253 participants (17.2 % of the total cohort). One hundred sixty-three (64.4 % of opioid recipients, 11.1 % of the total cohort) were on chronic opioids only, and 90 (35.6 % of opioid recipients, 6.1 % of the total cohort) were co-prescribed an opioid plus a benzodiazepine and/or a muscle relaxant. Hydrocodone-acetaminophen and oxycodone were the most commonly prescribed opioids (125 [49 %] and 30 [12 %] of all opioid prescriptions, respectively); clonazepam and alprazolam were the most commonly prescribed benzodiazepines (87 [54 %] and 33 [20 %] of all benzodiazepine prescriptions, respectively); and cyclobenzaprine and tizanidine were the most commonly prescribed muscle relaxants (43 [49 %] and 15 [17 %] of all muscle relaxant prescriptions, respectively) (Table 2). For a complete list of medications investigated and frequencies of prescription, see Tables in Supplemental Electronic Content 1, 2, and 3. In the year prior to July 29, 2012, the following other medications were prescribed: acetaminophen (80, 5 %), non-steroidal anti-inflammatory drugs (254, 17 %), and selective serotonin reuptake inhibitors (406, 27.5 %).

Participant factors associated with chronic opioid prescription are shown in Table 3. In multivariable analyses, age >50 (OR 1.5, 95 % CI 1.1–2.1), public insurance as compared to private insurance (AOR 2.1, 95 % CI 1.5–3.1), symptoms of depression and anxiety (AOR 1.8, 95 % CI 1.1–2.8), and moderate or severe pain (AOR 7.6, 95 % CI 5.1–11.2) were significantly associated with chronic opioid prescription; at-risk alcohol use (AOR 0.6, 95 % CI 0.3–1.0) was protective. Current substance use was not associated with chronic opioid prescription.

Participant factors associated with chronic co-prescription of opioids with other sedating medications (benzodiazepines and/or muscle relaxants) are shown in Table 4. In multivariable analyses, female gender (AOR 1.8, 95 % CI 1.1–3.2), white race (AOR 4.1, 95 % CI 2.4–7.1), public insurance as compared to private insurance (AOR 1.9,

Table 1 Socio-demographic and clinical characteristics of study participants

Characteristic	N = 1474 n (%)
Age ≥50 years	512 (34.7)
Female	312 (21.2)
Race	
White	694 (47.1)
Black	757 (51.4)
Other/unknown	23 (1.5)
Health insurance	
Public	371 (25.2)
Uninsured	517 (35.1)
Private	586 (39.7)
CD4 ≥200 cells/μL	1305 (89.9)
Viral load ≥200 copies/mL	196 (13.4)
HIV transmission risk factor	
Injection drug use	123 (34.5)
Heterosexual	594 (34.5)
Men who have sex with men	832 (57.0)
Depression[a] and/or anxiety/panic[b]	
Both	132 (9.0)
Depressive symptoms only	94 (6.4)
Anxiety/Panic only	171 (11.6)
Unknown	97 (6.5)
Neither	980 (66.5)
Substance use (excluding Marijuana)[c]	
Current	105 (7.1)
Prior	413 (28.0)
Never	869 (59.0)
Unknown	87 (5.9)
Alcohol use[d]	
At risk	175 (11.9)
Unknown	92 (6.2)
No/low	1207 (81.9)
Pain[e]	
Yes (moderate/severe)	618 (41.9)
Unknown	67 (4.6)
No	789 (53.5)

Missing data: Race (n = 11), CD4 (n = 22), Viral load (n = 12), HIV transmission (n = 15)

[a] Patient Health Questionnaire-9 instrument (PHQ-9): score ≥10

[b] Patient Health Questionnaire-5 for Anxiety (PHQ-A) instrument

[c] Alcohol, Smoking, Substance Involvement Screening Test (ASSIST)

[d] Alcohol Use Disorders Identification Test (AUDIT-C)

[e] EUROQOL health related quality of life instrument

Table 2 Chronic prescriptions of opioids, benzodiazepines, and muscle relaxants in the study-eligible HIV-infected patients attending the UAB 1917 clinic

Medication	N = 1474 n (%)
Opioid (O) only	163 (11.1)
Benzodiazepine (B) only	90 (6.1)
Muscle relaxant (M) only	31 (2.1)
O + B	45 (3.0)
O + M	29 (2.0)
O + B + M	16 (1.1)
B + M	11 (0.7)
None	1089 (73.9)

Chronic opioid prescription (any) = 163 + 45 + 29 + 16 = 253 (17.2 %)

Chronic co-prescription of opioids with benzodiazepines and/or muscle relaxants

= 45 + 29 + 16 = 90 (6.1 %)

Prescription covering ≥90 consecutive days immediately prior to July 2012

95 % CI 1.1–3.3), depression and anxiety (AOR 2.7, 95 % CI 1.4–5.0), and moderate to severe pain (AOR 9.1, 95 % CI 4.2–19.7) were significantly associated with chronic co-prescription.

During the year following July 29, 2012, 11 cohort participants died. Seven were taking chronic opioids (2.8 % of the chronic opioid group), and 4 were not (0.3 % of that group) ($p < 0.0001$, Chi square test). Similarly, 3 were chronically co-prescribed opioids and another sedating medication (3.3 % of the co-prescribed group), and 8 were not (0.6 % of that group) ($p = 0.03$, Fisher's exact test).

Discussion

This study is the first investigation of factors associated with chronic opioid prescription and co-prescription of opioids and other sedating medications among individuals with HIV in the modern HIV treatment era. We found that chronic opioid prescription and co-prescription with sedating medications were common; 17 % of participants were prescribed opioids, and of those, 36 % were co-prescribed benzodiazepines and/or muscle relaxants. Additionally, our results suggest that the patients at the most risk of adverse consequences of opioids, including those

Table 3 Univariate and multivariable analyses examining factors associated with chronic opioid prescription

Factor	Chronic opioid prescription		Univariate analysis		Multivariable analysis[a]	
	Yes N = 253 n (%)	No N = 1221 n (%)	Unadjusted OR (95 % CI)	p-value	Adjusted OR (95 % CI)	p-value
Age, years						
≥50	116 (45.8)	396 (32.4)	1.8 (1.3–2.3)	<0.001**	1.5 (1.1–2.1)	0.001**
<50*	137 (54.2)	825 (67.6)	1.0		1.0	
Gender						
Female	67 (26.5)	245 (20.1)	1.4 (1.1–2.0)	0.02**	1.2 (0.8–1.7)	0.40
Male*	186 (73.5)	976 (79.9)	1.0		1.0	
Race						
White	133 (52.8)	561 (46.3)	1.3 (1.0–1.7)	0.06	1.2 (0.9–1.7)	0.18
Non-White*	119 (47.2)	650 (53.7)	1.0		1.0	
Health insurance						
Public	113 (44.7)	258 (21.1)	3.4 (2.4–4.8)	<0.001**	2.1 (1.5–3.1)	<0.0001**
Uninsured	73 (28.8)	444 (36.4)	1.3 (0.9–1.8)	0.18	1.1 (0.7–1.7)	0.59
Private*	67 (26.5)	519 (42.5)	1.0		1.0	
CD4 (cells/μL)						
≥200	224 (89.2)	1081 (90.0)	0.9 (0.6–1.4)	0.71	–	–
<200*	27 (10.8)	120 (10.0)	1.0			
Viral load (copies/mL)						
≥200	38 (15.1)	158 (13.1)	1.2 (0.8–1.7)	0.39	–	–
<200*	214 (84.9)	1052 (86.9)	1.0			
Substance use[b]						
Current	24 (9.5)	81 (6.6)	1.5 (0.9–2.5)	0.09	1.4 (0.8–2.4)	0.22
Unknown	20 (7.9)	67 (5.5)	1.5 (0.9–2.6)	0.11	1.5 (0.6–3.7)	0.37
Prior/never*	209 (82.6)	1073 (87.9)	1.0		1.0	
Depression[c] and/or Anxiety/Panic[d]						
Both	46 (18.2)	86 (7.0)	3.8 (2.5–5.7)	<0.001**	1.8 (1.1–2.8)	0.01**
Depression only	27 (10.7)	67 (5.5)	2.9 (1.8–4.6)	<0.001**	1.5 (0.9–2.5)	0.16
Anxiety/panic only	34 (13.4)	137 (11.2)	1.8 (1.2–2.7)	0.01**	1.1 (0.7–1.7)	0.71
Unknown	25 (9.9)	72 (5.9)	2.5 (1.5–4.0)	<0.001**	1.9 (1.0–3.6)	0.04**

Table 3 continued

Factor	Chronic opioid prescription		Univariate analysis		Multivariable analysis[a]	
	Yes N = 253 n (%)	No N = 1221 n (%)	Unadjusted OR (95 % CI)	p-value	Adjusted OR (95 % CI)	p-value
Neither*	121 (47.8)	859 (70.4)	1.0		1.0	
Alcohol use[e]						
At risk	20 (7.9)	155 (12.7)	0.6 (0.4–1.0)	0.04**	0.6 (0.3–1.0)	0.03
Unknown	20 (7.9)	72 (5.9)	1.3 (0.8–2.2)	0.33	0.7 (0.3–1.6)	0.38
No/low risk*	213 (84.2)	994 (81.4)	1.0		1.0	
Pain[f]						
Yes(moderate/severe)	203 (80.2)	415 (34.0)	9.9 (6.9–14.4)	<0.001**	7.6 (5.1–11.2)	<0.0001**
Unknown	13 (5.2)	54 (4.4)	4.9 (2.5–9.8)	<0.001**	2.7 (1.0–7.2)	0.04**
No	37 (14.6)	752 (61.6)	1.0		1.0	

Univariate and multivariable analyses conducted using logistic regression method

CI confidence interval, *OR* odds ratio, *UAB* University of Alabama at Birmingham, Birmingham, AL, USA

* Reference category

** Statistically significant at 0.05 level

Prescription covering ≥ 90 consecutive days as of July 2012

[a] Multivariable model performance: Hosmer–Lemeshow test p-value = 0.72; c-statistics = 0.800; Max-rescaled r-square = 0.2647

[b] Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

[c] Patient Health Questionnaire-9 instrument (PHQ-9): score ≥ 10

[d] Patient Health Questionnaire-5 for Anxiety (PHQ-A) instrument

[e] Alcohol Use Disorders Identification Test (AUDIT-C)

[f] EUROQOL health related quality of life instrument

Table 4 Univariate and multivariable analyses examining factors associated with chronic co-prescription of opioids with other sedating medications

Factor	Co-prescription of sedating medications		Univariate analysis		Multivariable analysis[a]	
	Yes N = 90 n (%)	No N = 1384 n (%)	Unadjusted OR (95 % CI)	p-value	Adjusted OR (95 % CI)	p-value
Age, years						
≥50	43 (47.8)	469 (33.9)	1.8 (1.2–2.7)	0.01**	1.3 (0.8–2.1)	0.28
<50*	47 (52.2)	915 (66.1)	1.0		1.0	
Gender						
Female	26 (28.9)	286 (20.7)	1.6 (1.0–2.5)	0.07	1.8 (1.1–3.2)	0.03
Male*	64 (71.1)	1098 (79.3)	1.0		1.0	
Race						
White	67 (75.3)	627 (45.6)	3.6 (2.2–5.9)	<0.001**	4.1 (2.4–7.1)	<0.0001**
Non-White*	22 (24.7)	747 (54.0)	1.0		1.0	
Health insurance						
Public	47 (52.2)	324 (23.4)	3.4 (2.0–5.7)	<0.001**	1.9 (1.1–3.3)	0.02**
Uninsured	19 (21.1)	498 (36.0)	0.9 (0.5–1.7)	0.72	0.7 (0.4–1.4)	0.32
Private*	24 (26.7)	562 (40.6)	1.0		1.0	
CD4 (cells/μL)						
≥200	81 (92.0)	1224 (89.7)	1.3 (0.6–2.9)	0.49	–	–
<200*	7 (8.0)	140 (10.3)	1.0			
Viral load (copies/mL)						
≥200	11 (12.4)	185 (13.5)	0.9 (0.5–1.7)	0.77	–	–
<200*	78 (87.6)	1188 (86.5)	1.0			
Substance use[b]						
Current	7 (7.8)	98 (7.1)	1.1 (0.5–2.5)	0.79	1.2 (0.5–2.9)	0.69
Unknown	6 (6.7)	81 (5.9)	1.2 (0.5–2.7)	0.74	0.5 (0.1–2.7	0.44
Prior/never*	77 (85.6)	1205 (87.1)	1.0		1.0	
Depression[c] and/or Anxiety/Panic[d]						
Both	22 (24.4)	110 (8.0)	5.2 (3.0–9.2)	<0.001**	2.7 (1.4–5.0)	0.002**
Depression only	9 (10.0)	85 (6.1)	2.8 (1.3–6.0)	0.01**	1.4 (0.6–3.2)	0.46
Anxiety/Panic only	13 (14.4)	158 (11.4)	2.2 (1.1–4.2)	0.02**	1.3 (0.6–2.6)	0.50
Unknown	10 (11.1)	87 (6.3)	3.0 (1.4–6.3)	0.003**	2.5 (1.0–6.3)	0.05**
Neither*	36 (40.0)	944 (68.2)	1.0		1.0	
Alcohol use[e]						
At risk	9 (10.0)	166 (12.0)	0.8 (0.4–1.7)	0.61	0.9 (0.4–2.0)	0.84
Unknown	7 (7.9)	85 (6.1)	1.3 (0.6–2.8)	0.57	0.9 (0.2–3.9)	0.89
No/low risk*	74 (82.2)	1133 (81.9)	1.0		1.0	

Table 4 continued

Factor	Co-prescription of sedating medications		Univariate analysis		Multivariable analysis[a]	
	Yes N = 90 n (%)	No N = 1384 n (%)	Unadjusted OR (95 % CI)	p-value	Adjusted OR (95 % CI)	p-value
Pain[f]						
Yes (moderate/severe)	76 (84.4)	542 (39.2)	13.7 (6.6–28.6)	<0.001**	9.1 (4.2–19.7)	<0.0001**
Unknown	6 (6.7)	61 (4.4)	9.6 (3.2–28.6)	<0.001**	9.1 (2.1–39.7)	0.003**
No	8 (8.9)	781 (56.4)	1.0		1.0	

Univariate and multivariable analyses conducted using logistic regression method

CI confidence interval, *OR* odds ratio, *UAB* University of Alabama at Birmingham, Birmingham, AL, USA

* Reference category

** Statistically significant at 0.05 level

Prescription covering ≥90 consecutive days as of July 2012

With benzodiazepines and/or muscle relaxants

[a] Multivariable model performance: Hosmer–Lemeshow test p-value = 0.64; c-statistics = 0.841; Max-rescaled r-square = 0.2584

[b] Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

[c] Patient Health Questionnaire-9 instrument (PHQ-9): score ≥ 10

[d] Patient Health Questionnaire-5 for Anxiety (PHQ-A) instrument

[e] Alcohol Use Disorders Identification Test (AUDIT-C)

[f] EUROQOL health related quality of life instrument

over age 50, those with depression and anxiety are the most likely to be prescribed opioids. Further, we found those with anxiety are likely to be co-prescribed sedating medications such as benzodiazepines as might be expected, and we also found white and female participants had greater odds of co-prescription as compared to non-whites and males. Although numbers of deaths in our cohort were small, our results were consistent with findings from other studies of individuals with HIV [33] and in the general population [14, 21, 34]: mortality was higher in participants prescribed chronic opioids, and in individuals co-prescribed opioids and other sedating medications. These findings have important implications for developing interventions to improve safety of opioid prescribing in HIV care.

Two prior studies have examined rates of chronic opioid prescription among individuals with HIV. Edelman and colleagues found that the rate of chronic opioid prescription among HIV-infected Veterans with chronic pain was approximately 10 % in 2006; this was similar to matched HIV-negative veterans [11]. Silverberg et al. found a similar (8 %) rate of chronic opioid prescribing among HIV-infected individuals seeking care in a Kaiser cohort between 1997 and 2005, which was twice the rate of chronic opioid prescribing among individuals without HIV in that cohort during that time [12]. In these studies, chronic opioid prescription among individuals with HIV was at least as high if not higher than the general population. In our study, rates of chronic opioid prescription were almost double those reported in either of those studies. This could be due to differences in study design and comorbidities of the population. Another potential reason for this is the high rate of opioid prescription observed in the Southeastern US. A recent MMWR reported that Alabama's rate of opioid prescribing was the highest in the US, 2.7 times higher than the rate of prescribing in Hawaii, the lowest opioid prescribing state [35]. Therefore, it is possible that our finding of relatively high opioid prescription in our cohort reflects high use in HIV-infected individuals, and/or high opioid prescribing in our state. Additionally, data used in the two previous studies are now nearly a decade old, and HIV and chronic opioid prescribing epidemiology have both evolved: HIV-infected patients' life expectancy has dramatically increased, and opioid prescription has become more common in the general population. Our results may likely reflect these trends.

Few studies have examined chronic opioid prescription co-prescription of sedating medications among HIV-infected individuals or in the general population. In the only study of an HIV-infected cohort that we are aware of, Gaither et al. found that 25 % of HIV-infected veterans on chronic opioid therapy received at least a week's supply of a benzodiazepine during the 10-year study period, compared to 20 % among HIV-negative controls [36]. In a study of HIV-negative veterans, 24 % of those on chronic opioid therapy received a benzodiazepine prescription during the one year study period [37]. Our criteria for chronic sedative use was more conservative ($\geq$90 days as compared to 1 week or any prescription in the prior studies), and we looked at chronic co-prescription at a single snapshot in time (July 29, 2012). We found that 61 participants (24 %) were prescribed opioids and benzodiazepines. This suggests that co-prescription was at least as common in our cohort as in prior studies among individuals with HIV and the general population [11, 36–38]. Additionally, this study one of the first studies to characterize factors associated with co-prescription of sedating medications, and is consistent with the findings of a recently published study in a criminal justice population [39]. To our knowledge, this is the first study to investigate muscle relaxants (for which there is little evidence of efficacy [40]) alone and in combination with other medications in any patient population.

Even when controlling for pain, we identified several patient factors that were associated with chronic opioid prescription and chronic co-prescription. We found that age >50, public insurance, and depression and anxiety, were significantly associated with chronic opioid prescription, and that public insurance and depression and anxiety were associated with co-prescription of sedating medications. Our findings raise concern that opioids and other sedating medications are disproportionately prescribed for patients in whom use was risker. Although not examined in HIV-infected cohorts to date, this been described in the general population of individuals prescribed chronic opioid therapy, and has been dubbed "adverse selection" [41, 42]. "Adverse selection" of the riskiest patients for long-term opioid therapy may reflect the complexity of these patients, whose pain is often very difficult to manage and who suffer a significant degree of functional impairment as a result. However, it is particularly concerning in light of the paucity of evidence supporting the efficacy of long-term opioid therapy, alone and in combination with other sedating medications, for chronic non-malignant pain [13].

The patient characteristics we found to be associated with chronic opioid prescription are consistent with findings from general populations of patients with chronic pain, with the exception of age. In the general population, some studies suggest that younger individuals are more likely to be prescribed chronic opioid therapy, although the majority of patients in published studies were of older age (e.g., >50) [37, 42–47]. In our study and the two other studies among individuals with HIV that have asked this question, older participants were more likely to be prescribed chronic opioid therapy [11, 12]. We speculate that increased opioid prescribing among older HIV patients may be due to the

substantial burden of multimorbidity among the aging HIV-infected population, which leads to the accumulation of painful conditions and the addition of opioids to the therapeutic approach.

We also noted a large racial difference in co-prescription, with white participants having higher odds of co-prescription than non-whites. The reason for this racial difference is unknown. Other recent studies have suggested that whites are more likely to be prescribed benzodiazepines than non-whites, and of concern, that whites co-prescribed opioids and benzodiazepines have higher rates of death compared to other racial groups [48]. This phenomenon, along with the small gender difference (females more likely to be co-prescribed opioids and other sedating medications than males), merits further investigation.

Of note, our study found that despite opioids, participants remained in moderate to severe pain; this is consistent with prior studies suggesting limited opioid efficacy in the general population [13] and in individuals with HIV [12]. It is also important to note the lack of evidence for long-term benzodiazepine use in the treatment of chronic pain. This underscores the need for widely available alternatives to chronic opioid and benzodiazepine prescription in this population, and for approaches to managing the large group of patients chronically taking these risky therapies who may have difficulty stopping them due to the expected physical dependence these medications produce, or due to the development of an opioid or benzodiazepine use disorder.

Our study findings can inform future patient- and provider-targeted interventions to improve opioid prescribing in HIV clinics. Prior work has shown that HIV providers feel unprepared to manage chronic pain, and lack confidence recognizing opioid use disorders [49]. Providers may be unaware of the lack of evidence as to benefit of opioids, the phenomenon of adverse selection, and the risk of oversedation and overdose when opioids are combined with other sedating medications. HIV provider education about these issues, and about high rates of opioid prescribing and co-prescribing could play an important role in improving patient safety. Providers need training regarding not only when to start opioids and sedating medications, but also when and how to discontinue or taper them when the harms exceed the benefits. Therefore, it follows that safe and effective non-opioid pharmacologic and non-pharmacologic modalities for managing HIV-infected patients with chronic pain must be accessible. Providers may also simply not know when patients are co-prescribed sedating medications; in this case, an alert to this effect could be helpful. Patient education about the harms of opioids and recent shifts in thinking regarding the role of opioids and sedating medications in treating pain is also needed.

In addition to investigation of the racial and gender differences in prescribing reflected in our results, and non-opioid pain treatment strategies, an important area of future investigation is how to address the large numbers of individuals with HIV already on long-term opioid therapy, whether alone or in combination with other sedating medications. In some such individuals, medications are taken safely, functional gains are measurable, and the benefit outweighs the risk. However, in others, concerning behaviors arise, and there may be concern for an opioid use disorder. Strategies for how to recognize and manage patients in such situations are lacking in the general or HIV-specific literature and represent an important area of future investigation.

Our study has limitations. It was conducted at one clinical site, which may limit generalizability to other settings, and was cross-sectional. Additionally, the database does not reliably include data about why opioids were prescribed, though we believe based on prior data from our cohort [50], and from others [51, 52], that most chronic opioid therapy was prescribed for chronic non-malignant pain, primarily musculoskeletal and neuropathic.

In sum, our study highlights the high rate of chronic opioid prescription and co-prescription of other sedating medications among participants from a Southeastern US cohort of HIV-infected individuals. Further, we identified adverse selection that raises additional safety concerns. Our work serves as an important first step towards addressing high rates of opioid prescribing and improving opioid safety among individuals with HIV.

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