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Medicaid trends in prescription opioid and non-opioid use by HIV status

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ABSTRACT

Background: Pain is more common among people living with HIV (PLWH) than their counterparts; however, it is unclear whether analgesic use differs by HIV status.
Methods: We analyzed Medicaid pharmacy claims from adults in 14 US states from 2001 to 2009 to identify opioid and non-opioid analgesic prescriptions and compared prescribing trends by HIV status. We accounted for clinical and demographic differences by using inverse probability weights and by restricting the sample to a subgroup with a common comorbidity, diabetes, chosen for its high prevalence and association with lifestyle and chronic pain. We estimated the incidence of chronic opioid therapy (COT) (≥90 consecutive days with an opioid prescription) among opioid-naïve individuals.
Results: Rates of opioid and non-opioid use increased approximately two-fold from 2001 to 2009. PLWH received approximately twice as many prescriptions as those without HIV. In an unadjusted Cox regression, PLWH were three times more likely to receive COT compared to those without HIV (hazard ratio (HR) = 3.06, 95% CI 2.76–3.39). When restricting to patients with diabetes and adjusting for age, sex, state, comorbidity score, depression, bipolar disorder, and schizophrenia, the HR decreased to 1.26 (95% CI 0.97–1.63).
Conclusions: Higher opioid use among PLWH was largely a function of patients' demographic characteristics and health status. The high incidence of COT among PLWH underscores the importance of practice guidelines that minimize adverse events associated with opioid use.

1. Introduction

Chronic pain is common among people living with HIV (PLWH), with prevalence estimates ranging from 25% to 80% among PLWH (Miaskowski et al., 2011) and from 61% to 80% among individuals with AIDS (Frich and Borgbjerg, 2000). In addition to pain from headaches, lower back pain and other musculoskeletal causes (Singer et al., 1993), PLWH also experience HIV-associated neuropathy and ART-toxic neuropathy (Tsao et al., 2007). The development of improved combination antiretroviral therapy has decreased the prevalence of symptomatic peripheral neuropathy (Lee et al., 2015), but PLWH continue to report an increased level of pain compared to their uninfected counterparts (Tsao et al., 2012). Because pain is a complex multidimensional construct influenced by both physiological and psychological factors, high rates of psychological symptoms among PLWH may also contribute to their higher prevalence of pain (Tsao et al., 2012).

Between 1999 and 2010, the use of prescription opioids in clinical practice increased more than fourfold (Benyamin et al., 2008; Bohnert et al., 2011; Edlund et al., 2014; Manubay et al., 2011), leading to rapidly rising rates of addiction, overdose and other adverse events. Prescription opioid sales have declined modestly since 2010, though levels remain far higher than the historical baseline in the mid-1990s. Likely because of the high-risk characteristics exhibited by PLWH, including a higher prevalence of drug abuse and psychological co-morbidities compared to the general population (Tsao et al., 2007), there have been reports of under-treatment of pain among individuals living with HIV since 1997 (Breitbart et al., 1996; Larue et al., 1997; Lazarus and Neumann, 2001). Recent studies have found an increased prevalence of opioid prescribing among PLWH compared to the general population (Becker et al., 2016; Edelman et al., 2013); however, these studies do not discuss trends in non-opioid analgesic prescriptions, which represent an important alternative means of controlling pain, and do not describe the incidence of chronic opioid use.

We compared trends in the prescription of both opioid and non-

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opioid analgesics among PLWH and individuals without HIV from 2001 to 2009 using total number of prescriptions dispensed and the proportion of days covered. We then estimated the incidence of the development of chronic opioid therapy (COT), defined as ≥90 consecutive days with an opioid prescription, among opioid-naïve individuals and estimated the association between HIV and COT.

2. Methods

2.1. Study sample

We analyzed data from Center for Medicare and Medicaid Services (CMS) Medicaid Analytic eXtract (MAX) claims files. MAX pharmacy claims include comprehensive information on medications prescribed to Medicaid-eligible individuals, regardless of the prescribing physician. Because individuals receiving opioid medications occasionally seek prescriptions from multiple providers, a single database that captured all prescriptions was optimal for this analysis. Approximately 40% (Kates et al., 2014) of insured PLWH are covered under Medicaid, indicating that Medicaid is a rich data source from which to glean healthcare utilization information about PLWH.

The sample included HIV-infected individuals between the ages of 18 and 65 years who were insured under Medicaid between 2001 and 2009 in one of 14 states: Alabama, California, Colorado, Florida, Georgia, Illinois, Massachusetts, Maryland, North Carolina, New York, Ohio, Pennsylvania, Texas, and Washington. The sample was assembled using a closed cohort of individuals who were enrolled in Medicaid on January 1, 2001. Individuals remained in the cohort for every month in which they were enrolled in Medicaid until December 31, 2009. Because the dataset comprised a closed cohort, data were not available on individuals who were new Medicaid enrollees after January 1, 2001, but the longitudinal nature of the cohort allowed for the identification of incident opioid use and chronic opioid use.

We excluded individuals with secondary insurance, as Medicaid claims files do not contain information on prescriptions covered by other insurance. This exclusion criterion applied to individuals who had supplemental private insurance and those who were dual-eligible for both Medicaid and Medicare. Also, patients with gaps in coverage were excluded from the analysis for all years following the gap.

2.2. Identification of drugs and co-morbidities of interest

We identified opioid and non-opioid oral analgesic prescriptions using pre-identified National Drug Code (NDC) codes (see Supplementary Table 1[2]). Demographic characteristics of the study participants, including age, sex, and state of residence, came from the enrollment record of the MAX files. We identified medical conditions using the Johns Hopkins ACG® System 11.1 (Baltimore, MD), which applies propriety algorithms to identify chronic diseases using inpatient medical claims, pharmaceutical claims, and enrollment files. We used five chronic conditions identified through the ACG® System, each of which we hypothesized to be related to the receipt of prescription analgesics: HIV, diabetes, depression, schizophrenia, and bipolar disorder, and we used the categorical risk score, “major ADG count” as a summary measure for the individual’s overall chronic disease burden.

2.3. Statistical methods

2.3.1. Prevalence of opioid and non-opioid analgesics

To explore trends in opioid and non-opioid prescription oral analgesics over time, we examined the standardized rate of opioid and non-opioid analgesic prescriptions per 100 people by HIV status. First, we defined a prescription as a single fill of an opioid or non-opioid oral analgesic regardless of days supplied. Refills were considered a second prescription. Then, to account for different durations of individual prescriptions, we examined the proportion of days covered (PDC) by an opioid or non-opioid analgesic prescription, which describes the proportion of total days in a given year that an individual has a prescription for a medication. We calculated PDC using information on days supplied and credited overlapping days by shifting the start date of prescriptions that began before the prior prescription ended (Scott, 2007).

We first calculated standardized rates among the full analytic sample and then, to create a more homogenous study sample and consequently improve comparability between the HIV and non-HIV groups, we restricted the sample to a subset of patients who had a common comorbidity. We chose diabetes as the comorbidity due to its relatively high prevalence, its known association with neuropathy, and its classification as a lifestyle disease, the latter of which can help to account for behavioral characteristics such as diet and exercise that are otherwise unavailable in claims data. Because the subset with diabetes included patients who all shared a common disease, these individuals were more homogenous than the entire cohort of Medicaid enrollees. This restriction, in combination with Medicaid eligibility criteria that limits the sample to a particular socioeconomic subset of the population, addresses some of the residual confounding that remains, even after adjusting for clinical characteristics, because of the inability to account for important social and behavioral characteristics using claims data.

To further ensure comparability between the HIV and non-HIV groups, we then applied two sets of weights. First, we weighted the population to standardize the sample to the distribution of the characteristics among the HIV-infected individuals using inverse probability of HIV weights, as follows: PLWH were assigned a weight of 1 and individuals without HIV were given a weight corresponding to their estimated odds of having HIV according to a logistic regression model where HIV was modeled as a function of age, sex, state of residence, and major ADG count (Austin and Stuart, 2015). Second, we applied inverse probability of censoring weights (IPCW) to account for differential censoring by HIV status. We calculated the IPCW using a logistic regression model for Medicaid dis-enrollment as a function of year, age, sex, state of residence, major ADG count, and HIV status.

2.3.2. Incidence of chronic opioid therapy

We examined the incidence of COT, defined using a standard definition of 90 continuous days with an opioid prescription (Chou et al., 2009), among a population of opioid-naïve individuals using a time-to-event analysis, specifically comparing PWLH to those without HIV. To create a subset of opioid-naïve individuals, we identified and excluded all patients who received at least one opioid prescription during the first year of follow-up, as they represent prevalent opioid users. Individuals remaining had either never been prescribed opioids or had not been prescribed opioids recently, and were considered opioid-naïve for the purposes of this analysis. The time origin for the analysis was then defined as January 1, 2002. Patients were followed until the first of: the 90^{th} day of continuous opioid therapy, loss of Medicaid coverage (due to a change in insurance status or death), or December 31, 2009. We weighted the population by the inverse probability of censoring weights to account for differential dropout by HIV status.

To ease computational burden, we selected a 10% random sample containing 456,199 individuals enrolled in 2001 as the analytic sample for the incidence of COT. Of these individuals, 110,565 (24.2%) were prevalent opioid users in 2001 and were excluded from the analysis. We excluded an additional 121,837 individuals with no follow-up after 2001. The final analytic sample for the incident COT analysis included 223,797 opioid-naïve individuals who contributed 940,329 person-years of follow-up. The subset with diabetes contained 13,383 patients who contributed 78,376 person-years of follow-up.

We plotted the cumulative incidence of COT using a Kaplan-Meier estimator and assessed the proportionality of the hazard of COT with

[2] Supplementary material can be found by accessing the online version of this paper at https://doi.org/10.1016/j.drugalcdep.2018.11.034.

Table 1
Baseline demographic characteristics.

	N (%)	
	HIV N = 54,120	Non-HIV N = 4,507,019
Age, median (IQR)	42 (37, 48)	34 (25, 45)
Sex		
Female	25,414 (46.96)	3,291,573 (73.03)
Male	28,705 (53.04)	1,215,429 (26.97)
State		
Alabama	427 (0.79)	114,118 (2.53)
California	6,674 (12.33)	1,673,938 (37.14)
Colorado	106 (0.20)	38,021 (0.84)
Florida	6,379 (11.79)	326,491 (7.24)
Georgia	1,780 (3.29)	121,603 (2.70)
Illinois	2,606 (4.82)	252,942 (5.61)
Massachusetts	2,480 (4.58)	263,398 (5.84)
Maryland	2,588 (4.78)	131,057 (2.91)
North Carolina	1,619 (2.99)	142,488 (3.16)
New York	23,949 (44.25)	609,068 (13.51)
Ohio	907 (1.68)	241,346 (5.35)
Pennsylvania	1,931 (3.57)	282,882 (6.28)
Texas	2,353 (4.35)	201,426 (4.47)
Washington	321 (0.59)	108,241 (2.40)
Opioid prevalent		
No	31,628 (58.44)	3,421,929 (75.92)
Yes	22,492 (41.56)	1,085,090 (24.08)
Major ADG count		
0	36,280 (67.04)	4,1911,135 (93.0)
1	5,907 (10.91)	193,922 (4.30)
2	6,521 (12.05)	78,267 (1.74)
3+	5,412 (10.00)	43,695 (0.97)
Diabetes	4,540 (8.39)	283,487 (6.29)
Depression	21,022 (38.84)	767,935 (17.04)
Bipolar	625 (1.15)	18,242 (0.40)
Schizophrenia	1,568 (2.90)	41,478 (0.92)

Characteristics of the analytic study sample in 2001 by HIV status; N = 4,561,139.

respect to HIV-status. We then fit Cox proportional hazards models to estimate the crude and adjusted associations between HIV-status and COT among the weighted sample and among a subset of the weighted sample with diabetes. In the adjusted models, we considered characteristic including age, sex, state of residence, overall comorbidity score, bipolar disorder, schizophrenia, and depression.

3. Results

Of 15.9 million individuals, 4.6 million were eligible for inclusion after application of our exclusion criteria. Of these, 54,120 (1.19%) had a diagnosis of HIV in 2001 and 288,027 (6.31%) had a diagnosis of diabetes in 2001. Those with HIV differed from their counterparts with respect to many characteristics (Table 1). For example, slightly more than half (53%) of PLWH were male, whereas only 27% of individuals without HIV were male. PLWH were older, with a median age of 42 (IQR 37–38), compared to a median age of 34 (IQR 25–45) among individuals without HIV. Approximately 42% of PLWH were prevalent opioid users in 2001, compared to only 24% of individuals without HIV.

3.1. Prevalence of opioid and non-opioid analgesics

3.1.1. Unadjusted trends

In unadjusted analyses, PLWH received approximately twice the number of opioid prescriptions, defined as a single fill of any duration (mean = 2.50 per person per year in 2001 and 3.89 in 2009), compared to patients without HIV (mean = 1.09 in 2001 and 1.99 in 2009). Trends were more comparable among the subset with diabetes: PLWH with diabetes received 25–35% more opioid prescriptions (mean = 3.41 in 2001 and 4.94 in 2009) compared to individuals with diabetes but without HIV (mean = 2.73 in 2001 and 3.67 in 2009) (Fig. 1).

The absolute number of non-opioid analgesic prescriptions was higher than that of opioid prescriptions, but the patterns were similar: prescriptions increased over time in all groups, and the prevalence among PLWH was higher than that among individuals without HIV. The full sample of PLWH received approximately twice the number of non-opioid analgesics compared to patients without HIV (mean among PLWH = 3.22 in 2001 and 4.83 in 2009; mean among individuals without HIV = 1.67 in 2001 and 2.91 in 2009). When restricting the sample to patients with diabetes, PLWH received between 15–25% more non-opioid analgesic prescriptions than their non-HIV infected counterparts (mean among individuals with diabetes and HIV = 5.17 in 2001 and 7.25 in 2009; mean among individuals with diabetes and no HIV = 4.60 in 2001 and 5.89 in 2009) (Fig. 2).

3.1.2. Adjusted trends

When we applied the weights, trends in the non-HIV group increased resulting in PLWH receiving only 50–65% more opioid prescriptions and about 20–30% more non-opioid prescriptions compared to similar patients without HIV. Among individuals with diabetes, the difference in opioid prescriptions by HIV status decreased to about 13–15%. Among the weighted subset with diabetes, the prevalence of non-opioid analgesics was similar by HIV status until 2004, at which point PLWH received approximately 10% more non-opioid analgesic prescriptions.

3.2. Proportion of days covered

The proportion of individuals receiving an opioid analgesic was higher among PLWH than individuals without HIV (49.6% vs. 40.1% in 2009). More individuals received non-opioid analgesic prescriptions compared to opioid analgesics; however, like the opioid analgesic prescriptions, a higher proportion of PLWH received non-opioid analgesics compared to individuals without HIV (59.4% vs. 51.6% in 2009).

Not only were PLWH more likely to receive analgesic prescriptions, but among only patients who received at least one prescription, PLWH also had a higher proportion of total days covered (PDC). Opioid PDC increased each year, from a mean of 0.24 among PLWH and 0.19 among people without HIV in 2001 to 0.34 and 0.28 in 2009 among patients with and without HIV, respectively (Fig. 3). The difference in PDC for non-opioid analgesic prescriptions by HIV status was less pronounced. Non-opioid PDC among PLWH increased from 0.33 in 2001 to 0.43 in 2009 and from 0.35 in 2001 to 0.41 in 2009 among individuals without HIV (Fig. 4). Both opioid and non-opioid PDC increased when we restricted the sample to patients with diabetes.

3.3. Incident chronic opioid therapy

Overall, 9049 of 223,797 individuals (4.0%) were prescribed COT during the 8-year follow-up period for an incidence rate of 9.6 per 1000 person-years. Rates of COT were significantly greater among those with HIV (incidence rate: 29.1 per 1000 person-years) than those without HIV (incidence rate: 9.3 per 1000 person-years). Fig. 5 shows cumulative incidence of COT by HIV status, weighted by IPCW, for the full and subsamples with diabetes.

In an IPCW-weighted unadjusted Cox proportional hazards model, PLWH had 3.06 times the hazard for COT compared to patients without HIV (95% CI 2.76–3.39). After adjustment for age, sex, state of residence, and comorbid conditions, the hazard ratio comparing PLWH to patients without HIV decreased to 1.46 (95% CI 1.31–1.63). Among the subset with diabetes, the unadjusted and adjusted hazard ratios were 1.61 (95% CI 1.25–2.09) and 1.26 (95% CI 0.97–1.63), respectively (Table 2).

In the fully adjusted model, adjusted for age, sex, state of residence, and comorbid conditions, depression was associated with an increased incidence of COT (HR = 4.28, 95% CI 4.01–4.49 [full sample] and HR = 2.26, 95% CI 2.06–2.49 [subset with diabetes]), while both bipolar disorder and schizophrenia were associated with a lower hazard

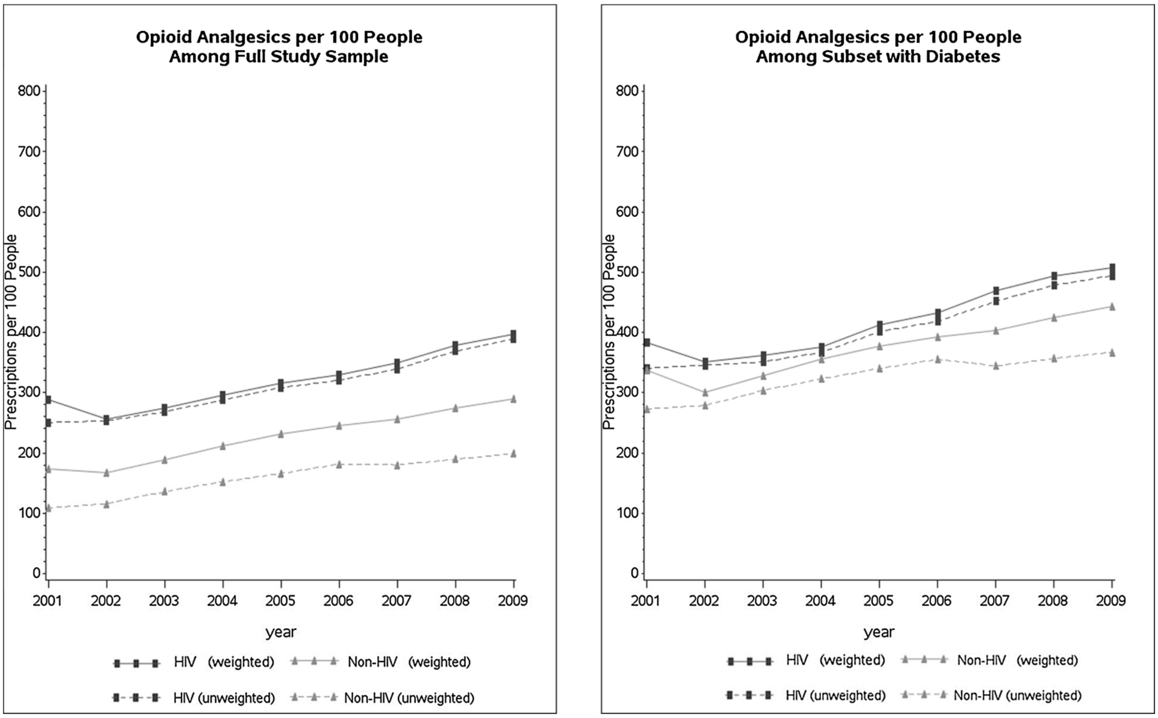

Fig. 1. Total number of opioid analgesic prescriptions dispensed from 2001 to 2009 per 100 people, by HIV status. Left panel: full analytic sample; right panel: restricted to patients with diabetes. Dashed lines depict unadjusted trends; solid lines depict trends weighted by inverse probability of HIV weights and by the inverse probability of censoring.

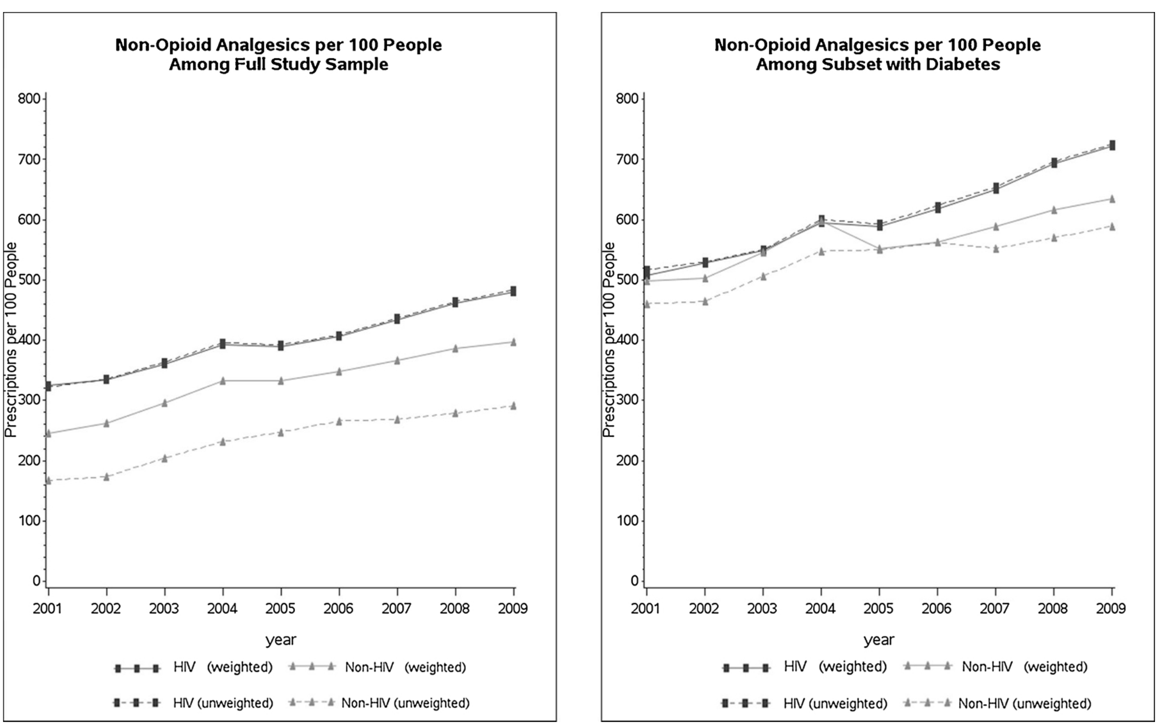

Fig. 2. Total number of non-opioid analgesic prescriptions dispensed from 2001 to 2009 per 100 people, by HIV status. Left panel: full analytic sample; right panel: restricted to patients with diabetes. Dashed lines depict unadjusted trends; solid lines depict trends weighted by inverse probability of HIV weights and by the inverse probability of censoring.

of COT (HR = 0.83, 95% CI 0.73–0.94 [full sample], HR = 0.72, 95% CI 0.57–0.92 [subset with diabetes] for bipolar disorder and HR = 0.41, 95% CI 0.38–0.46 [full sample], HR = 0.46, 95% CI 0.38–0.54 [subset with diabetes] for schizophrenia).

4. Discussion

In this analysis of 4.5 million individuals enrolled in Medicaid from 2001 to 2009, we found increasing rates of both opioid and non-opioid

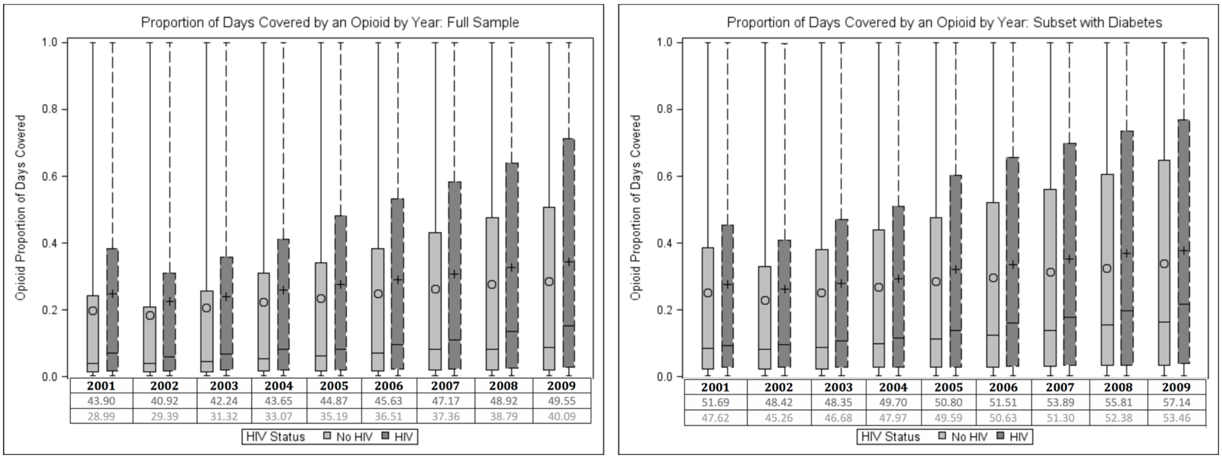

Fig. 3. Proportion of days covered by an opioid analgesic prescription among individuals with at least one opioid analgesic prescription in the given year, weighted by inverse probability of HIV and by the inverse probability of censoring (left panel: all individuals; right panel: subset with diabetes). The shaded box depicts the interquartile range, the whiskers indicate the minimum and maximum values, the horizontal line shows the median, and the open circle (HIV group) or cross (non-HIV group) shows the mean. The table below the x-axis displays the proportion of individuals in each year with at least one opioid prescription.

analgesics. At baseline, rates of opioid use were approximately 2.5 times higher among those with HIV than their counterparts, while rates of non-opioid analgesic use were approximately twice as high. These differences generally persisted with only a slight decline over time, implying that we could likely see similar differences by HIV status if we were to extrapolate the trends beyond 2009. Notably, we found that differences in prescription rates by HIV status were almost entirely accounted for by patients' socio-demographic and clinical characteristics rather than their HIV status. These findings are important because the prior reports that suggested a systematic under-treatment of pain among PLWH raised the question as to whether patients were in fact treated differentially because of HIV status itself, possibly as a result of HIV-related stigma or concerns about misuse among a population with co-occurring mental health conditions. High rates of analgesic prescriptions among PLWH indicate a need for pain medication among this population. However, the considerably lower rates of COT among patients with co-morbid schizophrenia and bipolar disorder suggest that pain medications are prescribed less to patients who are at highest risk for misuse.

Our study provides additional new knowledge regarding the use of opioids among PLWH. We found that PLWH use more opioids than individuals without HIV. However, the characteristics of PLWH and individuals without HIV varied considerably, indicating a likely disparate need for pain medication between the two groups. When we accounted for the differences between PLWH and those without HIV, we found that difference prescription rates were largely accounted for by observable characteristics including age, sex, and co-morbidities, and un-observable characteristics such as lifestyle and behavioral factors associated with developing diabetes. Though weighting and restricting the study population is an imperfect means of controlling for all differences between the HIV and non-HIV populations, it does minimize the differences considerably. Our assumption is that these two methods improve the comparability by HIV status sufficiently to assume that the primary difference between the two groups is their HIV status.

Interestingly, we found that non-opioid analgesic use increased in parallel with use of opioids. Randomized trials have found similar effects of non-opioid and opioid medications for the treatment of both acute (Chang et al., 2017) and chronic (Krebs et al., 2018) pain, suggesting that a movement towards greater use of non-opioid analgesic medications may be beneficial. Despite a wealth of studies describing general trends in opioid prescribing, less is known regarding how the epidemic has affected use of non-opioid analgesics. In one study using nationally representative ambulatory data, increased opioid use was not found to be accompanied by similar increases in non-opioid

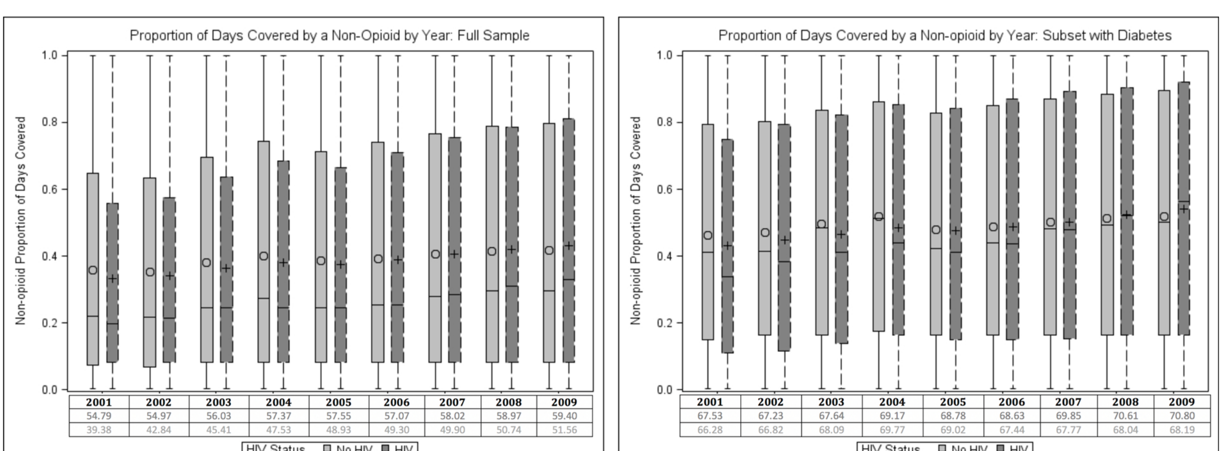

Fig. 4. Proportion of days covered by a non-opioid analgesic prescription among individuals with at least one non-opioid analgesic prescription in the given year, weighted by inverse probability of HIV and by the inverse probability of censoring (left panel: all individuals; right panel: subset with diabetes). The shaded box depicts the interquartile range, the whiskers indicate the minimum and maximum values, the horizontal line shows the median, and the open circle (HIV group) or cross (non-HIV group) shows the mean. The table below the x-axis displays the proportion of individuals in each year with at least one non-opioid prescription.

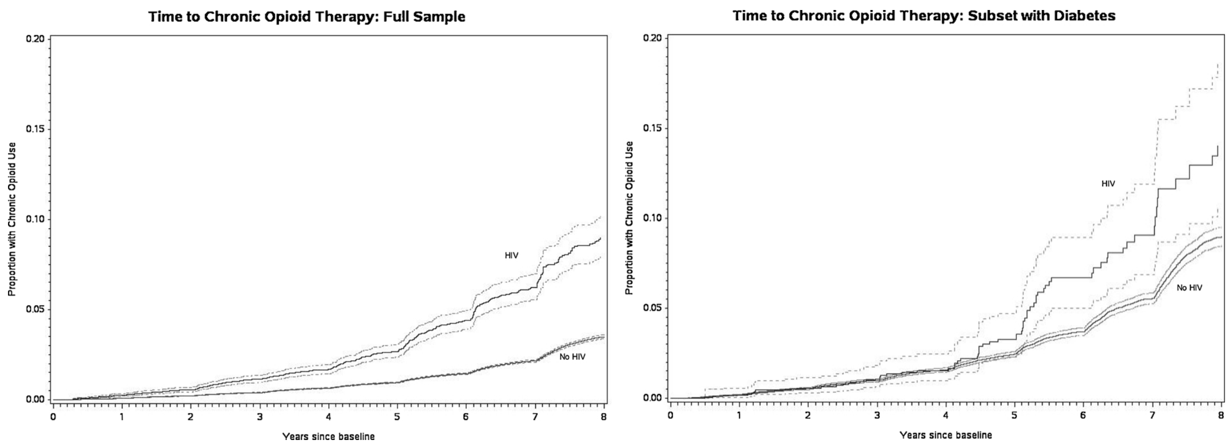

Fig. 5. Cumulative incidence of chronic opioid therapy (COT) among a sample of opioid-naïve individuals (left panel) and subset with diabetes (right panel) followed from January 1, 2002 until the first day of COT (defined as the 90th day of consecutive opioid use), Medicaid dis-enrollment, or December 31, 2009, weighted by inverse probability of censoring.

Table 2
Chronic opioid therapy[1] among opioid-naïve individuals.

	Hazard Ratio (95% CI)		
	Unadjusted Model	Adjusted Model 1	Adjusted Model 2
Full Sample			
Persons without HIV	Ref	Ref	Ref
PLWH	3.06 (2.76-3.39)	2.37 (2.13-2.63)	1.46 (1.31-1.63)
Subset with Diabetes			
Persons without HIV	Ref	Ref	Ref
PLWH	1.61 (1.25-2.09)	1.72 (1.32-2.23)	1.26 (0.97-1.63)

Results from Cox proportional hazards models for chronic opioid therapy among opioid-naïve individuals between January 1, 2002 and December 31, 2009. Sample selected from a 10% random sample of eligible study population; N = 223,797 individuals contributing 940,329 person-years of follow-up for the full sample and N = 13,383 individuals contributing 78,376 person-years of follow-up for the subset with diabetes. Adjusted Model 1: adjusted for categorical age, sex, and state of residence. Adjusted Model 2: adjusted for categorical age, sex, state of residence, major ADG count, bipolar disorder, schizophrenia, and depression. All models weighted by the inverse probability of censoring.

[1] Chronic opioid therapy (COT) defined as ≥90 consecutive days with an opioid prescription.

analgesics (Daubresse et al., 2013). It is unclear if the trends we describe reflect care patterns specific to the population observed, or any improvement in the management of pain among these individuals, as there are many factors that drive prescription drug utilization rates, including clinical guidelines, pharmaceutical marketing and promotion and Medicaid coverage and reimbursement policies.

Chronic opioid use was significantly more likely among PLWH compared to individuals without HIV. Although we did not stratify the analyses by dose, we found over three times the rate of COT among PLWH compared to those without HIV in unadjusted analyses. This is clinically important because of the well-described risks of chronic opioid use for non-cancer pain (Baldini et al., 2012). Minimizing the transition from acute to chronic opioid use represents a focus of the CDC Guidelines for chronic pain management (Dowell et al., 2016) and should also be a focus of HIV care providers treating PLWH with chronic pain. Recent guidelines for the treatment of pain among PLWH also highlight the importance of screening to identify the causes of chronic pain, beginning treatment with non-opioid options, and tailoring treatment strategies for patients with underlying conditions such as a history of substance use disorder (Bruce et al., 2017).

The prevalence of mental health disorders was high in our population, particularly among PLWH. Individuals with mental health conditions are at a greater risk for developing addiction and other opioid use disorders, underscoring the high-risk nature of treating PLWH for chronic pain. While HIV did appear to be related to the receipt of pain medication, the impact of HIV may be smaller than previously thought. Conversely, schizophrenia and bipolar disorder were both independently associated with a lower incidence of COT, regardless of HIV status, suggesting that any alleged undertreatment of pain among PLWH may be due to co-occurring mental health conditions. It is important for providers to be aware of their patients' risk of overdose and addiction while maintaining appropriate treatment practices.

Our analyses took place from 2001 to 2009, and thus should be interpreted within the context of this temporal period. This was during a period of a nearly fourfold increase in opioid sales, after which sales have plateaued. Likely due to the characteristics of our study population of Medicaid enrollees, we observed a higher number of opioids prescribed per capita compared to a recently published study examining national trends in opioid prescribing between 2006–2015 (Guy et al., 2017). However, the trends we observed regarding the dramatic increase in prescribing rates through 2009 were consistent with the national data. If the trends in opioid use in the Medicaid population follow those seen nationally (Guy et al., 2017), we would expect to see a similar stabilization or decline in opioid prescriptions among Medicaid enrolled PLWH beyond 2009.

There were some limitations to this study. We were unable to measure the prevalence of a large portion of non-opioid analgesics, as a majority of non-opioid analgesics are purchased over-the-counter and do not appear in Medicaid prescription claims. Similarly, we did not know the indication for the non-opioid analgesics prescribed; many of the non-opioid analgesics included in the analysis have non-pain related indications and are only occasionally used off-label to treat pain. We report the proportion of the non-opioid analgesics included in the analysis that is primarily used for pain (i.e. NSAIDs) versus anticonvulsants, anti-depressants, and muscle relaxants in Supplementary Table 2[2]. Finally, to conform with federal regulations surrounding substance abuse confidentiality, we were unable to examine the impact of alcohol and substance use disorders on prescription rates, which are strong predictors of both chronic pain and the receipt of opioid medications.

Despite the limitations, our study also incorporated several strengths. First, we analyzed a large sample of patients and were able to examine a comprehensive list of all prescriptions dispensed to our study sample. The closed cohort allowed us to follow the same individuals over time, enabling the examination of COT among opioid-naïve individuals. Also, despite being unable to measure over-the-counter medications, we did attempt to account for alternative analgesic treatments by examining prescription non-opioid analgesic medications. Finally, by using only Medicaid-eligible participants (Medicaid eligibility criteria varies by state, but in all cases requires individuals to earn below a threshold income, often below 138% of the federal poverty level ("Medicaid Income Eligibility Limits for Adults as a Percent of the Federal Poverty Level | The Henry J. Kaiser Family Foundation, " n.d.)), we restricted our population to a particular socioeconomic subset of the US population. This helps mitigate residual confounding that was likely present due to our inability to adjust for unmeasured socio-demographic and behavioral characteristics.

Overall, the trends we observed in analgesic prescription rates do not directly support an under-treatment of pain among PLWH. In fact, we found that PLWH were more likely to receive opioid analgesics and, when they did receive opioids, they received greater numbers than individuals without HIV. The increased proportion of days covered by an opioid among PLWH may be due to a higher prevalence of pain in these individuals; however, the similarity by HIV status in the standardized number of opioid prescriptions after accounting for demographic and clinical differences, and the higher incidence of COT among PLWH after adjustment for confounders suggest that PLWH receive at least equal, if not greater, opioid therapy compared to their HIV-uninfected counterparts. Unlike PLWH, individuals with schizophrenia and bipolar disorder were less likely to receive COT, which may be a reflection of an increased prevalence of opioid misuse among patient with mental health conditions. Pain is highly prevalent among PLWH; focusing on the appropriate treatment of chronic pain, especially among PLWH with a history of substance abuse, is an important component to managing HIV.

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Contributors

Chelsea Canan conducted the primary analysis and drafted the manuscript; Caleb Alexander provided pharmacoepidemiologic guidance; Richard Moore was the primary investigator responsible for obtaining the data; Irene Murimi provided analytic support with Medicaid data; Geetanjali Chander provided clinical guidance; and Bryan Lau provided guidance on the study design and analysis. All authors assisted with manuscript preparation. All authors have seen and approved the final manuscript and contributed significantly to the work.

Conflicts of interest

Dr. Alexander is Chair of FDA's Peripheral and Central Nervous System Advisory Committee; serves as a paid advisor to IQVIA; serves on the advisory board of MesaRx Innovations; holds equity in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. Dr. Moore was a consultant for Medscape. No other authors have conflicts of interest relevant to the contents of this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.11.034.

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