Published in final edited form as:

J Acquir Immune Defic Syndr. 2015 June 1; 69(2): 223–233. doi:10.1097/QAI.0000000000000591.

Long-term prescription opioids and/or benzodiazepines and mortality among HIV-infected and uninfected patients

DF Weisberg, MD¹, KS Gordon, MS², DT Barry, PhD⁹, WC Becker, MD^{2,3}, S Crystal, PhD⁴, EJ Edelman, MD, MHS^{3,6}, J Gaither, RN, MPH⁵, AJ Gordon, MD, MPH^{7,8}, J Goulet, PhD^{2,9,10}, RD Kerns, PhD^{2,9,10}, BA Moore, PhD^{2,6,9,10}, J Tate, MPH, ScD^{2,3}, AC Justice, MD, PhD^{2,3,6}, and DA Fiellin, MD^{3,6}

¹Yale University School of Medicine, New Haven, CT

²VA Connecticut Healthcare System, West Haven, CT

³Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

⁴Institute for Health, Health Care Policy, and Aging Research, Rutgers University, New Brunswick, NJ

⁵Yale University School of Public Health, New Haven, CT

⁶Center for Interdisciplinary Research on AIDS, Yale University School of Public Health, New Haven, CT

⁷Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

⁸VA Pittsburgh Healthcare System, Pittsburgh, PA

⁹Department of Psychiatry, Yale University School of Medicine, New Haven, CT

¹⁰Pain Research, Informatics, Multi-morbidities and Education (PRIME) Center, VA Connecticut Healthcare System, West Haven, CT

Abstract

Background—Increased long-term prescribing of opioids and/or benzodiazepines necessitates evaluating risks associated with their receipt. We sought to evaluate the association between long-term opioids and/or benzodiazepines and mortality in HIV-infected patients receiving antiretroviral therapy and uninfected patients.

Methods—Prospective analysis of all-cause mortality using multivariable methods and propensity score matching among HIV-infected patients receiving antiretroviral therapy and uninfected patients.

Results—From 64,602 available patients (16,989 HIV-infected and 47,613 uninfected), 27,128 (long-term opioids and/or benzodiazepines exposed and unexposed) were 1:1 matched by propensity score. The hazard ratio (HR) for death was 1.40 (95% confidence interval [CI] 1.22–1.61) for long-term opioid receipt, 1.26 (95% CI 1.08–1.48) for long-term benzodiazepine receipt, and 1.56 (95% CI 1.26–1.92) for long-term opioid and benzodiazepine receipt. There was

an interaction ($p=0.01$) between long-term opioid receipt and HIV status with mortality. For long-term opioid receipt, the HR was 1.46 (95% CI 1.15-1.87) among HIV-infected patients, and 1.25 (95% CI 1.05 – 1.49) among uninfected patients. Mortality risk was increased for patients receiving both long-term opioids and benzodiazepines when opioid doses were 20mg morphine equivalent daily dose (MEDD) and for patients receiving long-term opioids alone when doses were 50mg MEDD.

Conclusions—Long-term opioid receipt was associated with an increased risk of death; especially with long-term benzodiazepine receipt, higher opioid doses and among HIV-infected patients. Long-term benzodiazepine receipt was associated with an increased risk of death regardless of opioid receipt. Strategies to mitigate risks associated with these medications, and caution when they are co-prescribed, are needed particularly in HIV-infected populations.

Background

In the US, prescribing and co-prescribing of opioid analgesics and benzodiazepines are increasing.¹⁻⁷ While some patients benefit from long-term (90 days) opioid therapy (e.g., for chronic pain), many do not; furthermore, side effects are common and serious adverse events are associated with higher doses.^{8,9} Similarly, the role of long-term benzodiazepines in treating anxiety¹⁰⁻¹³ and chronic insomnia¹⁴ is limited given the relative safety and efficacy of alternative treatments.¹⁵ Trends in increased prescribing of opioid and benzodiazepine medications, individually and in combination, warrant assessment of the associated risks, especially in vulnerable populations such as HIV-infected individuals. While analyses of accidental overdose deaths in the US have raised concern over concurrent opioid and benzodiazepine use, overdose may not be the exclusive driver of increased mortality associated with opioid or benzodiazepine use. For example, in observational studies, opioids and/or benzodiazepines have been associated with increased risk of admission to hospital because of falls, automobile accidents, and developing more frequent and severe pneumonia.¹⁶⁻²² Moreover, the mortality risk of combined long-term opioid and benzodiazepine receipt has not been previously evaluated.

Long-term exposure to opioids and/or benzodiazepines may elicit safety concerns due to the populations to which they are prescribed and the individual properties of these medications. Opioids and benzodiazepines are often prescribed to individuals with mental health and substance use disorders.^{23,24} In addition, the sedative properties and addiction potential of these medications may increase in combination.^{25,26} HIV-infected patients may be at increased risk for unsafe use of these medications due to their higher prevalence of polypharmacy, diminished capacity for drug metabolism and elimination²⁷ and higher rates of mental health and substance use disorders.^{28,29}

We have previously demonstrated an association between polypharmacy and mortality among HIV-infected and uninfected patients.³⁰ The harms of long-term opioid and/or benzodiazepine receipt beyond increasing medication count are unknown. The current study was designed to quantify and compare the mortality risk associated with long-term opioid and/or benzodiazepine receipt among HIV-infected patients on anti-retroviral therapy (ART) and uninfected patients. Our analysis both considers the impact of opioid dose on mortality and uses propensity score matching to address confounding by indication.³¹

Methods

Study Overview

We extracted data from the Veterans Aging Cohort Study-Virtual Cohort (VACS-VC) for fiscal year (FY) 2009 (October 1, 2008 through September 30, 2009). This period was chosen to ensure that we examined current prescribing practices, and had sufficient follow up time to test for an association with mortality. The VACS-VC has been described in detail elsewhere.³²⁻³⁵ Briefly, the VACS-VC is a prospective observational cohort consisting of HIV-infected patients matched 1:2 by age, sex, race/ethnicity, and site of care to uninfected patients identified from the US Veterans Health Administration (VHA) administrative database. The data compiled from this cohort originates from the Immunology Case Registry, a registry of HIV-infected patients, the VHA paperless electronic medical record, and the Decision Support System.^{36,37} Prior to analyses, the data are extensively cleaned and validated following established protocols. The Institutional Review Boards at Yale University and the VA Connecticut Healthcare System approved the conduct of the analyses described herein.

Study Population

We excluded individuals who 1) did not have at least 1 inpatient or outpatient clinical encounter in 2009, 2) did not have active pharmacy data, 3) had an ambiguous HIV status, 4) had any cancer diagnosis other than minor skin cancers (non-epithelial). In addition, HIV-infected patients not on ART were excluded due to their small number and the profound mortality benefit of ART, such that including patients not on ART would introduce excessive heterogeneity of mortality risk to the sample.

Opioid and Benzodiazepine Receipt

Opioid receipt was determined by pharmacy data indicating all outpatient oral and transdermal opioids as previously described.³⁸ Medications prescribed for the treatment of opioid dependence (methadone and buprenorphine) were excluded. Long-term opioid receipt, based on prescription information and the assumption that medications were taken as directed, was defined as 90 consecutive days of opioid therapy, allowing for a 30-day refill window.³⁹ Patients meeting these criteria at any point during FY 2009 were considered to have long-term opioid receipt. Average morphine equivalent daily dosages (MEDD) were estimated using standard conversion factors described in detail elsewhere.^{38,39}

Benzodiazepine receipt was determined by pharmacy data indicating receipt of the following medications: alprazolam, chlorthalidopoxide, clonazepam, clorazepam, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, and triazolam. Long-term benzodiazepine receipt was defined using the same criteria as for opioids. Long-term opioid receipt and benzodiazepine receipt was defined as 90 days of receipt of both medications at any point during 2009 whether or not the timeframes overlapped.

All-cause Mortality

Data for all-cause mortality was obtained from the VHA Vital Status File (VSF), which includes data from the VHA through the Beneficiary Identification Records Locator

Subsystem, as well as social security and Medicare data. The reliability and validity of the VSF has been established with the National Death Registry.^{40,41} We conducted surveillance for death in FY 2010, and time to death was calculated from the start of FY 2010.

Covariates

Socio-demographic variables including age, gender, and race/ethnicity were collected from hospital administrative data. Clinical variables, which included serious mental illness (major depression, bipolar disorder, post-traumatic stress disorder [PTSD], and schizophrenia), substance use disorders (drug and alcohol abuse or dependence disorders), smoking, acute and chronic pain diagnoses,³⁸ were based on International Classification of Diseases, Ninth Revision (ICD-9) diagnostic and procedure codes. Respiratory and renal diagnoses as well as factors such as hospitalization, which are thought to be associated with increased risk for benzodiazepine-related mortality,¹⁵ were identified. Hepatitis C status was based on ICD-9 codes and laboratory data.

Average long-term outpatient medication count (all medications excluding opioids, benzodiazepines, and ART) was calculated based on pharmacy data. ART was excluded from medication count due to its known mortality benefit and to facilitate appropriate comparisons between HIV-infected and uninfected patients. For HIV-infected patients, CD4 count and viral load averaged over FY2009 were collected from laboratory data. A score greater than or equal to 4 on the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C),⁴² collected as part of routine clinical care in the VHA, was used to define unhealthy alcohol use.⁴³

We used the VACS index as a measure of overall severity of illness. The VACS index is a validated prognostic measure that includes age, CD4 count, viral load, hemoglobin, FIB-4, eGFR, and hepatitis C infection, and has been shown to predict mortality in patients with HIV on ART.⁴⁴ The VACS index predicts 30-day mortality after medical intensive care unit admission in HIV-infected and uninfected patients,⁴⁵ and is correlated with functional performance,⁴⁶ fragility fractures,⁴⁷ and markers of inflammation (IL-6, D-Dimer, soluble CD14)⁴⁸ in HIV-infected patients. We assumed “normal” CD4 count (> 500 cells/mm³) and an undetectable viral load (< 20 copies/ml) in calculating the VACS Index for uninfected patients.

Statistical Analysis

Descriptive statistics were performed and stratified by HIV status. We utilized t-tests for continuous variables, or a non-parametric counterpart for non-normally distributed variables, and chi-square for categorical variables, considering $p < 0.05$ to be statistically significant.

Bivariate analyses and Cochran-Mantel Haenszel statistics established associations with the outcome of all-cause mortality. We tested for an interaction between long-term opioid receipt and long-term benzodiazepine receipt and their association with death, as well as an interaction between HIV status and long-term opioid and/or benzodiazepine receipt and their association with death.

Long-term opioid and/or benzodiazepine exposure was represented by one variable with four mutually exclusive levels: long-term opioid receipt, long-term benzodiazepine receipt, both long-term opioid and benzodiazepine receipt, and neither. Risk of death was determined by multivariable Cox proportional hazards regression adjusting for race/ethnicity, major depression, bipolar disorder, PTSD, schizophrenia, drug use disorder, alcohol use disorder, smoking status, medication count, acute pain and chronic pain diagnoses, and VACS index score.

Propensity Score Analysis

Observational studies, especially those focusing on medication receipt and mortality, are susceptible to confounding by indication, whereby patients with higher mortality risks are more likely to receive certain medications.⁴⁹ We conducted propensity score analyses to address this concern.^{50,51} A propensity score was generated based on patients' probability to receive long-term opioids and/or benzodiazepines using logistic regression, which included demographics, HIV and Hepatitis C (HCV) status, smoking, pain diagnoses, among 43 medical and psychiatric conditions. Variables were selected based on bivariate analyses and the consensus of the research team as those variables considered to have potential associations with exposure and/or outcome.⁵² We evaluated model discrimination with c-statistics and model estimates. We used the model based on exposure to long-term opioids and/or benzodiazepines because results of separate logistic regressions for receipt of long-term opioid, benzodiazepine, opioid or benzodiazepine and both opioid and benzodiazepine did not differ meaningfully. Exposed and unexposed individuals were 1:1 matched by propensity score using a greedy algorithm.⁵³ The matched sample was tested for balance based on clinical and demographic variables.

Hazard ratios for long-term opioid receipt, long-term benzodiazepine receipt, and long-term opioid and benzodiazepine receipt were generated using unadjusted Cox regression. In sensitivity analyses, separate propensity score and matching models were evaluated by HIV status. Different combinations of variables in the logistic regressions that generated the propensity scores for the HIV-infected and uninfected samples did not improve model discrimination, and the final propensity score models utilized the same variables as for the overall model. Additional sensitivity analyses were performed wherein we restricted ART exposure to 3 months, 6 months, and 12 months.

To assess the impact of opioid dose on mortality risk, we sub-categorized opioid receipt into mutually exclusive dose categories of <20, 20 to <50, 50 to <100, and 100 mg MEDD, based on previous analyses evaluating opioid overdose,^{54,55} in the overall, HIV-infected, and uninfected propensity-matched samples.

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Patient Characteristics

Our sample consisted of 64,602 individuals (16,989 HIV-infected and 47,613 uninfected). HIV-infected patients were more likely to be male, younger, and white compared to uninfected patients (Table 1). Long-term opioid receipt, benzodiazepine receipt, and long-term opioid and benzodiazepine receipt were lower in HIV-infected individuals compared to uninfected individuals. Average days with long-term opioid or benzodiazepine receipt did not differ by HIV status.

Long-term Opioid and/or Benzodiazepine Receipt and Mortality

There were 1,570 deaths: 539 (3.2%) among HIV-infected patients and 1,031 (2.2%) among uninfected patients, $p < 0.001$. Among those who died, the median time to death was 180.1 days (25th percentile, 92.0 days; 75th percentile 265 days).

Table 2 demonstrates the results of unadjusted and adjusted Cox proportional hazards models in the overall sample and stratified by HIV status.

The adjusted analyses show incremental increasing harm for long-term opioid receipt (HR 1.39, 95% CI 1.21-1.60), long-term benzodiazepine receipt (HR 1.33, 95% CI 1.10-1.62), and long-term opioid and benzodiazepine receipt (HR 1.51, 95% CI 1.22-1.87). The interaction between HIV status and long-term opioid receipt with regard to mortality was of borderline significance ($p = 0.06$), and other tested interactions were not statistically significant. The risk of death was higher among HIV-infected patients with long-term opioid receipt (1.54, 95% CI 1.21 – 1.96) compared to uninfected patients (HR 1.35, 95% CI 1.14 – 1.61). Among HIV-infected patients, the adjusted risk of death for long-term benzodiazepine receipt was not statistically significant ($p = 0.45$).

In addition, the VACS Index and several other factors were associated with mortality. Black and Hispanic individuals had lower mortality compared to White individuals. In the overall sample, each additional long-term medication count (excluding ART, opioid, benzodiazepine medications) was associated with a 5% increased relative risk of mortality (HR 1.05, 95% CI 1.04-1.07). Alcohol use disorder was associated with an increased the risk of mortality (HR 1.63, 95% CI 1.39-1.90).

Patient Characteristics in Propensity-matched Sample

Logistic regression had good discrimination (c-statistic = 0.77). From 64,602 eligible individuals, with 15,911 long-term opioid and/or benzodiazepine recipients, 13,564 pairs were included in the matched sample. Table 3 shows the baseline characteristics of the matched sample. The sample was well balanced on variables included in the logistic regression that generated the propensity score (e.g., serious mental illnesses). VACS index score was higher among patients who had not received opioids and/or benzodiazepines.

Separate propensity score models for HIV-infected and uninfected patients also showed good fit (c-statistic= 0.77 for HIV-infected and 0.76 for uninfected), and the matched samples likewise showed good balance on clinical and demographic variables.

Long-term Opioid and/or Benzodiazepine Receipt and Mortality in Propensity-matched Patients

Risk of death associated with long-term opioid receipt, long-term benzodiazepine receipt, and long-term opioid and benzodiazepine receipt in the propensity-matched sample yielded similar trends, with attenuated effect sizes, compared to the unmatched analysis. (Table 4) Long-term opioid receipt alone and long-term benzodiazepine receipt alone were associated with an increased risk for mortality (HR 1.40, 95% CI 1.22-1.61 for long-term opioid receipt, HR 1.26, 95% CI 1.08-1.48, for long-term benzodiazepine receipt); patients with both long-term opioid and benzodiazepine receipt had an increased risk for mortality above opioid or benzodiazepine receipt alone (HR 1.56, 95% CI 1.26-1.92).

The interaction between HIV status and long-term opioid receipt was significant ($p=0.01$), while other tested interactions were not statistically significant. Separate analyses for propensity-matched samples of HIV-infected patients ($n=6076$) and uninfected patients ($n=20,980$) are presented alongside the overall matched sample in Table 4. Long-term opioid receipt was associated with higher risk of mortality among HIV-infected patients compared to uninfected patients, HR 1.46 (95% CI 1.15-1.87) and HR 1.25 (1.05-1.49), respectively.

Sensitivity analyses that restricted ART exposure to 3 months, 6 months and 12 months yielded results that were similar to any ART exposure.

Opioid Dose, Benzodiazepine Receipt, and Mortality in Propensity-matched Patients

Unadjusted Cox proportional hazards models in propensity-matched patients showed a dose dependent association with death (Figure 1). Among patients receiving long-term opioids, those who received doses <50mg MEDD did not have an increased risk of death, while patients who received doses from 50mg to <100mg of morphine/day, and doses 100mg MEDD were at significantly greater risk of death, with hazard ratios of 2.00 (95% CI, 1.53-2.62) and 2.34 (95% CI, 1.91-2.86), respectively. Long-term opioid and benzodiazepine receipt was associated with increased risk of death for opioid dosages 20mg MEDD in the overall sample ($p=0.03$) and the HIV-infected sample ($p=0.06$).

Discussion

Using propensity score matching to control for confounding by indication, long-term opioid receipt was associated with a 40% increased risk of all-cause mortality; this risk was increased among those with long-term benzodiazepine receipt, and among HIV-infected patients. In addition, long-term benzodiazepine receipt was associated with increased risk of death – 26% increased risk – regardless of long-term opioid receipt. These trends were similar to the results from the multivariable adjusted Cox regression, but attenuated potentially due to confounding by indication that was unaccounted for in the multivariable model. When long-term opioid receipt was sub-categorized into dose categories, there was a dose dependent association with mortality, and a threshold of 50mg MEDD was associated with increased risk of death. Among patients with receipt of long-term opioid and benzodiazepine receipt, the threshold for increased risk of death was 20mg MEDD.

This study is the first to establish the risk for all-cause mortality among HIV-infected and uninfected patients who have received long-term opioids and/or benzodiazepines while controlling for confounding by indication. In addition, this study adds to the literature in establishing a risk of mortality for long-term benzodiazepine receipt alone and in the setting of long-term opioid receipt.¹³

The use of long-term opioids for chronic pain is the subject of scientific debate and public scrutiny due to limited evidence for their long-term efficacy and safety,^{8,56} their potential for abuse,⁵⁷ their contribution to addiction^{58,59} and increasing trends in fatal and non-fatal prescription drug overdose.^{54,55,60,61} Of the many potential reasons for our findings of increased mortality in individuals with long-term opioid and benzodiazepine receipt, one is the risk of overdose conferred by these medications. Opioids and benzodiazepines have independent and synergistic effects that can lead to overdose.^{25,62} Studies have shown that receipt of greater than 50mg MEDD is associated with an increased risk of overdose death.^{54,55,61} However, these studies did not use propensity score matching, or consider benzodiazepine receipt or HIV status.

In comparison to opioids, benzodiazepines, used alone, have a wider therapeutic index. However, in combination with opioids, benzodiazepines are more prone to pharmacodynamic and pharmacokinetic interactions that can lead to respiratory depression. Alprazolam, midazolam, triazolam, codeine, fentanyl, hydrocodone, oxycodone, and methadone all undergo metabolism by CYP3A4.⁶² Of particular relevance to HIV-infected individuals, protease inhibitors, some macrolides and some azoles may also interact with both benzodiazepines and opioids via CYP3A4 and CYP2D6 inhibition leading to increased blood levels of opioids and benzodiazepines among patients co-prescribed these medications.^{63,64} These pharmacokinetic interactions may contribute to our finding of increased risk of death among HIV-infected patients who received long-term opioids and benzodiazepines compared to uninfected patients, and the lower opioid dose threshold associated with mortality among HIV-infected patients. HIV-infected patients have higher rates of overdose than uninfected patients.⁶⁵

Overdose is not the only potential cause of mortality for patients who have received long-term opioids and/or benzodiazepines. Opioids are known to cause cardiac, endocrine, gastrointestinal, and central nervous system disturbances, which may precipitate hospitalizations and/or interact with other disease processes.⁶⁶ In addition, falls, fractures, and motor vehicle accidents are associated with opioid and/or benzodiazepine receipt.^{13,67,68} Patients receiving long-term opioids are more likely to have alcohol and drug use disorders,⁶⁹ and patients receiving opioids and benzodiazepines are likely to receive multiple additional medications.^{1,70} We observed increased risk associated with alcohol use disorders and polypharmacy. Polypharmacy is associated with non-adherence, adverse drug reactions, drug-drug interactions, diminished activities of daily living, increased health service utilization, and cognitive impairments and falls, even after controlling for disease burden.^{27,71-73}

Our results also showed that Black race and Hispanic ethnicity were negatively associated with all-cause mortality in multivariable Cox regression. Other studies have found that

Blacks and Hispanics are less likely to receive opioids and benzodiazepines compared to Whites,^{5,38,74} and that Black race is inversely associated with opioid overdose.⁵⁵ In contrast, among HIV-infected patients, non-white race has been shown to be associated with increased risk of mortality.⁷⁵ Future research should investigate whether protective factors independent of and related to opioid and benzodiazepine receipt mitigate harm among Black and Hispanic patients.

Our study has limitations. First, although propensity score matching offers the potential to control for confounding by indication, it can account for only known and observed patient characteristics.⁵⁰ It is possible that unknown or unmeasured characteristics (eg. pain intensity, degree of disability) affected our results. In addition, the use of administrative codes may have limited our ability to identify conditions important to long-term opioid and/or benzodiazepine receipt.⁷⁶ Our analysis accounted only for long-term opioid and/or benzodiazepine receipt during 2009. As is standard in large-scale epidemiologic studies, our exposure variables were based on prescription fills, not medication consumed. Patients may not have still been receiving the long-term prescriptions at the time of death. Prior analyses of opioid overdose have demonstrated that 40% of overdose victims did not have active opioid prescriptions at the time of death, highlighting the challenges in ascribing a causal relationship to prescription and overdose.⁵⁵

Of note, surveillance for death occurred in FY 2010, and patients who died in FY 2009 were excluded, creating the potential for biasing our results toward the null hypothesis.⁷⁷ In addition, we studied only VHA pharmacy usage; patients may have accessed other licit or illicit medication sources. Use of opioids and/or benzodiazepines obtained illicitly can increase the risk for overdose.⁶⁰ Finally, our results may not be generalizable to women and men who do not receive medical care in the VHA system.

In recent years, the VHA has sought to restrain co-prescription of opioids and benzodiazepines as part of its Opioid Safety Initiative. In light of increasing prescriptions and limited efficacy of long-term opioids and benzodiazepines, our results support the imperative within the VHA and nationally to mitigate the risk associated with receipt of long-term opioids and/or benzodiazepines, and use caution in co-prescribing, especially among HIV-infected individuals, who are at increased overall risk for death. Our study adds to a nascent understanding of the overlapping harms associated with psychoactive substance co-prescribing, and should help inform interventions and research seeking to balance the risks and benefits in patients who are prescribed long-term opioids and benzodiazepines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: NIH Grants U01 AA020790; U24 AA020794; U10 AA 13566. Also, the Office of Medical Student Research, Yale School of Medicine, New Haven CT and

Conflicts of Interest: Dr. Fiellin has received honoraria from Pinney Associates for serving on an external advisory board monitoring the diversion and abuse of buprenorphine.

Role of the Funding Source: Funding for this study was provided by the Office of Medical Student Research, Yale School of Medicine, New Haven CT, and the Veterans Aging Cohort study, funded by the National Institute on Alcohol Abuse and Alcoholism [U10 AA 13566].

References

1. Mojtabai R, Olfson M. National trends in psychotropic medication polypharmacy in office-based psychiatry. *Arch Gen Psychiatry*. 2010; 67:26–36. [PubMed: 20048220]
2. Olsen Y, Daumit GL, Ford DE. Opioid prescriptions by U.S. primary care physicians from 1992 to 2001. *J Pain*. 2006; 7:225–35. [PubMed: 16618466]
3. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. *Journal of general internal medicine*. 2002; 17:173–9. [PubMed: 11929502]
4. Braden JB, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000–2005 among Arkansas Medicaid and HealthCore enrollees: results from the TROUP study. *J Pain*. 2008; 9:1026–35. [PubMed: 18676205]
5. Pletcher MJ, Kertesz SG, Kohn MA, Gonzales R. Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency departments. *JAMA*. 2008; 299:70–8. [PubMed: 18167408]
6. Becker WC, G K, Edelman EJ, Kerns R, Crystal S, Dziura J, Fiellin L, Gordon A, Goulet J, Justice A, Fiellin D. Trends in opioid analgesic receipt among patients with and without HIV. *SGIM national Meeting*. 2013
7. Hawkins EJ, Malte CA, Imel ZE, Saxon AJ, Kivlahan DR. Prevalence and trends of benzodiazepine use among Veterans Affairs patients with posttraumatic stress disorder, 2003–2010. *Drug Alcohol Depend*. 2012; 124:154–61. [PubMed: 22305658]
8. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010:CD006605. [PubMed: 20091598]
9. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med*. 2010; 363:1981–5. [PubMed: 21083382]
10. Uhlenhuth EH, Balter MB, Ban TA, Yang K. Trends in recommendations for the pharmacotherapy of anxiety disorders by an international expert panel, 1992–1997. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 1999; 9(Suppl 6):S393–8. [PubMed: 10622685]
11. Reinhold JA, Mandos LA, Rickels K, Lohoff FW. Pharmacological treatment of generalized anxiety disorder. *Expert Opin Pharmacother*. 2011; 12:2457–67. [PubMed: 21950420]
12. Offidani E, Guidi J, Tomba E, Fava GA. Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. *Psychotherapy and psychosomatics*. 2013; 82:355–62. [PubMed: 24061211]
13. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. *Pharmacoepidemiol Drug Saf*. 2009; 18:93–103. [PubMed: 19125401]
14. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *Journal of general internal medicine*. 2007; 22:1335–50. [PubMed: 17619935]
15. Amarasuriya UK, Myles PR, Sanders RD. Long-term benzodiazepine use and mortality: are we doing the right studies? *Current drug safety*. 2012; 7:367–71. [PubMed: 23373552]
16. Khademi H, Malekzadeh R, Pourshams A, et al. Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50,000 adults in Iran. *BMJ*. 2012; 344:e2502. [PubMed: 22511302]
17. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010; 170:1968–76. [PubMed: 21149752]
18. Gomes T, Juurlink DN, Dhalla IA, Mailis-Gagnon A, Paterson JM, Mamdani MM. Trends in opioid use and dosing among socio-economically disadvantaged patients. *Open Med*. 2011; 5:e13–22. [PubMed: 22046214]

19. Huang AR, Mallet L, Rochefort CM, Egualé T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. *Drugs Aging*. 2012; 29:359–76. [PubMed: 22550966]
20. Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med*. 2010; 170:1979–86. [PubMed: 21149754]
21. Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. *J Am Geriatr Soc*. 2011; 59:1899–907. [PubMed: 22091503]
22. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *Journal of internal medicine*. 2013; 273:511–26. [PubMed: 23331508]
23. Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain*. 2007; 23:307–15. [PubMed: 17449991]
24. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006; 166:2087–93. [PubMed: 17060538]
25. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug Alcohol Depend*. 2012; 125:8–18. [PubMed: 22857878]
26. Vogel M, Knopfli B, Schmid O, et al. Treatment or “high”: benzodiazepine use in patients on injectable heroin or oral opioids. *Addict Behav*. 2013; 38:2477–84. [PubMed: 23770646]
27. Edelman EJ, Gordon KS, Glover J, McNicholl IR, Fiellin DA, Justice AC. The Next Therapeutic Challenge in HIV: Polypharmacy. *Drugs Aging*. 2013; 30:613–28. [PubMed: 23740523]
28. Bing EG, Burnam MA, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of general psychiatry*. 2001; 58:721–8. [PubMed: 11483137]
29. 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; 42:893–902. [PubMed: 21802896]
30. Edelman, JE.; G, K.; Akgun, K.; Gibert, C.; Lo Re, V., III; McNicholl, I.; Rimland, D.; Skanderson, M.; Tate, J.; Womack, J.; Wyatt, C.; Justic, AC. ID Week 2013. San Francisco, CA: Oct 2-6. 2013 HIV+ individuals on ART are at risk of polypharmacy: more medication increases mortality. Abstract 76 <https://idsaconfexcom/idsa/2013/webprogram/Paper42415.html> 2013
31. Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. *American journal of epidemiology*. 1999; 149:981–3. [PubMed: 10355372]
32. Tetrault JM, Tate JP, McGinnis KA, et al. Hepatic safety and antiretroviral effectiveness in HIV-infected patients receiving naltrexone. *Alcoholism, clinical and experimental research*. 2012; 36:318–24.
33. Butt AA, Chang CC, Kuller L, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. *Arch Intern Med*. 2011; 171:737–43. [PubMed: 21518940]
34. Freiberg MS, Chang CC, Skanderson M, et al. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. *Circulation Cardiovascular quality and outcomes*. 2011; 4:425–32. [PubMed: 21712519]
35. Fultz SL, Skanderson M, Mole LA, et al. Development and verification of a “virtual” cohort using the National VA Health Information System. *Medical care*. 2006; 44:S25–30. [PubMed: 16849965]
36. Smith MW, Joseph GJ. Pharmacy data in the VA health care system. *Medical care research and review* : MCRR. 2003; 60:92S–123S. [PubMed: 15095548]
37. Centers for Medicare and Medicaid Services. [Accessed 8-20-2013] ICD-9 Provider and Diagnostic Codes. 2011. <http://www.cms.gov/Medicare/Coding/ICD9ProviderDiagnosticCodes/index.html>
38. Edelman EJ, Gordon K, Becker WC, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. *Journal of general internal medicine*. 2013; 28:82–90. [PubMed: 22895747]

39. Korff MV, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. *Clin J Pain*. 2008; 24:521–7. [PubMed: 18574361]
40. Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. *Annals of epidemiology*. 2002; 12:462–8. [PubMed: 12377423]
41. Fisher SG, Weber L, Goldberg J, Davis F. Mortality ascertainment in the veteran population: alternatives to the National Death Index. *American journal of epidemiology*. 1995; 141:242–50. [PubMed: 7840098]
42. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med*. 1998; 158:1789–95. [PubMed: 9738608]
43. Seale JP, Boltri JM, Shellenberger S, et al. Primary care validation of a single screening question for drinkers. *Journal of studies on alcohol*. 2006; 67:778–84. [PubMed: 16847548]
44. Justice AC, Modur SP, Tate JP, et al. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. *Journal of acquired immune deficiency syndromes*. 2013; 62:149–63. [PubMed: 23187941]
45. Akgun KM, Tate JP, Pisani M, et al. Medical ICU admission diagnoses and outcomes in human immunodeficiency virus-infected and virus-uninfected veterans in the combination antiretroviral era. *Critical care medicine*. 2013; 41:1458–67. [PubMed: 23507717]
46. Erlandson KM, Allshouse AA, Jankowski C. Prospective comparison of three functional assessments with the Veteran's Aging Cohort Study index in virologically suppressed HIV-infected adults. 2nd International Workshop on HIV and Aging. 2011
47. Womack JA, Goulet JL, Gibert C, et al. Physiologic frailty and fragility fracture in HIV-infected male veterans. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2013; 56:1498–504. [PubMed: 23378285]
48. Justice AC, Freiberg MS, Tracy R, et al. Does an index composed of clinical data reflect effects of inflammation, coagulation, and monocyte activation on mortality among those aging with HIV? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2012; 54:984–94. [PubMed: 22337823]
49. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic & clinical pharmacology & toxicology*. 2006; 98:253–9. [PubMed: 16611199]
50. Freemantle N, Marston L, Walters K, Wood J, Reynolds MR, Petersen I. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. *BMJ*. 2013; 347:f6409. [PubMed: 24217206]
51. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *American journal of epidemiology*. 1999; 150:327–33. [PubMed: 10453808]
52. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *American journal of epidemiology*. 2006; 163:1149–56. [PubMed: 16624967]
53. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Statistics in medicine*. 2014; 33:1242–58. [PubMed: 24122911]
54. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010; 152:85–92. [PubMed: 20083827]
55. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011; 305:1315–21. [PubMed: 21467284]
56. Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *Journal of Pain*. 2009; 10:147–59. [PubMed: 19187891]
57. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction

- and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Medicine*. 2008; 9:444–59. [PubMed: 18489635]
58. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007; 146:116–27. [PubMed: 17227935]
 59. Minozzi S, Amato L, Davoli M. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. *Addiction*. 2013; 108:688–98. [PubMed: 22775332]
 60. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008; 300:2613–20. [PubMed: 19066381]
 61. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011; 171:686–91. [PubMed: 21482846]
 62. Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract*. 2014; 27:5–16. [PubMed: 24436437]
 63. Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. *Current HIV/AIDS reports*. 2010; 7:152–60. [PubMed: 20532839]
 64. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. *Am J Addict*. 2010; 19:4–16. [PubMed: 20132117]
 65. Green TC, McGowan SK, Yokell MA, Pouget ER, Rich JD. HIV infection and risk of overdose: a systematic review and meta-analysis. *AIDS*. 2012; 26:403–17. [PubMed: 22112599]
 66. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008; 11:S105–20. [PubMed: 18443635]
 67. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *Journal of general internal medicine*. 2010; 25:310–5. [PubMed: 20049546]
 68. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009; 169:1952–60. [PubMed: 19933955]
 69. Saunders KW, Von Korff M, Campbell CI, et al. Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: prevalence and risk factors. *Journal of Pain*. 2012; 13:266–75. [PubMed: 22285611]
 70. Parsells Kelly J, Cook SF, Kaufman DW, Anderson T, Rosenberg L, Mitchell AA. Prevalence and characteristics of opioid use in the US adult population. *Pain*. 2008; 138:507–13. [PubMed: 18342447]
 71. Shah BM, Hajjar ER. Polypharmacy, adverse drug reactions, and geriatric syndromes. *Clinics in geriatric medicine*. 2012; 28:173–86. [PubMed: 22500537]
 72. Azar MM, Springer SA, Meyer JP, Altice FL. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. *Drug Alcohol Depend*. 2010; 112:178–93. [PubMed: 20705402]
 73. Cargiulo T. Understanding the health impact of alcohol dependence. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. 2007; 64:S5–11. [PubMed: 17322182]
 74. Yang HW, Simoni-Wastila L, Zuckerman IH, Stuart B. Benzodiazepine use and expenditures for Medicare beneficiaries and the implications of Medicare Part D exclusions. *Psychiatric services*. 2008; 59:384–91. [PubMed: 18378837]
 75. McGinnis KA, Fine MJ, Sharma RK, et al. Understanding racial disparities in HIV using data from the veterans aging cohort 3-site study and VA administrative data. *American journal of public health*. 2003; 93:1728–33. [PubMed: 14534229]
 76. Sinnott PL, Siroka AM, Shane AC, Trafton JA, Wagner TH. Identifying neck and back pain in administrative data: defining the right cohort. *Spine*. 2012; 37:860–74. [PubMed: 22127268]
 77. Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf*. 2007; 16:241–9. [PubMed: 17252614]

Figure 1. Daily opioid dose, benzodiazepine receipt, and mortality in propensity-matched samples

Table 1
Baseline patient characteristics by HIV status

	HIV -	HIV +	P value
Number of patients n	47613	16989	-
Age mean (SD)	48.59 (9.1)	45.82 (9.8)	<0.001
Gender, n (%)			
Male	46303 (97.3)	16584 (97.6)	0.01
Race/Ethnicity, n (%)			
White	19125 (40.2)	6901 (40.6)	0.004
Black	22489 (47.2)	8018 (47.2)	
Hispanic	4104 (8.6)	1332 (7.8)	
Other	1895 (4.0)	738 (4.3)	
Serious mental illness, n (%)			
Major Depression	3402 (7.2)	1353 (8.0)	0.0004
PTSD	7042 (14.8)	1237 (7.3)	<0.001
Bipolar Disorder	2840 (6.0)	870 (5.1)	<0.001
Schizophrenia	3006 (6.3)	372 (2.2)	<0.001
Drug use disorder, n (%)	4663 (9.8)	2234 (13.2)	<0.001
Receiving methadone as opioid agonist treatment, n (%)	429 (0.9)	189 (1.1)	0.02
Receiving buprenorphine as opioid agonist treatment, n (%)	127 (0.3)	55 (0.3)	0.23
Alcohol use disorder, n (%)	5385 (11.3)	1670 (9.8)	<0.001
AUDIT-C score mean (SD)	1.44 (2.4)	1.36 (2.1)	0.0002
AUDIT-C 4	5696 (12.0)	1625 (9.6)	<0.001
Smoking			
Never	13966 (30.1)	4838 (29.1)	<0.001
Current	23647 (51.0)	9282 (55.9)	
Past	8778 (18.9)	2501 (15.1)	
Pain-related diagnosis, n (%)			
No pain	22233 (46.7)	10228 (60.2)	<0.001
Acute pain ^a	2031 (4.3)	933 (5.5)	
Chronic pain ^b	23349 (49.0)	5828 (34.3)	
Medication count, mean (sd) ^c	4.9 (3.6)	4.2 (3.2)	<0.001
Hepatitis C, n (%)	7289 (15.3)	5572 (32.8)	<0.001
End Stage Liver Disease, n (%)	455 (0.96)	258 (1.52)	<0.001
Cirrhosis, n (%)	442 (0.93)	245 (1.44)	<0.001
CD4 count mean (SD)	-	359.9 (269.4)	-
Quartile 1	-	70.8 (50.0)	-
Quartile 2	-	242.7 (46.0)	-
Quartile 3	-	407.81 (51.5)	-
Quartile 4	-	717 (234.3)	-

	HIV -	HIV +	P value
Viral load<500 n (%)	-	6357 (37.4)	-
VACs Index ^d mean, (sd)	12.0 (12.1)	31.5 (22.6)	<0.001
Opioid receipt, n (%)			
Any receipt	20650 (43.4)	6548 (38.5)	<0.001
Long-term (90days)	9224 (19.4)	2550 (15.0)	<0.001
Days with receipt, mean (sd)	276.2 (81.9)	279.4 (81.9)	0.08
Without benzodiazepine ^e	6964 (14.7)	1943 (11.4)	<0.001
0 to <20 mg morphine ^f	2276 (4.8)	567 (3.3)	<0.001
20 to <50 mg morphine	3965 (8.4)	1013 (6.0)	
50 to <100 mg morphine	1111 (2.3)	315 (1.9)	
100 mg morphine	1872 (3.9)	655 (3.9)	
Benzodiazepine receipt, n (%)			
Long-term (90days)	5452 (11.5)	1552 (9.1)	<0.001
Without opioid ^g	3192 (6.7)	945 (5.6)	<0.001
Days with receipt, mean (sd)	282.2 (83.3)	281.6 (86.5)	0.65
Long-term opioid and benzodiazepine receipt, n (%)	2260 (4.8)	607 (3.6)	<0.001

^a Acute pain diagnoses include abdominal pain, chest pain, fracture, and kidney stone

^b Chronic pain diagnoses include back pain, extremity pain, headache, menstrual pain, neck pain, neuropathy, osteoarthritis, other pain, rheumatoid arthritis, and temporomandibular pain

^c Excludes opioid, benzodiazepine, ART receipt

^d VACS index score was considered in 5-point increments

^e Long-term opioid receipt with long-term benzodiazepine receipt

^f Milligrams of morphine denotes the equivalent milligrams of morphine per day based on standard conversion factors

^g Long-term benzodiazepine receipt without long-term opioid receipt

Table 2
Unadjusted and adjusted risk of death for opioid and/or benzodiazepine receipt by HIV status

Model	Variable	Overall (n=6441)		Uninfected (n=47452)		HIV-infected (n=16989)	
		HR (95% CI) ^a	P	HR (95% CI)	P	HR (95% CI)	P
Unadjusted Cox proportional hazards models	Long-term opioid receipt ^b	1.49 (1.33 – 1.67)	<0.001	1.36 (1.19 – 1.57)	<0.001	1.94 (1.28 – 2.06)	<0.001
	Long-term benzodiazepine receipt	1.38 (1.21 – 1.59)	<0.001	1.38 (1.17 – 1.63)	0.0002	1.51 (1.18 – 1.93)	0.002
	Long-term opioid and benzodiazepine receipt	1.54 (1.27 – 1.87)	<0.001	1.40 (1.10 – 1.78)	0.006	2.03 (1.47 – 2.81)	<0.001
	Long-term medication count ^c	1.06 (1.05 – 1.08)	<0.001	1.06 (1.05 – 1.08)	<0.001	1.07 (1.05 – 1.10)	<0.001
Adjusted Cox proportional hazards model	Long-term opioid receipt ^b	1.39 (1.21, 1.60)	<0.001	1.35 (1.14, 1.61)	0.0006	1.54 (1.21, 1.96)	0.001
	Long-term benzodiazepine receipt	1.33 (1.10, 1.62)	0.004	1.41 (1.12, 1.78)	0.003	1.16 (0.80, 1.68)	0.45
	Long-term opioid and benzodiazepine receipt	1.51 (1.22, 1.87)	0.0001	1.43 (1.10, 1.86)	0.008	1.82 (1.27, 2.62)	0.001
	Long-term medication count ^c	1.05 (1.04, 1.07)	<0.001	1.04 (1.03, 1.06)	<0.001	1.05 (1.02, 1.08)	0.0002
	Alcohol use disorder	1.63 (1.39, 1.90)	<0.001	1.56 (1.30, 1.88)	<0.001	1.53 (1.17, 2.02)	0.002
	Drug use disorder	0.95 (0.81, 1.13)	0.59	0.88 (0.70, 1.11)	0.28	1.16 (0.89, 1.51)	0.27
	Schizophrenia	1.14 (0.92, 1.40)	0.23	1.09 (0.86, 1.38)	0.49	1.45 (0.94, 2.25)	0.09
	Bipolar	0.92 (0.74, 1.14)	0.44	0.93 (0.71, 1.22)	0.60	1.03 (0.72, 1.47)	0.88
	Major Depression	0.95 (0.79, 1.15)	0.62	1.07 (0.84, 1.35)	0.59	0.86 (0.63, 1.17)	0.33
	PTSD	0.79 (0.68, 0.93)	0.004	0.75 (0.63, 0.91)	0.003	0.88 (0.64, 1.20)	0.41
	Acute pain ^d	1.72 (1.43, 2.08)	<0.001	1.76 (1.39, 2.23)	<0.001	1.70 (1.26, 2.31)	0.001
	Chronic pain ^e	0.93 (0.83, 1.05)	0.24	0.93 (0.81, 1.07)	0.29	0.95 (0.78, 1.17)	0.64
	Black vs. white	0.86 (0.77, 0.96)	0.006	0.81 (0.70, 0.92)	0.002	0.90 (0.74, 1.09)	0.28
	Hispanic vs. white	0.58 (0.45, 0.73)	<0.001	0.56 (0.42, 0.75)	<0.001	0.57 (0.38, 0.87)	0.009
	Other vs white	0.87 (0.63, 1.18)	0.37	0.88 (0.60, 1.29)	0.51	0.81 (0.47, 1.40)	0.46
	VACS Index score	1.12 (1.11, 1.13)	<0.001	1.23 (1.21, 1.25)	<0.001	1.08 (1.06, 1.10)	<0.001
	Current smoking vs. never	1.87 (1.62, 2.15)	<0.001	2.01 (1.69, 2.39)	<0.001	1.80 (1.41, 2.30)	<0.001
	Past smoking vs. never	1.43 (1.21, 1.70)	<0.001	1.37 (1.11, 1.68)	0.003	1.43 (1.04, 1.96)	0.03

^a CI indicates confidence interval

^b Opioid receipt, benzodiazepine receipt, both opioid and benzodiazepine receipt, and neither were represented by a 4-level, mutually exclusive variable, with “neither” as the reference category.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^c Excludes opioid, benzodiazepine, ART receipt

^d Acute pain diagnoses include abdominal pain, chest pain, fracture, kidney stone

^e Chronic pain diagnoses include back pain, extremity pain, headache, menstrual pain, neck pain, neuropathy, osteoarthritis, other pain, rheumatoid arthritis, temporomandibular pain

Table 3
Patient characteristics in propensity-matched sample

	Opioid and/or benzodiazepine receipt		
	Yes, n (%)	No, n (%)	P value
Number of patients n	13564	13564	-
Age mean (SD)	47.5 (8.3)	47.8 (9.1)	0.03
Gender, n (%)	13202 (97.3)	13227 (97.5)	0.34
Male			
Race/Ethnicity, n (%)			0.87
White	6632 (48.9)	6627 (48.8)	
Black	5315 (39.2)	5351 (39.2)	
Hispanic	1216 (9.0)	1205 (8.9)	
Other	401 (3.0)	381 (2.8)	
HIV+	3029 (22.3)	3039 (22.4)	0.88
Serious mental illness, n (%)			
Major Depression	1496 (11.0)	1440 (10.6)	0.27
PTSD	2510 (18.5)	2538 (18.7)	0.66
Bipolar Disorder	1127 (8.3)	1099 (8.1)	0.53
Schizophrenia	884 (6.5)	949 (7.0)	0.12
Drug use disorder, n (%)	1644 (12.1)	1725 (12.7)	0.14
Alcohol use disorder, n (%)	1591 (11.7)	1645 (12.1)	0.31
Hospitalization, n (%)	2572 (19.0)	2636 (19.4)	0.32
COPD ^a	1197 (8.8)	1181 (8.7)	0.73
Renal insufficiency	470 (3.5)	514 (3.8)	0.15
Smoking			<0.001
Never	3231 (23.8)	3701 (27.3)	
Current	8127 (59.9)	7061 (52.1)	
Past	2206 (16.3)	2802 (20.7)	
Pain-related diagnosis, n (%)			0.05
No pain	4308 (31.8)	4131 (30.5)	
Acute pain ^b	536 (4.0)	575 (4.2)	
Chronic pain ^c	8720 (64.3)	8858 (65.3)	
Long-term Medication count, mean (sd) ^d	5.8 (3.6)	5.7 (3.8)	0.12
Hepatitis C, n (%)	3184 (23.5)	3330 (24.6)	0.04
End Stage Liver Disease, n (%)	201 (1.5)	189 (1.4)	0.54
Cirrhosis, n (%)	193 (1.4)	181 (1.3)	0.53
VACs Index mean, (sd)	15.8 (16.8)	16.5 (17.3)	0.001

^a Chronic obstructive pulmonary disease

^b Acute pain diagnoses include abdominal pain, chest pain, fracture, kidney stone

^c Chronic pain diagnoses include back pain, extremity pain, headache, menstrual pain, neck pain, neuropathy, osteoarthritis, other pain, rheumatoid arthritis, temporomandibular pain

^d Excludes opioid, benzodiazepine, ART receipt

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4
Unadjusted risk of death for opioid and/or benzodiazepine receipt in propensity-matched samples

Variable	Overall		HIV -		HIV +	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Long-term opioid receipt	1.40 (1.22 – 1.61)	<0.001	1.25 (1.05 – 1.49)	0.01	1.46 (1.15 – 1.87)	0.002
Long-term benzodiazepine receipt	1.26 (1.08 – 1.48)	0.004	1.31 (1.08 – 1.58)	0.007	1.05 (0.79 – 1.41)	0.71
Long-term opioid and benzodiazepine receipt	1.56 (1.26 – 1.92)	<0.001	1.29 (0.98 – 1.71)	0.07	1.65 (1.15 – 2.38)	0.007