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Research Paper

The impact of high-dose opioid prescription on mortality rates among people living with HIV: A retrospective cohort study

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A B S T R A C T

Objectives: High-dose opioid use is associated with increased morbidity, mortality, and healthcare utilization. People living with HIV (PLHIV) are frequently prescribed these medications to manage their pain. However, little is known about the relationship between being prescribed high doses of opioids (> 90 MME/d) and mortality risk among this population. The objective of this study was to examine the trends in mortality and the relationship between high-dose opioid analgesic prescribing and mortality among PLHIV.

Methods: Utilizing the STOP HIV/AIDS cohort—a population-level linked database of treatment of PLHIV in British Columbia—we conducted bivariable and multivariable generalized estimating equation (GEE) models with a Poisson distribution to examine the relationship between high-dose opioid prescription and all-cause mortality rates in the study sample.

Results: Between 1996 and 2015, 9272 PLHIV were included in the study. Age- and sex-adjusted mortality rate (using the 2011 Canadian population as the reference) was 30.99 per 1000 person-years (95% confidence interval [CI]: 28.11–33.88). In a multivariable GEE model with adjustment for various demographic and clinical confounders, there was a positive and independent association between being prescribed high-dose opioids and all-cause mortality rates (adjusted rate ratio [ARR] = 3.01; 95%CI: 2.47–3.66).

Discussion: We found that mortality rates were significantly higher among PLHIV who were prescribed high-dose opioids compared to those who were prescribed lower doses. Our results highlight the risk associated with the prescribing of high-dose opioids to manage HIV-related pain and emphasize the need to explore non-opioid approaches to pain management.

Introduction

Many people living with HIV (PLHIV) experience HIV-related pain, frequently in the form of peripheral neuropathic pain and non-neuropathic pain (nociceptive pain due to tissue injury and musculoskeletal pain) (Bruce *et al.*, 2017; Krashin, Merrill & Trescot, 2012). Estimates suggest the prevalence of pain among PLHIV ranges from 30 – 90% and it has been noted that this proportion increases in the later stages of HIV (Krashin *et al.*, 2012). Furthermore, PLHIV also experience comorbidities and exposures to socio-structural environments that may increase their risk of pain. For instance, the literature suggests that PLHIV are more likely to have experienced significant trauma in forms such as intimate partner violence and childhood abuse than the general population (Nightingale, Sher, Mattson, Thilges & Hansen, 2011; Pence *et al.*, 2007; Plotzker, Metzger & Holmes, 2007). PLHIV also have a high prevalence of psychiatric comorbidities (e.g., Post-traumatic Stress Disorder (PTSD), depression, anxiety) that may make them more vulnerable to experiencing pain (Nightingale *et al.*, 2011; Pence *et al.*, 2007; Plotzker *et al.*, 2007).

Various pharmacological and non-pharmacological pain management modalities exist for PLHIV, including opioid and non-opioid pain relievers, adjuvant therapies, psychotherapies and physical therapies (Bruce *et al.*, 2017; Krashin *et al.*, 2012). However, recent guidelines caution against the prescribing of opioid analgesics as a first line agent for long term management of chronic neuropathic and non-neuropathic pain due to the risk profile of opioids which includes pronociception, cognitive impairment, addiction, misuse and more (Bruce *et al.*, 2017). These guidelines do, however, state that a time limited trial of opioid analgesics may be considered for PLHIV who are experiencing moderate to severe pain and are not responsive to first line therapies such as gabapentin for neuropathic pain or acetaminophen/NSAIDs for non-neuropathic pain (Bruce *et al.*, 2017; Busse *et al.*, 2017).

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Despite this, opioids are commonly, and at an increasing rate, being prescribed in potent, long-acting, high-dose formulations for pain management (Bruce *et al.*, 2017; Busse *et al.*, 2017; Ottawa, 2017). These prescribing patterns are not limited to North American populations only; in fact, studies in both Australia and other European countries (e.g., Britain, Germany and Spain) report significant increases in opioid prescribing over the last 10–20 years, albeit, at lower rates than in North America (Blanch, Pearson & Haber, 2014; Garcia del Pozo, Carvajal, Viloria, Velasco & Garcia del Pozo, 2008; Karanges, Blanch, Buckley, & Pearson, 2016; Schubert, Ihle & Sabatowski, 2013). Moreover, there is evidence to suggest that high-dose and/or long term opioid prescriptions may be particularly problematic for PLHIV (Becker *et al.*, 2016; Weisberg *et al.*, 2015). A 2015 study revealed that long term prescription opioid use is associated with increased mortality risk in HIV patients compared to the general population (Becker *et al.*, 2016; Weisberg *et al.*, 2015). In PLHIV, opioid abuse may accelerate disease progression by disrupting immune-mediated gut homeostasis and by exacerbating the neuropathogenic mechanisms of HIV itself (Liu, Liu & Tang, 2016; Meng, Sindberg & Roy, 2015; Weisberg *et al.*, 2015). Opioids have also been shown to interact with multiple antiretroviral medications, azoles and macrolides resulting in sub-optimal treatment of HIV infection and opioid toxicity (Becker *et al.*, 2016; Gruber & McCance-Katz, 2010; McCance-Katz, Sullivan & Nallani, 2010; Weisberg *et al.*, 2015).

A growing body of literature has demonstrated a wide array of negative outcomes associated with high-dose opioid prescription though much of the research to date has focused on the general population (Gomes, Mamdani, Dhalla, Paterson & Juurlink, 2011; Krashin *et al.*, 2012; Ottawa, 2017). Specifically, studies found a dose dependent relationship between opioid dosage and opioid-related mortality among the general population (Dasgupta *et al.*, 2016; Gomes *et al.*, 2011). These studies noted no distinct risk threshold for increased opioid overdose risk and found that while doses exceeding 200 MME/d posed a particularly high opioid overdose risk, intermediate opioid doses (50 – 199 MME/d) still posed elevated opioid-overdose risk (Dasgupta *et al.*, 2016; Gomes *et al.*, 2011). While the aforementioned studies have explored the adverse effects of high-dose opioid prescription in the general population, there is a limited understanding of the adverse effects of high-dose opioid prescription among PLHIV. It is evident that the prescription of high-dose opioids for PLHIV can have both serious short- and long-term adverse outcomes. However, a better understanding of this relationship, specifically in the context of high dose opioid prescription, is needed to ensure the safety and health of PLHIV. Using population level data, the objective of this study was to examine the adverse outcomes (i.e., mortality) associated with high-dose opioid prescription among PLHIV.

Methods

Study overview and population

We used data from the Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS) in British Columbia (BC) cohort. Specific details of this cohort and the validity of this linkage methodology have been described in detail elsewhere (Heath *et al.*, 2014; Nosyk *et al.*, 2013). In short, the STOP HIV/AIDS cohort is a database of all identified PLHIV in the province of BC, Canada (Heath *et al.*, 2014). The cohort, refreshed annually from 1996, links a number of BC provincial treatment, surveillance and administrative databases: The BC center for Excellence in HIV/AIDS Drug Treatment Program and Virology Registry (BC Centre for Excellence in HIV/AIDS, 2014; BC Centre for Excellence in HIV/AIDS [creator], 2014); BC center for Disease Control HIV testing database (BC Centre for Disease Control, 2015; British Columbia Centre for Disease Control Public Health Laboratory [creator], 2016); BC Medical Services Plan (MSP) (British Columbia Ministry of Health, 2016); Discharge Abstract Database (DAD) (Canadian Institute of Health Information [creator] 2016); the BC PharmaNet database (British Columbia Ministry of Health, 2016); and Vital Statistics Databases (British Columbia Vital Statistics Agency, 2016). These databases collect extensive demographic, clinical, laboratory, prescription drug usage and health service utilization data for all registered HIV patients, which allowed us to analyze key outcomes such as mortality while controlling for a variety of confounders (Heath *et al.*, 2014). This study was approved by the University of British Columbia – Providence Health Care's Research Ethics Board.

Study sample inclusion criteria

We included PLHIV who met the following criteria: 1) at least 18 years of age, 2) initiated antiretroviral therapy (ART), and 3) had a CD4 cell count and plasma viral load measurement within six months after their ART initiation date.

Measures

The main outcome measure was all-cause mortality, measured using the Vital Statistics Database. We also included descriptive data on overdose-related mortality, which was defined as death where the underlying and contributing cause was drug poisoning of all intents according to the following ICD-10 codes (and related ICD-9 codes): X40-X44, X60-X64, X85, or Y10-Y14 (CDC NCIPC DUIP PDO Team H, 2013). The main explanatory measure we examined was high-dose opioid prescription, defined as > 90 MME/d. We chose >90MME/d as our cut-off point to be consistent with recent North American opioid prescribing guidelines and other research studies that warrant caution to doses prescribed higher than >90MME/d (Busse *et al.*, 2017; College of Physicians & Surgeons of British Columbia, 2016; Dowell, Haegerich & Chou, 2016).

We considered a number of confounders we hypothesized would be associated with the main outcome of interest including: 1) sex (female versus [vs.] male), 2) ART initiation era (1996–1999 [reference] vs. 2000–2003 vs. 2004–2007 vs. 2008–2011 vs. 2012–2015), 3) diagnosed substance use disorder (yes vs. no), 4) co-prescription of opioids and benzodiazepines with overlap of prescriptions for at least one day (yes vs. no), 5) age at baseline (per 10-year increase), 6) Charlson comorbidity index (per unit increase), 7) CD4 cell counts (per 100 cells/mm^3 increase) and 8) viral load (per log10 copies/mL increase. Other than sex, ART initiation era, and age, all confounders were time varying in the analysis.

Statistical analyses

First, we performed descriptive statistics to characterize our patient sample at baseline, stratified by all-cause mortality. Kruskal-Wallis test was used to compare quantitative variables and Chi-square test (or Fisher's exact test) was used to compare qualitative variables. Next, we calculated all-cause and overdose-related mortality rates as crude measures, adjusted for age and sex using the 2011 Canadian population as a reference, and stratified by sex, age, and year. In total, there were 216,950 observations among 9272 individuals. 30,517 (14%) observations among 3287 individuals were excluded because of missing data, but no individuals were excluded from the analyses.

To estimate the relationship between high-dose opioid prescription (>90MME/d) and all-cause mortality, we used bivariable and multivariable generalized estimating equation (GEE) models with Poisson distribution after test for overdispersion. To fit the multivariable model, all demographic and clinical confounders that we hypothesized a priori were associated with the main effect of interest were included regardless of statistical significance in bivariable analyses.

As a secondary analysis, we were interested in examining whether there was an interaction effect between high-dose opioid prescription (>90MME/d) and: 1) the presence of a substance use disorder, 2) co-

Table 1
Descriptive characteristics of study sample at baseline.

Exposures of main interest	Total (%) (n = 9272)	All-cause mortality		p - value
		Yes (20.1%) (n = 1862)	No (79.9%) (n = 7410)	
High-dose opioid				
> 90 MME/d	187 (2.0)	50 (2.7)	137 (1.9)	0.022
≤ 90 MME/d	9085 (98.0)	1812 (97.3)	7273 (98.2)	
Covariates				
Sex				
Male	7596 (81.9)	1477 (79.3)	6119 (82.6)	0.001
Female	1676 (18.1)	385 (20.7)	1291 (17.4)	
ART era				
1996–1999	2596 (28.0)	966 (51.9)	1630 (22.0)	< 0.001
2000–2003	1353 (14.6)	392 (21.1)	961 (13.0)	
2004– 2007	1644 (17.7)	295 (15.8)	1349 (18.2)	
2008–2011	2175 (23.5)	166 (8.9)	2009 (27.1)	
2012–2015	1504 (16.2)	43 (2.3)	1461 (19.7)	
Substance use disorder				
Yes	1365 (14.7)	410 (22.0)	955 (12.9)	< 0.001
No	7907 (85.3)	1452 (78.0)	6455 (87.1)	
Co-prescription of opioids and benzodiazepines				
Yes	283 (3.1)	118 (6.3)	165 (2.2)	< 0.001
No	8989 (96.9)	1744 (93.7)	7245 (97.8)	
Age (years; median, Q1–Q3)	38 (31–45)	40 (34–38)	37 (31–44)	< 0.001
Charlson comorbidity index (median, Q1–Q3)	4 (4–6)	5 (4–6)	4 (4–6)	< 0.001
CD4 cell counts (Cells/mm^3; median, Q1–Q3)	260 (130–420)	190 (80–330)	280 (150–440)	< 0.001
Viral load (Log10 copies/ml; median, Q1–Q3)	4.8 (4.2–5)	5 (4.6–5)	4.8 (4.1–5)	< 0.001

MME/d: Morphine Milligram Equivalents per day; ART: Antiretroviral Therapy; Q: Quartile.

prescription of benzodiazepines on all-cause mortality rates, and 3) calendar year on all-cause mortality rates. Therefore, we constructed two additional multivariable GEE models to examine these potential interactions. All p-values are two-sided. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Study sample characteristics

Over the 19-year study period (1996–2015) of the STOP HIV/AIDS cohort, 9272 PLHIV met the study inclusion criteria; 1676 (18.1%) were female and the median age at baseline was 38 years (quartile[Q] 1–Q3: 31–45 years). In total, 1862 (20.1%) of the identified patients died during the study period; and among these deaths, 244 (13.1%) were overdose-related. In total, 2206 (23.8%) patients were prescribed opioids at >90MME/d at least once during the study period. The baseline characteristics of the included 9272 patients in the cohort are presented in Table 1.

Mortality rates

The crude all-cause mortality rate was 27.10 per 1000 person-years (95% confidence interval[CI]: 25.89–28.36 per 1000 person-years), whereas age- and sex-adjusted mortality rate (using the 2011 Canadian population as the reference) was 30.99 per 1000 person-years (95% CI: 28.11–33.88). In stratified analyses, among both men and women, mortality rates increased with increasing age groups: among women, from 19.97 per 1000 person-years (95% CI: 13.67 – 29.19) in the 19–30 age group to 29.38 per 1000 person-years (95% CI: 24.91–62.24) in the ≥ 60 age group, whereas among men, the mortality rate increased from 15.20 per 1000 person-years (95% CI: 10.77–21.44) in the 19–30 age group to 47.05 per 1000 person-years (95% CI: 41.55–53.27) in the ≥ 60 age group. Stratification by year revealed a significant decline in mortality rates from 84.43 per 1000 person-years in 1996 to 18.71 per 1000 person-years in 2015 (Figure 1).

We also analyzed crude, sex, age and year adjusted overdose-related mortality. The crude overdose-related mortality rate of the cohort was 3.55 per 1000 person-years (95% CI: 3.13–4.03). The overall female

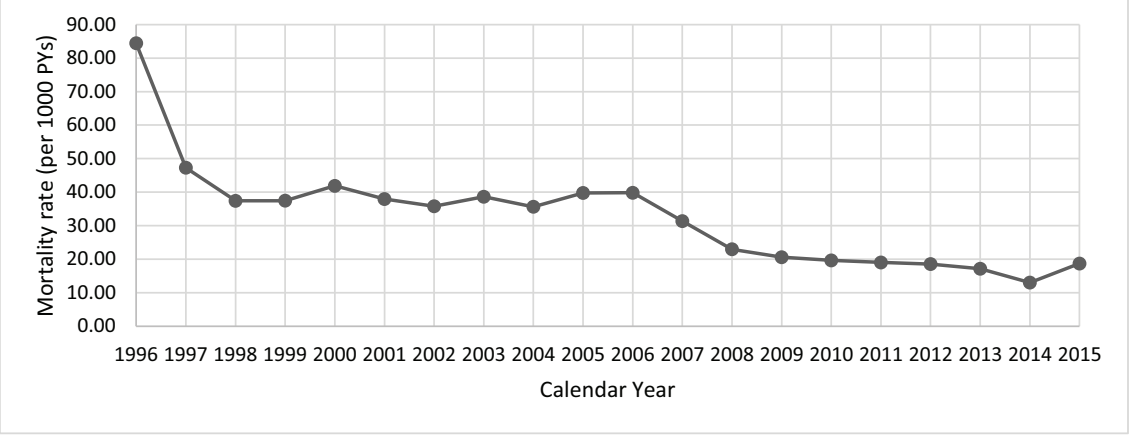

Fig. 1. All-cause mortality rate stratified by year.

Table 2
Bivariable and multivariable generalized estimating equation modeling of factors associated with all-cause mortality rates (n = 9272).

Characteristic	Risk Ratio (RR) Unadjusted RR (95% CI)	Adjusted RR (95% CI)
High-dose opioid regimen (>90MME/d vs. ≤90MME/d)	5.03 (4.38–5.78)	3.01 (2.47–3.66)
Sex (female vs. male)	1.22 (1.09–1.37)	1.21 (1.04–1.41)
ART Era		
2000– 2003 vs. 1996–1999	0.95 (0.84–1.07)	0.78 (0.67–0.91)
2004–2007 vs. 1996–1999	0.77 (0.67–0.88)	0.55 (0.46–0.65)
2008–2011 vs. 1996–1999	0.52 (0.44–0.61)	0.43 (0.35–0.52)
2012–2015 vs. 1996–1999	0.58 (0.43–0.79)	0.61 (0.44–0.84)
Substance use disorder (yes vs. no)	1.45 (1.30–1.62)	0.93 (0.79–1.09)
Co-prescription of opioid and benzodiazepine (yes vs. no)	3.95 (3.41–4.56)	1.80 (1.46–2.22)
Age at baseline (per ten years increase)	1.38 (1.33–1.45)	1.36 (1.28–1.44)
Charlson comorbidity index (per unit)	1.26 (1.24–1.28)	1.26 (1.23–1.28)
CD4 cell counts (per 100 cells/mm^3)	0.74 (0.72–0.77)	0.78 (0.75–0.81)
Viral load (per log10 copies/ml)	1.21 (1.17–1.25)	1.21 (1.16–1.27)

MME/d: Morphine milligram equivalents per day; ART: antiretroviral therapy; CI: confidence interval.

Table 3
Bivariable and multivariable generalized estimating equation modeling of factors associated with overdose-related mortality rates (n = 9272).

Characteristic	Risk ratio (RR) Unadjusted RR (95% CI)	Adjusted RR (95% CI)
High-dose opioid regimen (>90MME/d vs. ≤90MME/d)	3.14 (2.12–4.65)	1.42 (0.84–2.43)
Sex (female vs. male)	1.81 (1.36–2.39)	1.34 (0.96–1.87)
ART Era		
2000–2003 vs. 1996–1999	0.83 (0.60–1.16)	0.82 (0.56–1.19)
2004–2007 vs. 1996–1999	0.58 (0.39–0.85)	0.61 (0.40–0.93)
2008–2011 vs. 1996–1999	0.42 (0.26–0.69)	0.53 (0.32–0.88)
2012–2015 vs. 1996–1999	1.06 (0.57–1.96)	1.53 (0.82–2.89)
Substance use disorder (yes vs. no)	3.05 (2.35–3.96)	2.03 (1.47–2.81)
Co-prescription of opioid and benzodiazepine (yes vs. no)	4.75 (3.37–6.70)	2.97 (1.46–2.22)
Age at baseline (per 10 years increase)	0.89 (0.79–1.00)	0.91 (0.78 –1.05)
Charlson comorbidity index (per unit)	1.17 (1.13–1.21)	1.13 (1.07–1.18)
CD4 cell counts (per 100 cells/mm^3)	0.94 (0.89–1.00)	0.95 (0.89–1.01)
Viral load (per log10 copies/ml)	1.07 (0.98–1.17)	1.10 (0.98–1.24)

MME/d: Morphine milligram equivalents per day; ART: antiretroviral therapy; CI: confidence interval.

overdose-related mortality rate was 5.62 per 1000 person-years (95% CI: 4.42–7.13) whereas in males it was 3.11 per 1000 person-years (95% CI: 2.68–3.61).

Receipt of high-dose opioid analgesics and mortality rates

Table 2 shows unadjusted and adjusted GEE models examining the relationship between high-dose opioid analgesics and all-cause mortality rates. In an unadjusted GEE model, we found a positive and significant relationship between high-dose opioid prescriptions exceeding 90 MME/d and all-cause mortality (rate ratio [RR] = 5.03; 95% CI: 4.38–5.78). In a multivariable GEE model adjusted for various demographic and clinical confounders, patients receiving greater than 90 MME/d of opioids remained positively and significantly associated with all-cause mortality risk compared to those who received an opioid prescription of less than 90 MME/day (adjusted rate ratio [ARR] = 3.01; 95% CI: 2.47–3.66).

Table 3 shows unadjusted and adjusted GEE models examining the relationship between high-dose opioid analgesics and overdose-related mortality rates. In an unadjusted GEE model, we found a positive and significant relationship between high-dose opioid prescriptions exceeding 90 MME/d and overdose-related mortality (rate ratio [RR] = 3.14; 95% CI: 2.12–4.65). In a multivariable GEE model adjusted for various demographic and clinical confounders, we failed to find a statistically significant relationship between patients receiving greater than 90 MME/d of opioids and overdose-related mortality risk compared to those who received an opioid prescription of less than 90 MME/day (adjusted rate ratio [ARR] = 1.42; 95% CI: 0.84–2.43).

Secondary analyses: interactions with receipt of high-dose opioid analgesics

In secondary analyses, we constructed multivariable GEE models to assess whether the relationship between being prescribed greater than 90 MME/d of opioids and all-cause mortality was dependent on having a substance use disorder (data not shown). Compared to PLHIV who were prescribed ≤90MME/d and did not have a substance use disorder, those who were prescribed >90MME/d and had a substance use disorder (ARR = 1.86; 95%CI: 1.34–2.60) and those who were prescribed >90MME/d and did not have a substance use disorder (ARR = 3.98; 95%CI: 3.18–4.98) had an increased all-cause mortality risk. Upon further analysis, all-cause mortality rates among those who were prescribed >90MME/d without a substance use disorder was statistically significantly higher (ARR = 2.14; 95% CI: 1.49–3.07) compared to those who were prescribed >90MME/d and had a substance use disorder.

We also hypothesized that the relationship between being prescribed greater than 90 MME/d of opioids and all-cause mortality was dependent on being co-prescribed benzodiazepines (data not shown). Compared to PLHIV prescribed ≤90 MME/d without benzodiazepine co-prescription, PLHIV prescribed ≤90 MME/d with benzodiazepine co-prescription (ARR = 2.21; 95% CI: 1.72–2.83) had increased all-cause mortality rates. PLHIV prescribed >90MME/d without benzodiazepine co-prescription (ARR = 3.48; 95% CI: 2.79–4.34); and PLHIV

prescribed >90MME/d with benzodiazepine co-prescription (ARR =4.75; 95% CI: 3.68–6.13) also had increased all-cause mortality rates.

We also considered whether the association between high-dose opioid prescription and all-cause mortality changed over time. At baseline year (1996), in an adjusted multivariable model, patients receiving greater than 90 MME/d of opioids were positively and significantly associated with all-cause mortality risk compared to those who received an opioid prescription of less than 90 MME/day (adjusted rate ratio [ARR] = 5.35; 95% CI: 3.53–8.12). This rate ratio decreases by 5% as calendar year increases by 1 year (ARR = 0.95; 95% CI: 0.92–0.98).

Discussion

In an analysis of a province-wide cohort spanning a 19-year period, we found that approximately one-fifth of PLHIV experienced a mortality event. While both all-cause and overdose-related mortality decreased over the study period, we found a positive association between high-dose opioid prescription and all-cause mortality among our study population. In effect modification analyses, we further demonstrated that the relationship between high-dose opioid prescription and all-cause mortality was negatively associated with a) having a SUD and positively associated with b) being co-prescribed benzodiazepines. Our study is one of the first to estimate the relationship between high-dose opioid prescription and all-cause mortality in a population-level cohort of PLHIV.

We found that both all-cause and overdose-related mortality decreased over the 19-year study period in the study cohort. The decline in mortality of PLHIV may be largely explained by advancements in ART therapy, as well as optimization and increased reach of HIV-related care (Kok *et al.*, 2015; Nosyk *et al.*, 2017). While beyond our study period, it is noteworthy that given the opioid overdose public health emergency declared in 2016 in the province, it is anticipated that this decreasing mortality trend would not have continued beyond 2015 (BC Gov News, 2016). In fact, the Coroners Service of British Columbia estimated a tripling in the rate of opioid overdose-related mortality between 2015 and 2018, largely due to the increased fentanyl contamination of the illicit drug supply (Coroners Service B., 2012). Future research with data post 2015 should seek to explore the impact of the opioid epidemic on this population in further detail.

Our findings are consistent with studies performed among the general population and PLHIV that showed that all-cause mortality was higher among those who were prescribed high doses of opioids (Becker *et al.*, 2016; Dasgupta *et al.*, 2016; Gomes *et al.*, 2011; Weisberg *et al.*, 2015). Specifically, in the general population, a study in the US demonstrated almost a three-fold increase in mortality risk among those who were prescribed between 80 – 99.9 MME/d compared to those who were prescribed doses between 0 – 39.9 MME/d (Dasgupta *et al.*, 2016). Another study conducted in Canada also found a positive dose-dependent relationship between opioid dose and mortality in the general population (Gomes *et al.*, 2011). Furthermore, compared to the general population, high-dose opioid prescription among PLHIV is more prevalent and is associated with greater all-cause mortality (Becker *et al.*, 2016; Silverberg *et al.*, 2012; Tsao, Dobalian, & Stein, 2005; Weisberg *et al.*, 2015). Our failure to find an association between high-dose opioid prescription and overdose-related mortality may be because overdose is only one potential cause of mortality secondary to opioid use. Long term opioid receipt may contribute to medical mortality via cardiac, endocrine and gastrointestinal disturbances (Benyamin *et al.*, 2008; Brandenburg, 2019). Moreover, falls, fractures and vehicular accidents are associated with opioid prescription and may have contributed to all-cause mortality but not overdose-related mortality (Baldini, Von Korff & Lin, 2012; Benyamin *et al.*, 2008; Chihuri & Li, 2019; Saunders *et al.*, 2010; Woolcott *et al.*, 2009). Based on findings in the general population, regional, national and international guidelines warn physicians to reassess patient benefits when prescribing over 50 MME/d of opioids and to avoid prescribing over 90 MME/d of opioids unless there is significant evidence of benefit to the patient (Busse *et al.*, 2017; College of Physicians & Surgeons of British Columbia, 2016; Dowell, Haegerich & Chou, 2016).

In secondary analyses, we found that the relationship between being prescribed high-dose opioids and mortality was dependent on the presence of a SUD; however, contrary to our hypothesis, the risk of mortality among PLHIV who were prescribed >90MME/d with no SUD was significantly higher compared to those who were prescribed >90MME with a SUD. There may be a few reasons for these unexpected findings. Substance use disorders (SUD) are known to be underdiagnosed by physicians (Modesto-Lowe, Brooks, Freedman & Hargus, 2007) for multiple reasons such as lack of training, emergency medicine's focus on acute illnesses, clinicians not screening for SUDs in patients who do not fit the stereotype, and due to overlap between symptoms of substance use and other illnesses (Basco, Jacquot, Thomas & Knack, 2008; Bernstein & D'Onofrio, 2013). It is likely that the potential under-diagnosis of SUDs could have resulted in a large number of patients with SUDs being misclassified as patients without SUDs. Alternative explanations for this finding may be that patients with an opioid use disorder in particular may possess higher opioid tolerance, making them less likely to overdose. On the other hand, PLHIV with SUDs may be monitored more closely by physicians, which may in turn reduce their risk of mortality.

We also found that the relationship between being prescribed high-dose opioids and mortality was dependent on having been co-prescribed benzodiazepines. In alignment with the literature, we found that co-prescription of benzodiazepines with opioids resulted in a statistically significant increase in all-cause mortality even with low opioid doses (≤90MME/d) (Becker *et al.*, 2016; Bruce *et al.*, 2017; Chou *et al.*, 2009; Gomes *et al.*, 2011). In fact, a US study found that overdose mortality was ten times higher in patients co-prescribed opioids and benzodiazepines compared to those prescribed opioids alone (Dasgupta *et al.*, 2016). Since PLHIV often have higher rates of comorbid mental illness and pain, there are cases where benzodiazepine and opioid co-prescription may be indicated (Becker *et al.*, 2016; Reisfield & Webster, 2013 Oct, 1). Nevertheless, it is imperative that physicians prescribing opioids to PLHIV strike a safe balance between pain management concerns and common drug interactions that put the patient at risk for overdose or mortality (Dasgupta *et al.*, 2016; Reisfield & Webster, 2013).

Increased all-cause mortality among PLHIV who were prescribed high doses of opioids, alongside a higher prevalence of high-dose opioid prescription among this population, highlights an important need for optimized, well monitored prescription of opioids by physicians. National and international guidelines recommend non-opioid analgesics as a first line treatment for mild chronic pain, followed by a trial of opioids with adjuvant non-pharmacological and non-opioid pharmacological therapies for management of more persistent, moderate to severe pain (Busse *et al.*, 2017; Dowell, Haegerich & Chou, 2016; Miller, 2004). Therefore, strategies to ascertain the safety of PLHIV whose pain is managed using opioids should include: 1) improved education of physicians who provide HIV care in addiction medicine, including safer opioid prescribing and recognition and treatment of SUDs, 2) better adherence by physicians to prescribing guidelines for pain among PLHIV, and 3) development of multidisciplinary teams, consisting of pharmacists, addiction medicine specialists and opioid-prescribing physicians working together to monitor patients who are prescribed opioids (Debar *et al.*, 2012; Khidir & Weiner, 2016). Ultimately, we emphasize the need for an optimized opioid prescription that comprehensively considers patient risks and benefits in accordance with evidence-based guidelines, as opposed to stricter prescribing practices that may leave PLHIV with suboptimal chronic pain management.

Our study has limitations that need to be considered. First, our data is observational in nature and while controlled for a variety of

confounders, there may be unmeasured confounders not accounted for. Second, opioid doses were ascertained using drug prescription dispensation data; thus, we cannot determine whether the medications were taken as prescribed. It is noteworthy that pain medications are often consumed on an as needed basis, and therefore it is likely that we overestimated the MME/d for each patient. Relatedly, we were unable to incorporate MME/d of additional opioids that may have been prescribed outside of BC and/or obtained illicitly, and thus may have underestimated opioid use in these cases. Nevertheless, there are studies that suggest that this method of using drug prescription data is valid for measuring drug exposure in the population (Lau, de Boer, Beuning & Porsius, 1997). Additionally, misclassification in the reporting of ICD codes for overdose-related mortality may have not adequately captured the true rate in our sample. This may have contributed to our failure to find an association between high-dose opioid prescription and overdose-related mortality. Lastly, our findings may not be generalizable to other regions with varying demographics, opioid prescribing habits, and healthcare systems.

Within our large provincial sample of PLHIV, we found a positive association between high-dose opioid prescription and all-cause mortality. These findings demonstrate evidence for the risks associated with prescribing high-dose opioids to manage HIV-related pain and emphasize the importance of assessing patient risks and benefits periodically when prescribing opioids to PLHIV. Strategies and interventions to achieve a better balance between pain relief and related risks are importantly needed. Appropriate opioid prescribing, in alignment with national and international guidelines, is paramount given the comorbidities of PLHIV and in the context of North America's opioid overdose epidemic.

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Declaration of Competing interest

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