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HIGH-RISK PRESCRIPTION OPIOID USE AMONG PEOPLE LIVING WITH HIV

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Abstract

Background—Prescription opioid use is greater among people living with HIV (PLWH), yet little is known about the prevalence of specific types of high-risk use among these individuals.

Setting—We analyzed clinical and demographic data from the HIV Research Network (HIVRN) and prescribing data from Medicaid for non-cancer patients seeking HIV treatment at four urban clinics between 2006-2010.

Methods—HIVRN patients were included in the analytic sample if they received at least one incident opioid prescription. We examined four measures of high-risk opioid use: 1) high daily dosage; 2) early refills; 3) overlapping prescriptions; and 4) multiple prescribers.

Results—Of 4,605 eligible PLWH, 1,814 (39.4%) received at least one incident opioid prescription during follow-up. The sample was 61% male and 62% African American with a median age of 44.5 years. High-risk opioid use occurred among 30% of incident opioid users (high daily dosage: 7.9%; early refills: 15.9%; overlapping prescriptions: 16.4%; multiple prescribers: 19.7%). About half of the cumulative incidence of high-risk use occurred within one year of receiving an opioid prescription. After adjusting for study site, high-risk opioid use was greater among patients with IDU as an HIV risk factor (aHR=1.39, 95% CI 1.11-1.74), non-Hispanic whites (aHR=1.61, [1.21-2.14]), patients age 35-45 (aHR=1.94, [1.33-2.80]) and 45-55 (aHR=1.84, [1.27-2.67]) and patients with a diagnosis of chronic pain (aHR=1.32, [1.03-1.70]).

Conclusions—A large proportion of PLWH received opioid prescriptions, and among these opioid recipients, high-risk opioid use was common. High-risk use patterns often occurred within the first year, suggesting this is a critical time for intervention.

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Keywords

HIV; prescription opioids; Medicaid; opioid misuse

Introduction

Opioid use and opioid misuse have increased dramatically during the past two decades^{1–8}. Unintentional poisoning, such as drug overdose, is now the leading cause of accidental death in the United States, surpassing motor vehicle accidents as the leading cause of unintentional injury deaths in 2011⁹. Nearly 60% of overdose deaths in the United States involve an opioid¹, leading to a concerted effort by care providers across the country to carefully monitor the use of prescription opioids^{10, 11}.

Growing concern surrounding the increase of opioid use disorders has led to attempts to identify precursors to opioid misuse, with the intent of allowing health providers the opportunity to intervene before patients experience adverse consequences. Some such attempts include identifying patterns of high-risk use, such as the use of multiple prescribers and/or pharmacies, receiving overlapping opioid prescriptions, and high daily dosage. These use patterns have been used in both research and clinical settings to identify possible or probable opioid use disorders; while it is not possible to determine opioid misuse based on utilization patterns alone, a large body of evidence suggests that individuals with high-risk use patterns are at increased risk of injury or death^{12–21}.

One particularly vulnerable population at risk for morbidity and mortality associated with opioid use is people living with HIV (PLWH). The prevalence of chronic pain is high among PLWH, with prevalence estimates ranging from 25–80%^{22–25}. In addition, the prevalence of opioid use disorders is higher among PLWH than in the general population^{26–28}. In this study, we characterized utilization patterns of high-risk opioid use among PLWH and identified risk factors for high-risk opioid use.

Methods

Study Sample

Our sample was drawn from a subset of sites from the HIV Research Network (HIVRN), a multisite longitudinal observational cohort of PLWH seeking care. We included patients from four urban HIVRN sites in Maryland, Massachusetts, and New York that linked their study participants' records to the Medicaid database (for more information on the data linkage, see Fleishman 2016²⁹), allowing us to examine comprehensive pharmaceutical claims from Medicaid and clinical, behavioral, and social characteristics from HIVRN. Patients aged 18–65 with data from both HIVRN and Medicaid who received at least one incident oral analgesic opioid prescription between January 1, 2006 and December 31, 2010 were eligible for inclusion. Buprenorphine and methadone were not considered eligible prescriptions for this analysis.

Our exclusion criteria were based in part on Medicaid eligibility files, which contain information on the number of days in a calendar year that an individual is eligible for

Medicaid and/or for supplemental insurance. Using this information, we excluded patient-years for which patients were dually enrolled in either Medicare or private insurance, as prescription claims covered by supplemental insurance do not appear in Medicaid claims files. If patients had a gap in Medicaid coverage or had an ineligible year due to dual-enrollment, we excluded all time subsequent to the start of the gap or ineligible year. Additionally, we excluded patients on fee-for-service plans in Maryland and patients on comprehensive managed care plans in Massachusetts, since data exploration within our sample (Supplementary Table 1) and evidence from prior literature³⁰ indicate that these plans may incompletely capture prescription claims.

Finally, we excluded patient-years for the following reasons (Supplementary Figure 1 shows the number excluded for each reason): 1) age <18 or >65; 2) transgender (excluded because the small sample size precluded an analysis of transgender patients); 3) cancer diagnosis; 4) enrolled in Medicaid for <90 days; 5) resided in a state other than Massachusetts, Maryland, or New York; 6) discrepancy between Medicaid and HIVRN that called the validity of the match into question; 7) >1 record or >365 eligible days for the calendar year; 8) prevalent opioid user, determined using a 6-month washout period.

High-risk opioid use

We based our assessment of high-risk opioid use on four criteria, ascertained using Medicaid pharmacy claims: 1) daily dosage, 2) overlapping prescriptions, 3) multiple prescribers, and 4) early refills. While it is not possible to determine whether an individual is misusing opioids based on prescription claims alone, these criteria have been validated in prior research as a means to identify potential misuse^{12–21} and/or have been recommended by clinical experts as suggestive of high-risk opioid use. We use the term “high-risk use” to describe patterns of opioid dispensing that indicate a high likelihood of current or future opioid misuse.

The first outcome, high daily dosage, was based on a standardized measure for daily dosage: morphine milligram equivalents (MME). Recommendations vary for defining the cutoff for overuse, ranging from 80 to 200 MME^{3, 31}. For this analysis, we defined high-risk use as receiving over 100 MME/day for at least 30 consecutive days.

We defined the second criterion for high-risk use, overlapping prescriptions, as having at least one day with more than one opioid prescription from the same Drug Enforcement Agency (DEA) class, with DEA class categorized as: 1) long acting, 2) short acting non-Schedule II (i.e. codeine, tramadol), or 3) short acting Schedule II (i.e. hydrocodone, oxycodone). To ensure the drugs were not overlapping due to an early refill, we required that the overlapping prescriptions were either a different dosage or a different drug.

Receiving opioids from at least three distinct prescribers within a 90-day period defined the third measure of high-risk use. The timing of the opioid prescription refill defined the final criterion for high-risk opioid use, whereby a refill pickup was early if the individual refilled their prescription when at least 25% of the existing prescription remained, as determined by the prescription fill date and number of days supplied.

We examined modified definitions in the sensitivity analyses discussed below.

Explanatory variables

Exposures of interest were collected as part of the HIVRN study protocol, through medical record chart abstraction (age, sex, race, study site, and HAART use) or site-specific lab uploads processed by HIVRN (CD4 and HIV RNA). We defined nadir CD4 as the lowest CD4 value between 2006-2010. We defined baseline viral suppression as HIV RNA <200 copies/ml, determined using the closest available HIV RNA measurement within one year of baseline, where baseline was the date of the first opioid prescription.

We identified comorbidities (and one exclusion criterion) using diagnosis codes from the HIVRN database. Diagnoses of interest included: depression³² and chronic pain (as opposed to acute pain)³³, as these are diagnoses found to be associated with high-risk opioid use in prior literature and cancer, as this was an exclusion criterion^{25, 27, 34, 35}. We assessed cancer at any point during follow-up, while we assessed depression and chronic pain prior to the date of the first opioid prescription. Supplementary Table 2 lists the ICD-9 codes used to identify these three conditions.

Current illicit drug use was not captured directly in either the Medicaid claims or the HIVRN data. As a surrogate marker for illicit drug use, we examined HIV acquisition risk factor to identify patients with a history of injection drug use. We classified patients with an HIV risk factor of “injection drug use” recorded in the HIVRN database as having a history of illicit drug use (we classified patients with multiple HIV risk factors as IDU if one of the recorded risk factors was “injection drug use”).

Statistical methods

Our primary outcomes were: 1) binary indicator variables for each of the four definitions of high-risk opioid use and 2) a composite binary indicator variable for any high-risk opioid use pattern. Given that the four definitions of high-risk opioid use are not mutually exclusive, we first assessed the proportion of patients who ever experienced each of the four high-risk use dispensing patterns and calculated the incidence rates of each pattern. We then conducted a time-to-event analysis to determine the time to any high-risk opioid use. In the time-to-event analysis, we followed patients from the date of the first opioid prescription to the first date on which there was evidence for high-risk opioid use. Patients were censored on the first of either: 1) date of death, 2) last day of Medicaid coverage, or 3) December 31, 2010. We estimated the incidence rate of high-risk opioid and fit a Cox proportional hazards model to estimate the association between high-risk use and our hypothesized risk factors, including injection drug use (IDU), depression, chronic pain, age, sex, race, nadir CD4, baseline HIV viral suppression, and baseline HAART.

Sensitivity analyses

Unlike the indicators for multiple prescribers and overlapping prescriptions, which both require, by definition, the occurrence of a pattern more than once, the early refills indicator does not incorporate recurrence into its case definition. Therefore, as a sensitivity analysis, we calculated the proportion of patients who sought early refills repeatedly and estimated

the time to first event, time to second event, and time to third event. Among those with at least one early refill, we estimated the difference in 1-year restricted mean survival times to describe the time between first and second events and the time between the second and third events.

To evaluate the potential impact of misclassifying high-risk use in the scenario where a single provider prescribed multiple prescriptions to identify the correct dosage for an opioid-naïve patient, we conducted a sensitivity analysis whereby the overlapping prescriptions criterion was met only if distinct providers wrote the prescriptions. We used the revised definition to re-calculate the incidence rate of overlapping prescriptions and to re-define the composite outcome used in the survival analysis.

Results

Our sample included 1,814 PLWH with at least one incident opioid prescription between 2006-2010, which represents 39.4% of the 4,605 patients meeting the eligibility criteria (32.2% of eligible patients did not receive any opioid prescriptions during follow-up and 28.4% were prevalent opioid users). The final analytic sample was 61.5% male and the median age at study baseline was 44.5 years (interquartile range (IQR): 38-50 years). Nearly two-thirds (62.2%) were African American. Approximately one third (31.3%) of patients had an HIV acquisition risk factor of IDU, 30.6% had a diagnosis of depression, and 19.0% had a diagnosis of chronic pain (Table 1).

Among the 1,814 patients who received at least one incident opioid prescription, the median number of opioid prescriptions per patient per year was 2 (IQR: 1-6). Approximately one in four opioid recipients (27%) received exactly one opioid prescription during study follow-up, suggesting that these patients may have had an acute pain issue that was resolved after a single opioid prescription. The median daily dosage was 33 MME (IQR: 20-60; mean: 59). More than half of all opioid prescriptions (61.9%) were short-acting Schedule II, 13.6% were long acting, and 24.6% were short-acting non-schedule II. The most commonly prescribed opioid was short-acting oxycodone (49.0% of all prescription opioids) (Table 1).

Incidence of high-risk use

Approximately thirty percent (29.7%) of incident opioid users ever met one of the four high-risk use criteria. The most common high-risk use pattern was multiple prescribers, with 19.7% of patients ever receiving opioid prescriptions from 3 or more distinct prescribers in 90 days, for an incidence rate (IR) of 10.4 per 100 person-years (PY). 16.4% ever had overlapping prescriptions (IR=8.1 per 100 PY); 15.9% percent of patients ever refilled a prescription when at least 25% of the prior prescription remained (IR=7.9 per 100 PY); and 7.9% ever had a daily dosage over 100 MME for 30 or more consecutive days (IR=3.6 per 100 PY) (Table 2).

Time-to-event analysis

The incidence rate for any high-risk opioid use pattern was 17.4 events per 100 person-years. After 1 year of follow-up, the cumulative incidence was 23.1% and at 4 years of follow-up the cumulative incidence was 40.6%. Figure 1 displays the cumulative incidence

function for the composite high-risk opioid use outcome; the solid curve shows the total cumulative incidence of any high-risk use and the dashed lines depict the cumulative incidence that each of the four high-risk use patterns contribute individually. Because some patients fulfilled multiple criteria for high-risk use, we report the incidence rates of subsequent high-risk use events in Supplementary Table 3.

In a multivariable adjusted Cox regression model, IDU as an HIV acquisition risk factor, age, race, and chronic pain were associated with high-risk opioid use (Table 3). The adjusted hazard ratio (aHR) for high-risk opioid use was 1.39 (95% CI 1.11-1.74) comparing patients with IDU as an HIV acquisition risk factor to those with a non-IDU related risk factor (i.e. men who have sex with men, high-risk heterosexuals). Patients who were age 35-45 at study baseline had twice the hazard for high-risk use compared to patients less than 35 at study baseline (aHR=1.94, [1.35-2.80]). Patients older than 45 also had an increased hazard for high-risk use compared to patients in the lowest age category, but the increased hazard decreased with each increasing age category.

Non-Hispanic whites had a higher risk for high-risk opioid use compared to African Americans (aHR=1.61, [1.21-2.14]), while Hispanics had a non-significant decreased hazard for high-risk opioid use compared to African Americans. Males demonstrated a non-significant increased hazard of high-risk opioid use (aHR=1.05, 95% CI 0.86-1.30). Patients who were virologically suppressed and taking HAART at baseline showed a lower hazard for high-risk opioid use (aHR=0.91, [0.73-1.13] and aHR=0.83 [0.67-1.02], respectively).

Sensitivity analyses

Among patients who met early refill criteria (n=289), the mean number of early refills over the follow-up period was 2.7 (median 2, IQR 1-3). The incidence rates for first early refill, second early refill, and third early refills are 7.9 per 100 PY, 3.6 per 100 PY, and 2.4 per 100 PY, respectively. The top panel of Figure 2 displays the Kaplan-Meier survival curves for time to first, second, and third early refill; the bottom panel shows the time from the first (or second) early refill until the subsequent early refill. Among the full sample of 1,814 patients, the restricted mean survival time (RMST) up to 1 year of follow-up for the first early refill was 0.75 years (95% CI 0.72-0.78 years). Between the first and second early refills, the RMST up to one year was 0.40 years (95% CI 0.35-0.46 years). The comparable 1-year RMST for the time between the second and third early refill was 0.36 years (95% CI 0.29-0.42 years).

When we redefined overlapping prescriptions such that the overlapping prescription criteria was only satisfied when distinct prescribers provide the prescriptions, the incidence rate dropped to 6.6 per 100 person years (from 8.1 per 100 person-years). Because overlapping prescriptions only occasionally defined the endpoint of interest in the composite outcome survival analysis, the overall incidence rate for high-risk opioid use decreased only slightly: from 17.4 to 16.6 per 100 PY.

Discussion

We conducted a time-to-event analysis among PLWH receiving an incident opioid prescription to estimate the incidence of high-risk opioid use and determine factors associated with high-risk use. High-risk opioid use was common among these subjects, with 30% of patients exhibiting at least one of the four high-risk use outcomes. Of the four high-risk use metrics we studied, the incidence rate was highest for multiple prescribers, followed by overlapping prescriptions and then early refills. Because these dispensing patterns are associated with adverse outcomes, such as opioid abuse, dependence, and mortality, our findings underscore the importance of prescription drug monitoring programs to track prescribing patterns.

Of note, approximately half of the total cumulative incidence of high-risk use occurred within the first year after a patient received an incident opioid prescription. The first year of opioid use likely represents a critical period, as addiction and development of opioid use disorders often occur early in treatment³⁶. We defined an incident prescription using a six-month washout period to eliminate prevalent opioid-users, as is standard in pharmacoepidemiologic studies. However, this washout period does not guarantee that patients were entirely opioid-naïve. The incident opioid prescription in our analysis could be the first opioid prescription after a period of non-exposure rather than the first ever opioid prescription. Both cases, however, warrant careful and dedicated opioid counseling for patients starting or restarting opioid treatment. Opioid risk assessment screenings such as the Brief Risk Interview, which has been found effective in predicting aberrant opioid use³⁷, may be useful among high-risk populations.

Similar to research in HIV-negative populations, we found a higher hazard for high-risk opioid use among patients with a history of IDU. We also found a significantly increased hazard for high-risk opioid use among patients age 35-55 years compared to patients age 18-35, among non-Hispanic whites compared to African Americans, and among patients with a diagnosis of chronic pain. Interestingly, we did not find an association between depression and high-risk opioid use, which is in contrast to previous literature^{15, 16, 38, 39}. The use of ICD-9 diagnostic codes to define depression may have been an imperfect identifier, as psychiatric conditions that were undiagnosed and/or did not appear in ICD-9 claims could not be examined.

Because we defined the outcome for this study using prescription claims records as a surrogate marker for opioid misuse, the increased hazard for high-risk use could be due in part to patients having more severe pain symptoms, thereby increasing the likelihood of fulfilling high-risk use criteria. One must be cautious in interpreting these results, as our study does not necessarily identify patients most likely to misuse opioids; rather we identify patients at highest risk for obtaining opioid prescriptions in patterns that are suggestive of high-risk use. For example, patients in the youngest age category were least likely to receive opioids in a high-risk pattern. This does not necessarily mean they are least likely to misuse opioids; it simply indicates that they are least likely to receive opioids in patterns that are indicative and/or predictive of possible misuse, i.e. they may be more likely to have an acute pain condition that is treated with a single prescription.

Approximately half of all patients with at least one early refill had recurrent early refills. Over a one-year period of follow-up, patients who had at least one early refill spent an average of approximately 0.75 years (39 weeks) before receiving their first early refill. The one-year RMST between refills was then shorter for each subsequent early refill. This pattern indicates that while early refills become habitual among only some patients, those who meet the early refill metric numerous times may be of particular concern.

Modifying the definition of overlapping prescriptions to exclude overlapping prescriptions that were prescribed by the same provider reduced the incidence rate by nearly 20%. While the revised definition did not dramatically impact the incidence of the composite high-risk use outcome, investigators should be cautious when using overlapping prescriptions to flag possible or probable misuse. Overlapping prescriptions, especially if they are prescribed to opioid-naïve patients by a single provider, may be an artifact of dose titration rather than opioid misuse.

We chose to use a sensitive definition for overlapping prescriptions by requiring only a one-day overlap. More stringent criteria could be used; however, we found that 75% of patients who had an overlap of at least one day also had an overlap of at least 4 days and 90% had at least 2 days of overlap, with a median number of overlapping days of 11. Therefore, we used the conservative definition for overlapping prescriptions to ensure capture of all instances of overlapping prescriptions. Even with our sensitive definition, overlapping prescriptions was the third most likely high-risk outcome to occur first among the four patterns examined.

Our study had several limitations. We were unable to determine whether patients receiving opioids from multiple prescribers did so from two or more providers within the same clinic, a pattern that may reflect a trend in practice patterns within a clinic rather than a patient's high-risk use behavior. Because we analyzed claims data, we only know whether drugs were dispensed, but not if or how the patient took the drug. Similarly, we were unable to study adverse consequences of high-risk opioid use such as addiction, overdose, or diversion. Analyzing data only from patients who were enrolled in Medicaid restricted the generalizability of the study; however, Medicaid is the largest insurer of PLWH nationally, covering approximately 40% of nonelderly PLWH in care⁴⁰. Finally, we analyzed prescriptions claims from 2006-2010, which represents an era slightly before widespread adoption of recent opioid prescribing recommendations.

Despite these limitations, our study had several strengths. The combination of two distinct data sources allowed us to address some challenges of using Medicaid data alone, including the inability of studies using claims data to examine clinical outcomes (i.e. CD4 and HIV RNA lab values) and demographic data that are often missing and/or inaccurate in claims data (i.e. race/ethnicity). Additionally, the four distinct study sites allowed us to examine utilization practices that may vary by location; the addition of even more study sites could add further value to future research.

This study extends existing knowledge about characteristics associated with high-risk opioid use to PLWH and expands on prior studies examining utilization patterns indicative of opioid misuse. We simultaneously analyzed previously described metrics for multiple

providers, overlapping prescriptions, high daily dosage, and early refills and found the highest incidence for the multiple providers indicator. Finally, we found that high-risk opioid use among PLWH was associated with a history of injection drug use, age 35-55, and white race. Our results can be used to help identify patients who may benefit most from additional opioid screening and counseling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths—United States, 2000–2014. *MMWR Morb Mortal Wkly Rep.* 2016; 64(50–51):1378–1382. [PubMed: 26720857]
2. Chang HY, Daubresse M, Kruszewski SP, Alexander GC. Prevalence and treatment of pain in EDs in the United States, 2000 to 2010. *Am J Emerg Med.* 2014; 32(5):421–431. [PubMed: 24560834]
3. Katz JA, Swerdlow MA, Brass SD, et al. Opioids for chronic noncancer pain: A position paper of the American Academy of Neurology. *Neurology.* 2015; 84(14):1503–1504. [PubMed: 25846999]
4. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend.* 2006; 81(2):103–107. [PubMed: 16023304]
5. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. *MMWR Morb Mortal Wkly Rep.* 2011; 60(43):1487–1492. [PubMed: 22048730]
6. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000–2010. *Med Care.* 2013; 51(10):870–878. [PubMed: 24025657]
7. Gilson AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. *J Pain Symptom Manage.* 2004; 28(2):176–188. [PubMed: 15276196]
8. Mack KA, Zhang K, Paulozzi L, Jones C. Prescription practices involving opioid analgesics among Americans with Medicaid, 2010. *J Health Care Poor Underserved.* 2015; 26(1):182–198. [PubMed: 25702736]
9. Centers for Disease Control and Prevention. Ten Leading Causes of Death and Injury. Available at: <https://www.cdc.gov/injury/wisqars/leadingcauses.html>
10. U S Department Of Health And Human Services. Opioid abuse in the United States and Department of Health and Human Services actions to address opioid-drug-related overdoses and deaths. *J Pain Palliat Care Pharmacother.* 2015; 29(2):133–139. [PubMed: 26095483]
11. Office of National Drug Control Policy, Executive Office of the President of the United States. Prescription Drug Abuse Prevention Plan. Washington, D C: 2011.
12. Peirce GL, Smith MJ, Abate MA, Halverson J. Doctor and pharmacy shopping for controlled substances. *Med Care.* 2012; 50(6):494–500. [PubMed: 22410408]
13. White AG, Birnbaum HG, Schiller M, Tang J, Katz NP. Analytic models to identify patients at risk for prescription opioid abuse. *Am J Manag Care.* 2009; 15(12):897–906. [PubMed: 20001171]
14. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med.* 2010; 152(2):85–92. [PubMed: 20083827]
15. Rice JB, White AG, Birnbaum HG, Schiller M, Brown DA, Roland CL. A model to identify patients at risk for prescription opioid abuse, dependence, and misuse. *Pain Med.* 2012; 13(9):1162–1173. [PubMed: 22845054]
16. Cochran BN, Flentje A, Heck NC, et al. Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: mathematical modeling using a database of commercially-insured individuals. *Drug Alcohol Depend.* 2014; 138:202–208. [PubMed: 24679839]
17. Liu Y, Logan JE, Paulozzi LJ, Zhang K, Jones CM. Potential misuse and inappropriate prescription practices involving opioid analgesics. *Am J Manag Care.* 2013; 19(8):648–665. [PubMed: 24304213]
18. Parente ST, Kim SS, Finch MD, et al. Identifying controlled substance patterns of utilization requiring evaluation using administrative claims data. *Am J Manag Care.* 2004; 10(11 Pt 1):783–790. [PubMed: 15623267]

19. Yang Z, Wilsey B, Bohm M, et al. Defining risk of prescription opioid overdose: pharmacy shopping and overlapping prescriptions among long-term opioid users in medicaid. *J Pain*. 2015; 16(5):445–453. [PubMed: 25681095]
20. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011; 305(13):1315–1321. [PubMed: 21467284]
21. PDMP Center of Excellence. Prescription Behavior Surveillance System. Available at: <http://www.pdmpassist.org/content/prescription-behavior-surveillance-system>
22. Lee AJ, Bosch RJ, Evans SR, et al. Patterns of peripheral neuropathy in ART-naïve patients initiating modern ART regimen. *J Neurovirol*. 2015; 21(2):210–218. [PubMed: 25678143]
23. Singer EJ, Zorilla C, Fahy-Chandon B, Chi S, Syndulko K, Tourtellotte WW. Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study. *Pain*. 1993; 54(1):15–19. [PubMed: 8378098]
24. Tsao JC, Plankey MW, Young MA. Pain, psychological symptoms and prescription drug misuse in HIV: A literature review. *J Pain Manag*. 2012; 5(2):111–118. [PubMed: 23826434]
25. Frich LM, Borgbjerg FM. Pain and pain treatment in AIDS patients: a longitudinal study. *J Pain Symptom Manage*. 2000; 19(5):339–347. [PubMed: 10869874]
26. Robinson-Papp J, Elliott K, Simpson DM, Morgello S. Manhattan HIV Brain Bank. Problematic prescription opioid use in an HIV-infected cohort: the importance of universal toxicology testing. *J Acquir Immune Defic Syndr*. 2012; 61(2):187–193. [PubMed: 22820804]
27. Hansen L, Penko J, Guzman D, Bangsberg DR, Miaskowski C, Kushel MB. Aberrant behaviors with prescription opioids and problem drug use history in a community-based cohort of HIV-infected individuals. *J Pain Symptom Manage*. 2011; 42(6):893–902. [PubMed: 21802896]
28. Tsao JC, Stein JA, Dobalian A. Pain, problem drug use history, and aberrant analgesic use behaviors in persons living with HIV. *Pain*. 2007; 133(1–3):128–137. [PubMed: 17449182]
29. Fleishman JA, Monroe AK, Voss CC, Moore RD, Gebo KA. Expenditures for Persons Living With HIV Enrolled in Medicaid, 2006–2010. *J Acquir Immune Defic Syndr*. 2016; 72(4):408–415. [PubMed: 26977747]
30. Byrd V, Dodd A. Assessing the Usability of Encounter Data for Enrollees in Comprehensive Managed Care Across MAX 2007–2009. 2012
31. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009; 10(2):113–130. [PubMed: 19187889]
32. Fiest KM, Jette N, Quan H, et al. Systematic review and assessment of validated case definitions for depression in administrative data. *BMC Psychiatry*. 2014; 14 289-014-0289-5.
33. Tian TY, Zlateva I, Anderson DR. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J Am Med Inform Assoc*. 2013; 20(e2):e275–80. [PubMed: 23904323]
34. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res*. 2006; 6 46-6963-6-46.
35. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: The TROUP Study. *Pain*. 2010; 150(2):332–339. [PubMed: 20554392]
36. Sartor CE, Kranzler HR, Gelernter J. Rate of progression from first use to dependence on cocaine or opioids: a cross-substance examination of associated demographic, psychiatric, and childhood risk factors. *Addict Behav*. 2014; 39(2):473–479. [PubMed: 24238782]
37. Jones T, Lookatch S, Grant P, McIntyre J, Moore T. Further validation of an opioid risk assessment tool: the Brief Risk Interview. *J Opioid Manag*. 2014; 10(5):353–364. [PubMed: 25350477]
38. Dufour R, Markekian M, Schaaf D, Andrews G, Patel N. Understanding predictors of opioid abuse: predictive model development and validation. *Am J Pharm Benefits*. 2014; 6(5):208.
39. Michna E, Ross EL, Hynes WL, et al. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. *J Pain Symptom Manage*. 2004; 28(3):250–258. [PubMed: 15336337]
40. Kates J, Garfield R, Young K, Quinn K, Frazier E, Skarbinski J. Assessing the Impact of the Affordable Care Act on Health Insurance Coverage of People with HIV. The Henry J Kaiser Family Foundation. 2014

Figure 1. Cumulative incidence of high-risk opioid use

The solid curve (the sum of Regions A through D) depicts the total cumulative incidence of any high-risk use pattern. The dashed lines depict the portion of the total cumulative incidence that each of the four high-risk use patterns contributes. Region A depicts the cumulative incidence contributed by high-daily dosage. Region B depicts the cumulative incidence contributed by overlapping prescriptions. Region C depicts the cumulative incidence contributed by early refills. Region D depicts the cumulative incidence contributed by multiple providers.

Figure 2. Time to recurrent early refills

The top panel shows the Kaplan-Meier survival function for first early refill, second early refill, and third early refill from the date of the first opioid prescription. The bottom panel depicts the Kaplan-Meier survival curves for the second and third early refills from the date of the first or second early refill, respectively.

Table 1**Descriptive statistics**

N=1,814 patients receiving at least one incident opioid prescription

Patient Characteristics	N (%)
Age at baseline (years), <i>median (IQR)</i>	44.5 (38.2, 50.2)
Sex	
Male	1,115 (61.5)
Female	699 (38.5)
Race	
African American	1,128 (62.2)
White, not Hispanic	269 (14.8)
Hispanic	399 (22.0)
Unknown/Other	18 (1.0)
State	
Maryland	558 (30.8)
Massachusetts	117 (6.5)
New York	1,139 (62.8)
IDU as HIV risk factor	567 (31.3)
Depression prior to baseline	541 (30.6)
Chronic pain prior to baseline	336 (19.0)
Nadir CD4 ^I (cells/mm ³), <i>median (IQR)</i>	282 (131, 447)
Virally suppressed at baseline ^I (<200 copies/mL)	582 (40.4)
HAART-experienced at baseline	1,077 (59.4)
Duration of follow-up (years), <i>median (IQR)</i>	2.3 (1.1, 3.5)
Total person-years of follow-up	4,175.33
Died during follow-up	146 (8.0)
Prescription Characteristics	N (%)
Total number of opioid prescriptions	16,369
Annual opioid prescriptions per person, <i>median (IQR)</i>	2 (1, 6)
Daily dosage in morphine milligram equivalents, <i>median (IQR)</i>	33 (20, 60)
Drug Enforcement Agency Class	
Long acting	2,218 (13.6)
Short acting non-Schedule II	4,025 (24.6)

Patient Characteristics	N (%)
Short acting Schedule II	10,369 (61.9)

IQR: interquartile range; IDU: injection drug use

¹ 375 patients missing baseline viral load and 289 patients missing nadir CD4

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Table 2
Summary statistics for each high-risk use behavior

N=1,814 patients receiving at least one incident opioid prescription

	Number (%) of individuals	Incidence rate per 100 person-years
High daily dosage	144 (7.9)	3.6
Early refills	289 (15.9)	7.9
Overlapping prescriptions	297 (16.4)	8.1
Multiple prescribers	358 (19.7)	10.4

Table 3
Multivariable adjusted Cox regression model for time to first high-risk opioid use behavior

N=1,436 patients with complete covariate data representing 411 events. 378 patients were excluded due to missing HIV viral load or CD4 measurements; the incidence rate of high-risk opioid use was not differential among patients excluded due to missing lab values. Model adjusted for study site.

	HR (95% CI)	p-value
Age (years)		
18 to <35	Ref	
35 to <45	1.94 (1.35-2.80)	<0.001
45 to <55	1.84 (1.27-2.67)	0.001
55 to <65	1.50 (0.95-2.37)	0.085
Male sex	1.05 (0.86-1.30)	0.626
Race		
African American	Ref	
White, not Hispanic	1.61 (1.21-2.14)	0.001
Hispanic	0.87 (0.67-1.13)	0.297
Unknown/Other	1.02 (0.38-2.75)	0.975
IDU as HIV risk factor	1.39 (1.11-1.74)	0.004
Depression diagnosis	0.90 (0.72-1.13)	0.364
Chronic pain diagnosis	1.32 (1.03-1.70)	0.028
Nadir CD4 (cells/mm ³)		
<50	Ref	
50 to <200	1.21 (0.86-1.71)	0.268
200 to <350	0.92 (0.68-1.26)	0.621
350 to <500	0.82 (0.60-1.11)	0.194
500	0.91 (0.65-1.26)	0.561
Baseline HIV viral suppression (<200 copies/mL)	0.91 (0.73-1.13)	0.386
HAART use at baseline	0.83 (0.67-1.02)	0.074

HR: hazard ratio; CI: confidence interval; Ref: reference group