

**CHRONIC PAIN AND PAIN MANAGEMENT STRATEGIES AMONG PEOPLE
LIVING WITH HIV WHO USE UNREGULATED DRUGS IN CANADA**

by

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Abstract

Background: Although chronic pain is prevalent among people who use drugs (PWUD) and people living with HIV (PLWH), there have been few investigations of pain among PLWH who use drugs. To fill this gap, this thesis sought to evaluate the prevalence and correlates associated with chronic pain, analyze the associations of pain medication denial, and explore common pharmacologic and non-pharmacologic pain self-management strategies among PLWH who use drugs.

Methods: Data were derived from the AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS) study, an open prospective cohort study of HIV-positive people who use drugs linked to comprehensive HIV clinical data. Generalized linear mixed-effects modelling (GLMM) was used to estimate the prevalence of and identify exposures linked to chronic pain (study 1) and to analyze associations of pain management strategies with substance use and socio-structural exposures (study 3). Generalized estimating equations (GEE) were used to explore the independent relationships between pain medication denial with various substance use, social-, and healthcare access measures (study 2).

Results: In study 1, 374 (53%) participants reported recent moderate-to-extreme pain. Multivariable GLMM analysis revealed chronic pain was associated with pain self-management, non-fatal overdose, non-medical prescription opioid use, and mental illness. Being denied pain medication was reported by 84 (20%) participants in study 2. In a multivariable GEE model, recent pain medication denial was associated with recent incarceration, daily cocaine injection, pain self-management, attempted suicide, and not visiting a family physician. In study 3, pain self-management was reported by 342 (70%) participants; multivariable GLMM identified associations with homelessness, daily injection heroin and non-medical prescription opioid use, and being diagnosed with a chronic pain condition. Self-management strategies primarily involved unregulated substances (66%), however, 34% indicated non-substance-based strategies.

Conclusions: The findings of this research emphasize that chronic pain is often undertreated among PLWH who use drugs and frequently leads to use of higher-risk pain management alternatives and negative health outcomes. This research builds upon prior evidence calling for accessible, integrated care services that provide both pharmacologic and non-pharmacologic pain management strategies that may reduce the risks and consequences associated with being denied pain medication and self-managing pain.

Lay Summary

People living with HIV (PLWH) who use drugs face unique healthcare needs stemming from complications arising from HIV infection and the consequences of substance use. However, undertreatment of health concerns, especially chronic pain, is common. Given that little is known about the patterns and relationships between chronic pain, substance use, and HIV infection, this thesis aimed to explore different aspects of pain among PLWH who use drugs. In this research project, I found chronic pain to be common among this population and identified associations between pain and poorer physical and mental health outcomes, including significantly higher odds of attempting suicide, self-managing pain through higher-risk substance use patterns, (e.g., injection drug use) and high rates of denial of licit pain medication. The findings from this thesis provide a base of knowledge to inform the development of accessible integrative policies and services tailored for chronic pain management among PLWH who use drugs.

Preface

Work for this thesis was conducted using data from a United States National Institutes of Health-funded open prospective cohort study of people living with HIV who use drugs in Vancouver: the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). All data collection, coding, and cleaning was completed by staff at the British Columbia Center on Substance Use (BCCSU). These studies have been approved by the University of British Columbia/Providence Health Care Ethics Board (VIDUS: H05 – 50234; ACCESS: H05 - 50233).

With the guidance and assistance of my supervising committee (Dr. Jane Buxton, and Dr. Angela Kaida, and Dr. M-J Milloy) I conceptualized the empirical research designs for each chapter. I worked closely with statisticians from the BCCSU to develop a data analysis plan, which was carried out by them using R software. I created all tables and figures using Microsoft Word or Microsoft Excel.

Versions of chapters 2, 3, and 4 are currently undergoing co-author revision, and will be submitted for publication in peer-reviewed journals in the upcoming months. Findings from chapter 3 were presented in poster form at the 23rd International AIDS Conference (July 6-10, 2020. San Francisco, United States of America.) Additional findings from chapter 3 of this thesis will be presented in poster form at the 2021 International Association for the Study of Pain (IASP) World Congress on Pain. (June 27-July 1, 2021. Amsterdam, the Netherlands.)

Table of Contents

Abstract.....	iii
Lay Summary	iv
Preface.....	v
Table of Contents	vi
List of Tables	x
List of Abbreviations	xii
Acknowledgements	xiv
Dedication	xv
Chapter 1: Study Background, Rationale, and Objectives	1
1.1 BACKGROUND	1
1.1.1 Chronic Pain.....	1
1.1.2 Epidemiology of Chronic Pain.....	3
1.1.3 Pain, Opioid Analgesics, and Opioid Use.....	5
1.1.4 The Opioid Crisis	6
1.1.5 Pain and People who use Unregulated Drugs	9
1.1.6 Pain and People Living with HIV	11
1.1.7 Access to Care for PLWH who use Unregulated Drugs.....	12
1.2 RATIONALE.....	14
1.3 THESIS OBJECTIVES AND OVERVIEW OF CHAPTERS	14
1.4 STUDY SETTING AND SAMPLE	16

Chapter 2: Estimating prevalence and correlates of pain among people living with HIV who use unregulated drugs	19
2.1 INTRODUCTION	19
2.2 METHODS	20
2.2.1 Study design and population	20
2.2.2 Study sample and inclusion/exclusion criteria.....	20
2.2.3 Outcome of interest and explanatory variables.....	21
2.2.4 Data analysis	22
2.3 RESULTS	23
2.4 DISCUSSION.....	24
2.4.1 Conclusions.....	28
Chapter 3: Prevalence and correlates of self-reporting being denied pain medication among people living with HIV who use drugs with moderate-to-extreme pain	35
3.1 INTRODUCTION	35
3.2 METHODS	37
3.2.1 Study design and population	37
3.2.2 Study sample and inclusion/exclusion criteria.....	37
3.2.3 Outcome of interest and explanatory variables.....	37
3.2.4 Data analysis	39
3.3 RESULTS	40
3.4 DISCUSSION.....	42
3.4.1 Conclusions.....	49

Chapter 4: Characterizing self-management of pain among people living with HIV who use unregulated drugs58

4.1 INTRODUCTION 58

4.2 METHODS 60

 4.2.1 Study design and population 60

 4.2.2 Study sample and inclusion/exclusion criteria 60

 4.2.3 Outcome of interest and explanatory variables 61

 4.2.4 Data analysis 62

4.3 RESULTS 63

4.4 DISCUSSION 65

 4.4.1 Conclusions 70

Chapter 5: Summary of Findings, Implications for Policy and Research, and Future

Directions77

5.1 SUMMARY OF FINDINGS 77

 5.1.1 Estimating prevalence and correlates of pain among people living with HIV who use unregulated drugs 78

 5.1.2 Assessing the prevalence and correlates of being denied pain medication among people living with HIV who use unregulated drugs 79

 5.1.3 Characterizing self-management of pain among people living with HIV who use unregulated drugs 80

5.2 IMPLICATIONS FOR HEALTH POLICY AND RESEARCH 81

5.3 STRENGTHS AND LIMITATIONS 84

 5.3.1 Study Strengths 84

5.3.2	Study Limitations.....	85
5.4	FUTURE DIRECTIONS	87
	References	90

List of Tables

Table 2.1 Baseline characteristics of PLWH that use unregulated drugs in Vancouver, Canada, stratified by self-reported pain (n = 709)	30
Table 2.2 Bivariable and multivariable GLMM analysis of factors associated with self-reporting pain among a cohort of PLWH who use unregulated drugs (n = 469)	33
Table 3.1 Sociodemographic, behavioral, social/structural, and clinical characteristics at baseline of PLWH that use unregulated drugs living with pain stratified by recent denial of pain medication (n = 416)	50
Table 3.2 Baseline healthcare utilization characteristics of PLWH that use unregulated drugs living with pain stratified by denial of pain medication (n = 416)	53
Table 3.3 Bivariable and multivariable generalized estimating equations (GEE) analyses of factors associated with being denied pain medication among PLWH who use unregulated drugs with pain (n = 366)	54
Table 3.4 Bivariable and multivariable generalized estimating equations (GEE) analyses of healthcare utilization factors associated with being denied pain medication among PLWH who use unregulated drugs with pain (n = 366)	56
Table 3.5 Self-reported actions taken following being denied prescription medication among people living with HIV who use unregulated drugs in Vancouver, Canada (n = 345 reports)	57
Table 4.1 Baseline characteristics of PLWH that use unregulated drugs with pain in Vancouver, Canada, stratified by pain self-management in the previous six months (n = 486)	71
Table 4.2 Bivariable and multivariable GLMM analysis of factors associated with pain self-management among a cohort of PLWH who use unregulated drugs (n = 1649 observations)	73

Table 4.3 Self-reported pain self-management strategies employed in the last six months among PLWH who use unregulated drugs with pain in Vancouver, Canada (n = 555 reports)..... 75

Table 4.4 Self-reported use of illicitly-obtained substances or medications to manage pain within the past 24 hours among PLWH who use unregulated drugs with pain in Vancouver, Canada (n = 384 reports) 76

List of Abbreviations

ACCESS: AIDS Care Cohort to evaluate Exposure to Survival Services

ACT: Acceptance and commitment therapy

AIDS: Acquired immunodeficiency syndrome

AOR: Adjusted odds ratio

ART: Antiretroviral therapy

B.C.: British Columbia

CBT: Cognitive behavioral therapy

CD4+: Cluster of differentiation 4

CI: Confidence interval

DTES: Downtown Eastside

DTP: Drug Treatment Program

GBD: Global Burden of Disease

GEE: Generalized estimating equation

GLMM: Generalized linear mixed model

HCV: Hepatitis C virus

HIV-1: Human immunodeficiency virus

IASP: International Association for the Study of Pain

ICD: International Classification of Diseases

IQR: Interquartile range

LRT: Likelihood Ratio Test

MMT: Methadone maintenance therapy

MSP: Medical Services Plan

NSAIDs: Nonsteroidal anti-inflammatory drugs

OR: Odds ratio

PLWH: People living with HIV

PWUD: People who use drugs

RNA: Ribonucleic acid

QIC: Quasi-Akaike Information Criterion

QOL: Quality of life

USA: United States of America

VL: Viral load

WHO: World Health Organization

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Chapter 1: Study Background, Rationale, and Objectives

1.1 BACKGROUND

1.1.1 Chronic Pain

As defined by the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with, or resembling, actual or potential tissue damage.¹ Pain is a highly subjective experience and the definition of pain varies greatly within and between different cultural contexts.^{2–5} In addition, pain is more prevalent among certain sub-populations—in particular, members of vulnerable and marginalized groups—and experienced more severely by some compared to others.^{3,6–10}

Pain is categorized as either acute or chronic. Acute pain is short-term, and involves sympathetic hyperactivity and stimulation of peripheral pain receptors and their associated nociceptors, usually in response to some form of a stressor (e.g., coming into contact with a hot stove). Chronic pain is defined as pain persisting or recurring for greater than three months, and can further be categorized as either nociceptive (defined as pain arising from prolonged stimulation of peripheral pain receptors) or neuropathic, in which the sensory nervous system itself is damaged by a lesion or other pathology, such as HIV infection.^{1,11–13}

While the pathophysiological aspects of experiencing pain are intuitive (i.e., the human body reacting to stressors in an effort of self-preservation), studies have shown that pain may also occur as a result of emotional/psychological trauma; that is, in the absence of any physical damage.^{14,15} Research has suggested that prior exposure to negative or traumatic emotional experiences both increases vulnerability to physical pain and activates the same neural regions governing physical pain.¹⁶ Some sources of mental or emotional pain have been associated with

mental illness; stress and post-traumatic stress; and existential distress (e.g. social rejection, loneliness, and stigmatization).^{15,17-21} However, despite considerable exploration of pain and its underlying mechanisms, many chronic pain conditions and optimal chronic pain management strategies remain poorly understood.

Interventions to manage chronic pain vary considerably and are often used within a personalized pain management strategy developed by the patient's healthcare provider with minimal consultation with the patient. Typically, the first line of intervention to manage chronic pain is the use of opioid analgesics, such as morphine, hydrocodone, and oxycodone.²² When used appropriately, opioids have demonstrated effective relief of acute pain and chronic cancer pain, playing an integral role in pain management for cancer patients.²²⁻²⁴ However, there is conflicting evidence on the effectiveness of opioids used in chronic non-cancer pain treatment; despite this, many clinical guidelines recommend the use of opioids in chronic pain treatment regimens to supplement other non-pharmaceutical interventions.²⁵⁻²⁸ Non-opioid-based pharmaceutical treatments commonly used include nonsteroidal anti-inflammatory drugs (NSAIDs, such as acetylsalicylic acid and ibuprofen), anti-anxiety and antidepressant medications, and corticosteroids (e.g., prednisone, dexamethasone).^{24,29-31} While some studies have found evidence that cannabinoids are an effective pain management agent, there is no scientific or clinical consensus in this area.^{32,33}

In addition to pharmacological pain management strategies, a plethora of non-pharmacological treatments have shown efficacy and are widely regarded as safe, low-risk alternatives. Physical activity and exercise are often incorporated into pain management regimens and can be effective in alleviating various different types of pain (e.g., neuropathic pain, osteoarthritis, back pain).³⁴⁻³⁸ Other manual therapies, such as acupuncture and hot/cold

hydrotherapy, are also effective pain management strategies.³⁹⁻⁴³ Psychosocial therapies, such as cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT), as well as mindfulness-based approaches have also shown promise in managing pain.⁴⁴⁻⁴⁷ Though the mechanisms are not fully understood, previous studies have shown a relationship between pain and mental well-being.^{17,48-51} How a person thinks about their pain can negatively affect their ability to respond/cope with pain, may increase pain intensity and duration, and may lead to catastrophic thinking (i.e., overinterpretation/exaggeration of actual or anticipated pain).⁵² Mindfulness-based approaches, CBT, and ACT have been successful in managing pain and improving quality of life (QOL) in settings where therapy is the only administered treatment and when used in conjunction with other pain management strategies.^{44-47,53,54}

While opioid-based pharmaceutical treatments for chronic pain have historically been considered the primary approach, recent research has indicated that multimodal pain management regimens, incorporating both pharmaceutical and non-pharmaceutical interventions, yield better individual health outcomes and reduce the risk of opioid-related dependence.⁵⁵⁻⁶⁰

1.1.2 Epidemiology of Chronic Pain

Chronic pain is an important and growing multidimensional public health concern, affecting an estimated one in five adults globally.⁶¹ In 2017, the World Health Organization's (WHO) Global Burden of Disease (GBD) project reported that the leading cause of disability was chronic pain (in particular, lower back pain) and that this has been the leading cause of disability since 1990.⁶² In 2018, the WHO expanded the definition of chronic pain in the International Classification of Diseases (ICD-11) recognizing the condition as a disease—a critical step towards better understanding and recognizing the magnitude of the impact of chronic pain.⁶³ The most

recent GBD report (2019) found that although chronic pain rates have improved slightly in the past two years, it remains in the top ten leading causes of disability worldwide.⁶⁴

In Canada, chronic pain among the general population is prevalent, with some studies estimating an occurrence of between 18 to 29% among people aged 18 years or older.^{65,66} Similarly, the Canadian Pain Task Force estimated one-in-five Canadians lives with chronic pain.⁶⁷ Of note, chronic pain prevalence estimates tend to vary; this variability is attributed to the challenges with: assessing and measuring chronic pain; socioeconomic and demographic differences in populations; and the absence of a consistent definition of pain across the literature. While the most widely-accepted definition of chronic pain is pain persisting longer than three months, some studies have defined chronic pain as pain lasting as little as two weeks.¹²⁻⁶⁸

Globally, a wealth of evidence has found that the prevalence of chronic pain varies considerably between and within population subgroups and that some groups are disproportionately affected with pain compared to others.⁶⁹⁻⁷² For example, an elevated prevalence of chronic pain has been reported among certain key populations, including people living with neurological conditions, older adults, females, people who use drugs (PWUD), and people living with HIV (PLWH) both in and out of treatment.^{65,73-80} Chronic pain is unevenly distributed across socioeconomic strata, with individuals of lower socioeconomic status reporting increased rates of various types of pain.⁸¹⁻⁸⁴ Chronic pain also significantly affects QOL as it has debilitating consequences negatively impacting cognitive and physical capabilities, mental health, employment status, and sleep patterns, all of which may influence the intensity and duration of pain.⁷⁷

In addition to the effects of chronic pain at the individual level, pain also contributes a considerable financial cost at the societal level. In a Canadian study estimating the economic

burden of chronic pain, the direct cost of chronic pain was estimated to be over \$7.2 billion in 2014, though this estimate is likely an underrepresentation as it does not consider the indirect costs of chronic pain (e.g. loss of work productivity), which, in some studies, have been shown to be greater than direct costs.^{78,80,85,86}

1.1.3 Pain, Opioid Analgesics, and Opioid Use

Opioid analgesics have long been employed for pain relief and their use traces back to the Sumerians cultivating opium from poppy plants in what is now Iraq.^{87,88} From then, opium was distributed and spread around the world yet did not appear in North America until the 1700's.⁸⁹ Despite the long history of opioid use and scientific development of a multitude of opioid-based preparations (e.g., morphine in 1803, synthetic heroin in 1898, meperidine in 1939), our understanding of the body's opioid receptor systems is still incomplete.^{86,89,90} In brief, there are three major opioid receptors within the central nervous system and peripheral organs: *mu*, *delta*, and *kappa*.^{92,93} When exogenous opioids are introduced into the body, these molecules bind to and activate the receptor cells, acting either as agonists (e.g., morphine, heroin), antagonists (e.g., naloxone, naltrexone), or partial agonists (e.g., buprenorphine, aripiprazole) that elicit differing physical, emotional, and mental states.⁹³ While opioid analgesics have been widely used for their effective pain relieving properties throughout history, their use has also been associated with addictive properties, such as pleasure, which in turn, may lead to dependence.⁹⁴

The uses of opioids in modern medicine are far-reaching with significant roles in addressing morbidity and providing effective pain relief.^{58,95,96} Initially used as an effective method to relieve chronic cancer-related pain, opioids increasingly began being used with success as the first line of treatment for patients with chronic non-cancer pain.^{89,97-100} In the United States

between 1997 to 2006, retail sales of opioids increased 127% and medical use of opioids increased 347%.¹⁰¹ In Canada, opioid prescriptions increased by more than 3000% between 1980 and 2016.¹⁰² While nation-wide surveillance data has been inconsistent, a population-based survey found opioid dispensing rates increased 23% from 781 units per 1000 population in 2006 to 961 units per 1000 population in 2011.^{103,104} In 2018, analyses of dispensation records from community pharmacies in four provinces showed approximately one in eight Canadians (12.3%) were prescribed opioids.^{102,105} Alongside the unprecedented increase in prescription opioids for medical use, there was a parallel increase of non-medical use of prescription opioids – both of which contributed to escalating rates of opioid dependency and opioid-related overdose.^{97,100,101}

1.1.4 The Opioid Crisis

The roots of the current opioid overdose crisis can be traced back to the late nineteen-nineties and the surge in popularity of slow-release opioids and synthetic opioid formulations to treat chronic pain.⁸⁹ Since 1999, in North America – particularly evident in the United States – there have been three distinct surges of opioid-related overdose deaths: the first in 1999, before the dangers of nonmedical prescription opioid use became widely known; the second spike in 2010, corresponding with legislative changes in prescription opioid prescribing guidelines; and finally, the third wave beginning in 2013, in which highly potent synthetic opioids (e.g., fentanyl) contaminated the unregulated drug supply, resulting in a steady increase in overdose deaths.^{89,100,105,106} These factors contributing to surging drug-related mortality and morbidity rates in the past 20 years continue to fuel the ongoing overdose crisis today; between January 2016 and June 2019, there were over 13,900 opioid drug overdose deaths in the Canada.¹⁰⁷

The first wave of the opioid overdose crisis was driven by the rise of opioid prescriptions, resulting in the overdose mortality rate involving opioid analgesics more than tripling between 1999 to 2012 in the United States.¹⁰⁸ In the late 1980's and early 1990's, several publications called attention to the undertreatment of pain and underutilization of opioids in pain management.^{109–111} A letter published in the *New England Journal of Medicine* in 1980 by Porter and Jick claimed that addiction to opioids was a rare phenomenon in patients; this (now disputed) article is considered a contributing factor behind subsequent increases in opioid analgesic prescriptions and the ensuing opioid crisis.¹¹² However, many jurisdictions in North America at the time began launching legislative responses increasing access to adequate pain management, such as more lenient regulatory measures on opioid prescriptions.¹¹³ Coupled with the formulation and marketing of novel analgesics, such as the slow-release oxycodone (tradename: OxyContin)—which was incorrectly marketed as less addictive than other opioids—opioid use rapidly increased, and with it, reports of addiction and opioid-related disorders began to surge.^{112,114–116}

As the harms of opioid dependence became more apparent and mortality from opioid overdoses continued to increase, perspectives on liberal prescribing of opioid analgesics began to shift. In response, many jurisdictions began implementing measures to reduce the number of opioids being prescribed and curtail unregulated opioid use. Such strategies included increased surveillance of active and new opioid prescriptions, tighter prescription guidelines, and implementation of centralized, real-time electronic databases to mitigate so-called doctor-shopping, in which individuals solicit prescriptions from multiple healthcare providers in order to side-step prescription limits.^{99,100,113,117–120} By 2012 in the United States, opioid prescribing rates peaked at 81.3 prescriptions per 100 people before falling to 51.4 prescriptions per 100 people in

2018.¹²¹ In Canada, 14.3% of the population were prescribed opioids in 2013, though prescribing rates decreased to 12.3% in 2018.¹⁰²

On the supply side, efforts to control the opioid crisis by pharmaceutical companies such as Purdue Pharma led to reformulation of long-acting prescription opioids to be tamper-resistant (e.g. in 2012, Oxycontin™ was reformulated to OxyNEO™, which, upon being crushed, would turn into a viscous, gel-like substance, which would be challenging to inject).¹²² Unfortunately, some studies have found that the reformulation of opioids may have only had a negligible effect on efforts to curtail misuse. For example, one population-based study in Canada analyzing the impact of OxyNEO™ replacing OxyContin™ found that while there was a decrease in prescribing long-acting oxycodone, there was an increase in dispensing of long-acting hydromorphone, suggesting this may have led to diversion as opposed to acting as a deterrent.¹²²

In Canada, various interventions in the healthcare system have been made as a part of efforts to reduce opioid use and respond to unprecedented increases in opioid-related morbidity and mortality. In 2010, the Canadian National Opioid Use Guidelines were developed to provide standards for safe opioid prescribing practices.^{123,124} Unfortunately, these guidelines were criticized for not including recommendations on appropriate dosage and duration, and lacked direction with regard to utilizing pharmacologic and non-pharmacologic based interventions. Some Canadian jurisdictions also began implementing narcotics prescription monitoring systems, though the effectiveness of these systems were limited as they were highly underutilized, lacked coordination due to variation between provincial guidelines, and primarily driven to reduce prescribing rates, not taking into consideration the unintended outcomes of limiting access to licit analgesics (e.g., overdoses, increased unregulated substance use).^{118,125} At an individual level, many people living with chronic pain had their opioid prescriptions restricted or terminated

without clear direction from clinical guidelines and without the support of other non-pharmacologic based pain management methods, leading some to use unregulated substances, such as heroin.^{77,104,126,127} For example, one study of people in a treatment program for non-medical prescription opioid use found that 70% of respondents transitioned to heroin following the introduction of OxyNEO™, with many people citing the lower cost and greater accessibility of heroin as reasons for this switch.^{128,129} At face value, fewer people being prescribed opioids and decreasing doses among those on treatment appear to indicate an effective public health intervention. However, unintended negative consequences of these measures included a growing number people living with pain who were unable to access appropriate and safe pain management.^{130–134} An estimated one in five Canadians live with chronic pain, with many subpopulations—especially those subject to stigma and discrimination—disproportionately affected, and many reporting undertreated pain.^{67,135,136}

The ongoing opioid overdose crisis is a multi-layered public health emergency driven by a complex set of interrelated factors. The rapid expansion of opioid availability, followed by the implementation of ineffective opioid prescribing guidelines, and the contamination of the unregulated drug supply, have all contributed to increases in opioid-related deaths and undertreatment of chronic pain.¹⁰²

1.1.5 Pain and People who use Unregulated Drugs

In 2018, an estimated 269 million people (or 5.9% of the global adult population) had used unregulated injection or non-injection drugs in the previous year; significantly higher than prior years, with reports indicating a 28% global increase in unregulated drug use since 2009.¹³⁷ Findings from the 2017 GBD study estimated that, globally, illicit substance use-related mortality

and morbidity (measured as disability adjusted life years) increased by 81% and 134%, respectively, over the past 30 years, resulting in 585,000 deaths and 42 million years of healthy life lost in 2017 alone.¹³⁷ The global prevalence of illicit and non-prescription opioid use within the last year is estimated to be 1.2 % of the global population.¹³⁸ However, the prevalence of illicit opioid use is unevenly distributed around the world.¹³⁸ Injection drug use, well studied in its association with increased risk of acquiring HIV and other blood borne pathogens, affected an estimated 11.3 million adults worldwide—up 30% from 2009.¹³⁷

As a result of the role of nonmedical use of prescription opioids for pain management in the opioid crisis, the relationship between pain and unregulated drug use (both injection and non-injection) has garnered increased attention. As prescription opioids were once considered the first line of treatment for patients presenting with pain, the number of legitimate prescriptions rose, however, this was accompanied by an increase in the prevalence of non-medical prescription opioid use, as well.^{90,139} A wealth of evidence supports this association between pain and unregulated drug use. Notably, studies have estimated that between 16 to 74% of people with chronic pain have a history of unregulated drug use.^{73,140–142} There is also evidence supporting that the relationship between substance use and pain may be bidirectional; hyperalgesia, a condition in which the individual has an increased sensitivity to pain as a result of damage to their nociceptors due to opioid use, is well known, however, research in this area is limited.^{143–146}

Many people who use unregulated drugs (PWUD) often have multiple sources of pain drawing from intersecting physical, social/emotional, and structural exposures. PWUD are more likely to report traumatic life experiences (e.g., physical and sexual violence and personal loss) throughout their lives and that these experiences can manifest in physical and social pain.^{147,148} PWUD also experience high rates of criminalization, mental health conditions, homelessness,

economic vulnerability, and stigma—factors that have been shown to interact with and exacerbate each other and that all have previously established positive associations with pain.^{149–152} Prior qualitative research has analyzed potential structural sources of pain, finding that in some people, unregulated drug use followed being denied legitimate pain prescriptions.^{135,153} Stigmatization of unregulated drug use, coupled with a power imbalance between patients and their physicians, has also led to patients resorting to unregulated drugs and self-managing pain after exhausting legal methods of obtaining relief.^{138–142,145,146,147,148–160} Ultimately, this wide range of often intersecting physical, social, and structural factors that contribute to pain among PWUD add additional layers of complication of identifying the source of pain among patients who use unregulated drugs.

1.1.6 Pain and People Living with HIV

PWUD are at an especially high risk of acquiring HIV.¹⁷⁰ According to 2016 Canadian HIV estimates, 63,110 Canadians are living with HIV; of these, 10,986 Canadians (17.4%) reported that the main mode of HIV acquisition was through drug use.¹⁷¹ Prior evidence has shown that PLWH who use drugs are initiate antiretroviral therapy (ART) at lower rates and are more likely to have suboptimal virologic outcomes than PLWH from other risk categories.^{172–174} PLWH who use drugs are also at an increased risk for various comorbid conditions (e.g., hepatitis C virus [HCV], mental illness, and tuberculosis) that further complicate care and treatment.^{175–181}

Among PLWH, pain is a common experience; estimates of chronic pain among this population vary considerably, ranging between 30% to as high as 90%.^{182,183} For example, a study of hospitalized AIDS patients by Lebovits *et al.* found that more than half (54%) of patients reported chronic pain and required analgesics for treatment.⁷⁶ Similarly, in a study by McCormack *et al.*, it was found that 61% of PLWH reported having had pain at one point in their lives, and of

those patients, 60% reported that the pain they experienced resulted in moderate to extreme interference with their enjoyment of life.¹⁸⁴ Research exploring the multidimensional factors that influence pain has been informative. Del Borgo *et al.* found prevalence of pain was significant among PLWH (60.8%), and, among those who reported intravenous drug use, pain was observed more frequently (72.9%) when compared to those who reported HIV transmission via other routes (50.6%).¹⁸⁵ Further, some studies have found that, among PLWH with pain, women reported experiencing greater and more intense pain than men.^{186–189} These findings indicate that despite already being subject to marginalization and stigma, certain subgroups of PLWH are more vulnerable to development of inferior health outcomes, including chronic pain.

While the frequent occurrence of pain among PLWH is well recognized, there is an incomplete understanding of the causes of pain among this group. HIV-related pain is thought to be a result of an intersection of a number of stressors, including concurrent infections and side effects from ART.^{185,190–193} While the development of ART has improved survival of many PLWH, studies have shown that ART may contribute to manifestation of pain; in fact, some studies indicate that ART may be linked to increased arthralgia, myalgia, and atherosclerosis in PLWH.^{194–197} Due to the wide range of symptoms and complications associated with HIV, in addition to various socio-structural factors, pain is often a frustrating experience between patients and their providers and often left undertreated among PLWH—especially among individuals belonging to subpopulations such as PWUD and women.¹⁸⁹

1.1.7 Access to Care for PLWH who use Unregulated Drugs

While a plethora of evidence has indicated that pain is highly prevalent among both PLWH and PWUD, it is also well documented that individuals from both of these groups are often

burdened by internalized and enacted stigma and can encounter a range of barriers in healthcare settings.^{73,75,191,198,199} For PLWH, there are numerous steps along the HIV care continuum in which barriers complicate access, adequate utilization, and optimal adherence to ART; for PLWH who use drugs, a host of other additional structural and economic factors, for example criminalization and incarceration, can create further obstacles to care.^{166,200–205} As many PLWH enjoy improved survival due to the success of ART, HIV is now characterized as a chronic condition and pain is an important co-morbidity.^{206,207} Unfortunately, pain management practices lack clear guidelines for PLWH and PWUD. Currently existing guidelines are limited in their scope of appropriate, empathetic, and multimodal methods of managing pain that account for interaction of external factors, including drug use and stigma.^{123,208–210}

Although chronic pain is both prevalent and undertreated among both PLWH and PWUD, there has been minimal exploration characterizing and evaluating pain among PLWH who use drugs. For example, there is a lack of data on pain medication denial and its consequences among this population. One prior study among PWUD in a universal healthcare setting found that 66% had ever been denied analgesics by a physician and this was linked to new patterns of substance use, such as seeking the requested drug off the street, or transitioning to injecting to relieve pain.¹³⁵ Similarly, Fibbi *et al.* found among a sample of youth who had been denied pain medication, nearly all participants had histories of opioid use.¹⁵³ In these studies, being denied pain medication acted as a risk factor for higher-risk substance use patterns, revealing some of the negative consequences resulting from undertreatment of pain.¹⁵³

1.2 RATIONALE

Despite the increasing awareness that marginalized populations such as PLWH and PWUD are disproportionately burdened with chronic pain compared to the general population, little is known about pain at the intersection of these two groups: PLWH who use drugs. While it is well understood that a significant proportion of PWUD are also living with HIV, and that both PWUD and PLWH are, independently, more vulnerable to pain and physical, mental, and social harms, there is a lack of research on pain among the significantly large group of people belonging to both populations. Exploring the multidimensional factors that influence pain as a result of the complex interplay between living both as a person with HIV and as a person who uses unregulated drugs is critically needed and would serve as the foundation upon which appropriate interventions can be formulated, implemented, and improved.

Despite the restriction of prescription opioid availability due to its role as a potential driver in the opioid overdose crisis, there remain gaps in the understanding of the effects of pain medication denial, particularly among vulnerable populations such as PLWH who use unregulated drugs. Understanding the repercussions of pain medication denial and pain self-management strategies among PLWH who use unregulated drugs is needed to establish a basis for development of pain management policies and practices that reduce the prevalence and burden of pain among PLWH who use unregulated drugs and ultimately, reduce opioid-related overdose deaths.

1.3 THESIS OBJECTIVES AND OVERVIEW OF CHAPTERS

Through this thesis, I aim to address the knowledge gap that exists in the understanding of chronic pain among people living with HIV who use unregulated drugs. The objectives of this thesis are as follows:

- 1) **To characterize chronic pain among PLWH who use unregulated drugs in the context of the opioid crisis.** Using data collected from the ACCESS study (see below), chapter 2 will estimate the prevalence of self-reported pain among PLWH who use drugs and identify significant correlates associated with self-reported pain, including potential clinical correlates. Generalized linear mixed models (GLMMs) will be employed to identify correlates significantly associated with reported pain among this population.
- 2) **To investigate the relationships between pain medication denial and socio-structural, behavioral, substance use, clinical and healthcare access factors, and examine common actions taken after being denied pain medication.** Chapter 3 will use data from the same study period as the previous chapter. This analysis will employ generalized estimating equations (GEEs) to characterize factors associated with pain medication denial. Various studies have reported undertreatment of pain among PWUD and PLWH, however, none have explored denial of pain medication or associated actions following denial among PLWH who use drugs. This study will test the hypothesis that limiting access to pain medications may lead to higher-risk exposures, such as self-medication and riskier substance use patterns.
- 3) **To explore common pharmacologic and non-pharmacologic pain management strategies and investigate associations with sociodemographic, substance use, behavioral, socio/structural, and clinical factors.** Chapter 4 aims to build upon the results of chapter 3, further exploring various associations of pain self-management and commonly used pharmacologic and non-pharmacologic based methods in the last six months and in the last 24-hour period. GLMM will be used to identify factors significantly associated with pain self-management. This investigation seeks to identify prevalent

pharmacologic and non-pharmacologic based coping mechanisms among those with undertreated pain. This study will test the hypothesis that pain self-management is prevalent among PLWH who use unregulated drugs and that this frequently results in exposure to higher-risk structural and substance use factors. Given the growing body of evidence supporting multimodal pain management methods inclusive of both pharmacologic and non-pharmacologic strategies, I also seek to identify commonly used non-pharmacologic pain management methods.^{56,60}

- 4) **To synthesize and discuss key findings in the context of the current research landscape.** Chapter 4 will summarize the findings from the previous chapters and highlight how they contribute to the literature on chronic pain. In addition to discussing some of the implications of current policies and practices regarding pain management, this final chapter will identify and suggest potential areas for future research in the context of pain among PLWH who use unregulated drugs in a Canadian setting.

1.4 STUDY SETTING AND SAMPLE

To investigate these objectives, I used data from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing prospective cohort study launched in 2005. ACCESS consists of PLWH who use drugs, recruited predominantly from the Downtown Eastside (DTES) of Vancouver, an area characterized by high levels of marginalization, criminalization, substance use, and infection with blood-borne pathogens, including HIV. Participant recruitment is conducted via extensive outreach in community settings including the open drug market.

The eligibility criteria for the ACCESS study are: individuals be at least 18 years of age at the time of study enrolment; have used unregulated drugs (other than, or in addition to, cannabis)

in the previous 30 days; be HIV seropositive; currently reside in the Greater Vancouver Regional District; and provide written, informed consent. On the date of recruitment and every six months thereafter, participants complete a standardized questionnaire administered by a trained interviewer. The extensive, confidential questionnaire consists of questions related to health and wellbeing, socio-demographic characteristics, substance use patterns, addiction treatment and contact with the health care and criminal justice systems, and behavioral characteristics. Participants also receive a medical examination by a study nurse for an additional health-focused questionnaire eliciting information on interaction with the healthcare system, disability and pain experiences, pain medication history, and other physical and mental health factors. In addition to collecting blood samples for HIV clinical monitoring (e.g., plasma HIV-1 RNA viral loads [HIV VL] and CD4+ cell counts) and serological testing, study nurses also provide basic patient care and referral to community services, if needed. For their time, study participants receive \$40 for each study visit.

Participant responses recorded at each interview are combined with data from the Drug Treatment Program (DTP) at the British Columbia Centre for Excellence in HIV/AIDS. The DTP is a province-wide, centralized, ART dispensary and HIV clinical monitoring program. Here, each study participant has a complete retrospective and prospective clinical profile of all HIV clinical monitoring tests (e.g., plasma HIV viral load determinations, CD4+ cell counts) conducted through the study or through a patients' regular physician, as well as a full record of all ART dispensed and picked up by study participants. Through British Columbia's publicly-funded Medical Services Plan (MSP), all PLWH are eligible to receive HIV treatment and care, including prescribed medications, at no cost.

ACCESS participants are remunerated CAD \$40 for their participation at each follow-up interview. Both the ACCESS study and the present Master's thesis have been reviewed and approved by the University of British Columbia/Providence Health Care Ethics Board (ACCESS: H05-50233).

Chapter 2: Estimating prevalence and correlates of pain among people living with HIV who use unregulated drugs

2.1 INTRODUCTION

The advent of combination ART has rendered HIV a manageable, chronic condition for many PLWH, especially those living in high-income settings without other comorbidities. Among many key affected populations, HIV-related mortality has declined, and as survival has improved and people living with HIV reach older ages, they are more likely to experience age-related comorbidities, such as pain.^{211,212} Pain among PLWH can be attributed to a range of different sources, including the side effects of medications, damage to the peripheral nervous system, and psychosocial factors.^{185,213,214} Pain among PLWH may also be idiopathic in nature, complicating diagnosis and treatment.^{185,214}

Various studies have described the association between chronic pain and an increased likelihood of unregulated prescription opioid use; in Canada, recent estimates are that 14.3% of all new HIV infections are the result of injection drug use.^{199,215,216} Compared to the general population, PWUD face an elevated burden of acute and chronic disease, including higher rates of mental illness.²¹⁷ They also experience higher rates of pain compared to the general population.²¹⁸ Increased frequency of drug use, relapse following detox, and increased non-medical use of prescription medications (e.g., synthetic opioid analgesics) have each been significantly associated with pain among PWUD.^{219–221} PLWH who use unregulated drugs face a spectrum of challenges, including social/structural barriers, that impede their ability to access and adhere to care; for

example, they are more likely to be homeless, have higher rates of comorbid infections such as HCV infection, are more likely to be incarcerated, and experience stigma.^{150,222–225}

Although the occurrence of elevated rates of pain among both PLWH and PWUD is well recognized, research on pain at the intersection of HIV and substance use has not been well explored. In particular, there have been no studies to assess the prevalence of pain among PLWH who use unregulated drugs and investigate possible links between pain and sociodemographic characteristics, substance use patterns, social/structural exposures, or clinical measures of HIV disease. Thus, this study seeks to estimate the prevalence of moderate-to-extreme pain among a community-recruited cohort of PLWH who use unregulated drugs and to estimate significant associations with relevant explanatory factors.

2.2 METHODS

2.2.1 Study design and population

To address the study objective, this study included participants from the ACCESS study, an open prospective cohort study of PLWH who use unregulated drugs based in Vancouver, Canada. This study has been described in detail in chapter 1, section 1.4.

2.2.2 Study sample and inclusion/exclusion criteria

This study was restricted to participants who completed at least one interview between December 2011 and November 2018, were ART-exposed, who had contributed ≥ 1 CD4+ cell count, and ≥ 1 plasma HIV-1 RNA VL count within six months of their baseline interview.

2.2.3 Outcome of interest and explanatory variables

The primary outcome of interest was self-reported moderate-to-extreme pain or discomfort, ascertained using a standardized measure of pain severity. This measure is part of the EuroQol EQ-5D measure that has been previously validated and shown to be a reliable health utility instrument among people living with pain and PWUD.^{226,227} In brief, the EuroQol EQ-5D is a health utility instrument comprised of five health and wellness dimensions, including mobility, self-care, usual activities, anxiety/depression, and pain/discomfort, the latter of which was utilized in this analysis. Each dimension contains one categorized question, in which the participant can rate their pain as *no pain*, *moderate pain*, or *extreme pain*.

Explanatory variables with an *a priori* hypothesized relationship to pain included: age (in years); sex (male vs. female); ethnicity (white vs. non-white); highest level of education (\geq high school vs. $<$ high school); homelessness (yes vs. no); sex work (yes vs. no); incarceration (yes vs. no); engagement in methadone maintenance therapy (MMT) (yes vs. no); non-fatal overdose (yes vs. no); self-management of pain (yes vs. no); requested a pain prescription (yes vs. no); denied a requested pain prescription (yes vs. no); attempted suicide (yes vs. no); and mental illness diagnosis (yes vs. no). With the exception of gender, ethnicity, highest level of education, and mental illness diagnosis, all non-fixed variables were time-updated and refer to exposures occurring in the six-months preceding the study interview. Substance use measures included: binge alcohol use, defined as any point in time within the six month period prior to interview in which alcohol was used more than usual (yes vs. no); binge injection drug use, defined as any point in time within the six month period prior to interview in which drugs were injected more frequently than usual (yes vs. no); daily cannabis use (yes vs. no); daily crack use (yes vs. no); daily crystal methamphetamine injection (yes vs. no); daily heroin injection (yes vs. no); daily cocaine injection

(yes vs. no); and non-medical prescription opioid use (yes vs. no). Finally, various HIV-related clinical measures using data from the confidential linkage to the DTP were examined, specifically: CD4+ cell count (per 100 cells/mL); ART dispensation (0 days vs. ≥ 1 day); and HIV-1 RNA VL (< 50 vs. ≥ 50 copies/mL plasma). Both CD4+ cell counts and HIV-1 RNA VL measures used the median of all observations collected within the six-month follow up period prior to the study interview. If this measure was unavailable, the most recent observation was used in the analysis.

2.2.4 Data analysis

First, analysis of the explanatory variables at the baseline interview stratified by reporting pain (i.e., experienced moderate or extreme pain vs. experienced no pain) using Pearson's Chi squared test (for categorical variables) and Wilcoxon rank sum tests (for continuous variables) was conducted. Contingency tables with cell frequencies less than five were analyzed using Fisher's exact test. Next, estimates of the bivariable and multivariable relationships between each explanatory variable and the outcome were generated using generalized linear mixed models (GLMMs). To build the final multivariable model, explanatory variables in bivariable analyses that had a p -value < 0.05 were included in the initial full model. Next, a backwards selection procedure using Likelihood Ratio Tests (LRT) was employed to isolate the model with the best overall fit as determined by the lowest Akaike Information Criterion (AIC) value; goodness of fit was assessed using the Hosmer-Lemeshow test. All p -values were two-sided and the threshold for statistical significance was set at $p < 0.05$. All statistical analyses were performed using R version 1.1.456 (R Foundation for Statistical Computing, Vienna, Austria).

2.3 RESULTS

Among 769 participants who contributed ≥ 1 interview between December 2011 and November 2018, 709 participants with ≥ 1 CD4 and ≥ 1 VL measurement within 180 days of their baseline interview were included in the present study. They contributed 6,153 observations and a median of nine interviews (interquartile range [IQR]: 5–13) during the study period. At baseline, the median age of participants was 46.1 years old (IQR: 39.9–51.6 years); 454 (64%) identified as male; and 399 (56.3%) were white. Table 2.1 depicts the explanatory variables stratified by pain at the baseline interview.

Among the 709 participants, 374 (53%) self-reported experiencing moderate-to-extreme pain at baseline. As indicated in Table 2.1, 67 (18%) individuals with pain reported non-medical prescription opioid use in the previous six months and 264 (71%) had a mental illness diagnosis. Concerning pain medication characteristics among those with pain, 166 (44%) reported requesting a prescription for pain medication, 40 (11%) reported being denied pain medication, and 191 (51%) reported self-managing their pain.

Table 2.2 summarizes the results of the bivariable and multivariable GLMM analyses. In unadjusted analyses, older age (Odds Ratio [OR] = 1.04, 95% confidence interval [CI]: 1.02–1.05), white ethnicity (OR = 1.91, 95% CI: 1.40–2.59), daily injection heroin use (OR = 1.31, 95% CI: 1.02–1.67), non-medical prescription opioid use (OR = 1.95, 95% CI: 1.56–2.42), non-fatal overdose (OR = 1.56, 95% CI: 1.19–2.03), self-management of pain (OR = 2.43, 95% CI: 2.10–2.80), denial of pain medication (OR = 2.01, 95% CI: 1.52–2.66), mental illness diagnosis (OR = 1.63, 95% CI: 1.20–2.22), and requesting a prescription for pain medication (OR = 2.27, 95% CI: 1.94–2.66) were associated with moderate-to-extreme pain. Being on ART (OR = 0.99, 95% CI:

0.83 – 1.19), having a VL < 50 copies (OR = 0.95, 95% CI: 0.79 – 1.15), and CD4+ cell count (OR = 0.99, 95% CI: 0.83 – 1.19) were not significantly associated with reporting pain.

In the multivariable analysis, factors that remained significantly and positively associated with moderate-to-extreme pain included: older age (Adjusted Odds Ratio [AOR] = 1.04, 95% CI: 1.02 – 1.05), white ethnicity (AOR = 1.55, 95% CI: 1.18 – 2.05), non-medical prescription opioid use (AOR = 1.63, 95% CI: 1.30 – 2.05), non-fatal overdose (AOR = 1.46, 95% CI: 1.11 – 1.93), self-management of pain (AOR = 2.25, 95% CI: 1.94 – 2.61), mental illness diagnosis (AOR = 1.47, 95% CI: 1.11 – 1.94), and requesting a prescription for pain medication (AOR = 2.01, 95% CI: 1.69 – 2.38).

2.4 DISCUSSION

In this study of individuals in a community-recruited cohort of PLWH who use unregulated drugs, it was found that over half of individuals at baseline reported moderate-to-extreme pain (374, 53%). Pain was positively linked to older age, white ethnicity, non-medical prescription opioid use, non-fatal overdose, self-management of pain, mental illness diagnoses, and requesting pain prescriptions.

Compared to the 19% prevalence of pain among the general Canadian population, this finding underscores that PLWH who use unregulated drugs suffer a disproportionately high prevalence of pain.⁶⁶⁹ Findings from the present study are consistent with existing literature documenting high levels of pain among both PWUD and PLWH.^{66,75,215,228,229} For example, Heimer and colleagues found that chronic pain rates were up to three times higher among a suburban population of PWUD compared to the general population.^{73,142} Similarly, Dobalian and

colleagues observed that, among a population of PLWH, those who reported drug use also reported more pain and were less likely to receive adequate pain medication.⁷⁴ Several qualitative studies have also explored pain experiences among PLWH who use unregulated drugs.^{136,230–233} These have each found that the high prevalence of pain, along with the lack of adequate access to effective analgesia, often forces individuals to turn to high-risk behaviors, such as self-managing pain through injecting heroin and the non-medical use of prescription opioids.^{136,230–233}

In this study, it was also observed that older age was positively associated with moderate-to-extreme pain. While this may appear intuitive, the intersecting relationship between pain, older age, living with HIV, and substance use has not yet been explored in the literature. Chronic pain and undertreatment of pain are more commonly reported among older adults and rates of non-medical prescription drug use are increasing among this population; coupled with the evolution of HIV as a chronic condition among an aging HIV population, further research should investigate this complex relationship and develop strategies to better manage pain among older adults living with HIV who use unregulated drugs.^{234–238}

Despite previous evidence that rates of substance use are significantly higher among people living with mental illnesses, the literature on the intersecting relationship between substance use, pain, and mental illness is limited.^{165,217,239} The study finding that mental illness diagnosis is significantly associated with having moderate-to-extreme pain builds upon prior research; previous studies have shown that among PLWH, pain is associated with anxiety, depression, and being diagnosed with a mental illness.²⁴⁰ Whereas conventional clinical interventions typically isolate and treat conditions individually, there is strong evidence in the existing literature to suggest the relationship between pain and mental illness is bidirectional and, thus, a tailored combination of psychosocial and pharmaceutical interventions might be beneficial.^{152,241,242} This is especially

relevant for PLWH with pain who use unregulated drugs and presents an opportunity for integrated, collaborative healthcare interventions that address the broader spectrum of health and wellbeing. While collaborative healthcare is not a novel idea, in practice, it has not been widely implemented. Many past and current pain management interventions remain only loosely derived from clinical guidelines set forth by the Infectious Diseases Society of America and the United States Center for Disease Control (CDC).^{25,209,243–246}

This study found that white ethnicity was significantly associated with pain among the population of interest. This is in contrast to previous studies suggesting that pain (and pain severity) is higher among members of non-white groups (e.g., Indigenous, Blacks, and other ethnic groups) compared to white individuals.^{247,248} For example, in Canada, Indigenous individuals are more likely to suffer from pain and a higher burden of disease than their white counterparts, but are also less likely to receive pain assessments from healthcare providers and adequate referral to specialist care.^{249–251} Similarly, studies have shown that Indigenous populations in Australia experience higher rates of pain compared to non-Indigenous Australians, yet are less likely to have access to and receive adequate pain management services.^{252–254} Given the discrepancy between the present study findings and the existing literature, further research in this area is warranted.

Finally, a significant association between moderate-to-extreme pain and both self-management of pain and non-fatal opioid overdose was observed, suggesting that pain is undertreated among PLWH who use unregulated drugs and is contributing to high-risk behaviors. Despite the well-known risks associated with use of unregulated opioids during the ongoing fentanyl overdose crisis, these findings suggest that some individuals living with pain in the study population are turning to unregulated drug use in an attempt to self-medicate. Previous studies on self-management of pain indicate that inadequate pain treatment may foster self-medication via

high-risk alternatives, including non-medical prescription opioid and initiation of injection drug use.^{135,153,230,255} This finding has important implications on clinical practice and public policy, as it underscores the serious consequences of inadequate pain management and the subsequent need for improved pain medication regimens, especially among marginalized populations who experience a host of other socio-structural barriers to care. Notably, in this analysis, no significant association between pain and cannabis use was identified. However, one recent study from same study setting identified a negative association between cannabis use and unregulated opioid use, suggesting that cannabis could be an effective substitute for opioids in treating pain.²⁵⁶

The present study findings should be viewed within the context of recent studies which have highlighted healthcare provider practices that restrict patient access — especially those patients with a history of substance use—to prescription pain analgesics.^{135,136} Many PWUD report experiencing stigma/discrimination from their clinicians in the form of suspicion of drug-seeking and mistrust, which can lead to an increase in risk-taking behaviors.^{136,257} This, coupled with an influx of fentanyl contaminating the unregulated drug supply, continue to fuel the ongoing opioid crisis.^{258–260} For example, so-called doctor shopping, in which patients seek out different clinicians in the pursuit of obtaining multiple opioid prescriptions, has also been associated with overdose deaths.^{261–263} Doctor shopping may be attributed to PWUD patients feeling a lack of effective communication regarding pain management strategies with their providers, causing them to seek out the requested drugs from other clinicians, from unregulated suppliers, or by turning to higher risk alternatives, such as injecting illicitly obtained opioids.^{263,264} This emphasizes the importance of an open, stigma-free patient-provider relationship and may have potential to mitigate higher risk pain management methods.

In the present analysis, no significant association between pain and HIV clinical measures (CD4+ cell count; ART exposure, and HIV VL) were observed. This is contrary to some prior studies that found pain among PLWH is associated with poorer ART adherence and lower likelihood of achieving viral suppression.^{265–268} However, the present analysis is not the first to observe a lack of association between pain and ART adherence and VL suppression.^{269–271} One possible explanation for conflicting evidence on this relationship is the variability in the way pain is measured and defined in the literature. Pain is interpreted and experienced uniquely across genders, cultures, and individual factors, such as drug use.^{9,71,272–274} Therefore, the fluid definition of pain in the literature may affect the observable association between pain and clinical factors, leading to inconsistent evidence in different studies and settings.^{266,267,269,271} Future research investigating the association between pain and HIV clinical outcomes is warranted.

This research should be considered in light of some limitations. In addition to the limitations addressed in chapter 5, section 5.3 that are applicable to all the chapters in the present thesis, the limitations specific to this chapter are presented here. The findings from this study illustrate chronic pain is common among PLWH who use unregulated drugs. While this quantitative evaluation of pain has unique strengths, such as providing a numerical basis for interpretation of chronic pain prevalence, quantitative measures of pain are limited by the subjectivity of different pain causes and experiences. As such, mixed-methods research in this area may be beneficial.

2.4.1 Conclusions

In sum, this study is one of the first to investigate prevalence and correlates of pain among a population of PLWH who use unregulated drugs. More than half of the study population reported

moderate-to-extreme pain and several significant correlates of pain, including pain self-management and non-fatal overdose, were identified. These findings emphasize that pain is considerably undertreated among this population, raising concerns regarding the accessibility and availability of effective treatment. Undertreated pain as a result of limited access to treatment may ultimately predispose PLWH who use drugs to greater morbidity and mortality risks as they look to unregulated drugs to manage their pain. Efforts to establish integrated pain management services that enable patients to receive non-pharmacologic treatments and a consistent and safe supply of pain analgesics could be a potential pathway to supporting people with multidimensional healthcare needs, and could ultimately alleviate the burden of pain among this already heavily burdened population.

Table 2.1 Baseline characteristics of PLWH that use unregulated drugs in Vancouver, Canada, stratified by self-reported pain (n = 709)

Characteristic	Total, (100%) <i>n</i> = 709	Experienced Moderate-to-Extreme Pain		<i>p</i> - value
		Yes (52.75%) <i>n</i> = 374	No (47.25%) <i>n</i> = 335	
Age (med, IQR)	46 (40 – 52)	47 (41 – 53)	45 (38 – 51)	0.005
Sex				
Male	454 (64)	245 (66)	209 (62)	0.251
Female	235 (33)	116 (31)	119 (36)	
Ethnicity				
White	399 (56)	224 (60)	175 (52)	0.032
Non-White	171 (41.1)	26 (31)	145 (43.7)	
Highest education level				
≥ High school	329 (46)	184 (49)	145 (43)	0.129
< High school	355 (50)	178 (48)	177 (53)	
Sex work*				
Yes	68 (10)	30 (8)	38 (11)	0.136
No	638 (90)	342 (91)	296 (88)	
Homelessness*				
Yes	117 (17)	58 (16)	59 (18)	0.449
No	590 (83)	315 (84)	275 (82)	
Incarceration*				
Yes	40 (6)	23 (6)	17 (5)	0.519
No	666 (94)	348 (93)	318 (95)	
Binge alcohol use*				
Yes	169 (24)	95 (25)	74 (22)	0.292
No	539 (76)	278 (74)	261 (78)	
Binge injection drug use*				
Yes	149 (21)	83 (22)	66 (20)	0.456
No	547 (77)	285 (76)	262 (78)	
Daily cannabis use*				
Yes	151 (21)	86 (23)	65 (19)	0.252

Characteristic	Experienced Moderate-to-Extreme Pain			<i>p</i> - value
	Total, (100%) <i>n</i> = 709	Yes (52.75%) <i>n</i> = 374	No (47.25%) <i>n</i> = 335	
No	557 (79)	288 (77)	269 (80)	
Daily crack use*				
Yes	128 (18)	61 (16)	67 (20)	0.196
No	580 (82)	313 (84)	267 (80)	
Daily crystal meth injection*				
Yes	46 (7)	28 (8)	18 (5)	0.258
No	662 (93)	346 (93)	316 (94)	
Daily heroin injection*				
Yes	83 (12)	52 (14)	31 (9)	0.056
No	625 (88)	322 (86)	303 (91)	
Daily cocaine injection*				
Yes	33 (5)	20 (5)	13 (4)	0.378
No	674 (95)	353 (95)	321 (96)	
Daily non-medical prescription opioid use*				
Yes	100 (15)	67 (18)	33 (10)	0.002
No	604 (85)	306 (82)	298 (90)	
Enrolled in MMT*				
Yes	344 (49)	178 (48)	166 (50)	0.602
No	212 (51)	196 (52)	169 (50)	
Non-fatal overdose*				
Yes	42 (6)	28 (8)	14 (4)	0.063
No	667 (94)	346 (92)	321 (96)	
Self-managed pain*				
Yes	299 (42)	191 (51)	108 (32)	<.001
No	233 (33)	100 (27)	133 (40)	
Requested pain medication*				
Yes	230 (32)	166 (44)	64 (19)	<0.001
No	331 (47)	142 (38)	189 (56)	
Denied pain medication*				

Characteristic	Experienced Moderate-to-Extreme Pain			<i>p</i> - value
	Total, (100%) <i>n</i> = 709	Yes (52.75%) <i>n</i> = 374	No (47.25%) <i>n</i> = 335	
Yes	49 (7)	40 (11)	9 (3)	<0.001
No	485 (68)	253 (68)	232 (69)	
Mental illness diagnosis[†]				
Yes	458 (65)	264 (71)	194 (58)	0.005
No	250 (35)	110 (29)	140 (42)	
Attempted suicide*				
Yes	20 (3)	14 (4)	6 (2)	0.109
No	671 (95)	348 (93)	323 (96)	
CD4+ cell count (med, IQR)*	419 (270 – 570)	390 (265 – 565)	440 (270 – 580)	0.336
Viral load*				
≥ 50 copies/mL	308 (43)	156 (42)	152 (45)	0.369
< 50 copies/mL	394 (56)	213 (57)	181 (54)	
ART*				
≥ 1 day	624 (88)	328 (88)	296 (88)	0.788
0 days	85 (12)	46 (12)	39 (12)	

* Refers to the six-month period prior to interview

† Refers to ever

CI: confidence interval; IQR: interquartile range; Med: median; MMT: methadone maintenance therapy; ART: antiretroviral therapy

Table 2.2 Bivariable and multivariable GLMM analysis of factors associated with self-reporting pain among a cohort of PLWH who use unregulated drugs (n = 469)

Characteristic	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	<i>p</i> - value	Odds Ratio (95% CI)	<i>p</i> - value
Age				
Per year older	1.04 (1.02 – 1.05)	<.001	1.04 (1.02 – 1.05)	<0.001
Sex				
Male vs. Female	1.17 (0.84 – 1.63)	0.341		
Ethnicity				
White vs. non-White	1.91 (1.40 – 2.59)	<.001	1.55 (1.18 – 2.05)	0.020
Highest Education Level				
≥ High school vs. < High School	1.21 (0.89 – 1.65)	0.224		
Sex work*				
Yes vs. no	0.88 (0.65 – 1.20)	0.421		
Homelessness*				
Yes vs. no	1.14 (0.89 – 1.45)	0.299		
Incarceration*				
Yes vs. no	1.43 (0.95 – 2.15)	0.088		
Binge alcohol use*				
Yes vs. no	0.97 (0.80 – 1.18)	0.759		
Binge injection drug use*				
Yes vs. no	1.12 (0.93 – 1.35)	0.233		
Daily cannabis use*				
Yes vs. no	1.08 (0.87 – 1.33)	0.484		
Daily crack use*				
Yes vs. no	0.90 (0.71 – 1.15)	0.408		
Daily crystal meth injection*				
Yes vs. no	1.15 (0.83 – 1.59)	0.414		
Daily heroin injection*				
Yes vs. no	1.31 (1.02 – 1.67)	0.031	1.17 (0.91 – 1.51)	0.218
Daily cocaine injection*				
Yes vs. no	1.28 (0.90 – 1.82)	0.161		

Characteristic	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	<i>p</i> - value	Odds Ratio (95% CI)	<i>p</i> - value
Non-medical prescription opioid use*				
Yes vs. no	1.95 (1.56 – 2.42)	<.001	1.63 (1.30 – 2.05)	<0.001
Enrolled in MMT*				
Yes vs. no	0.94 (0.76 – 1.16)	0.557		
Non-fatal overdose*				
Yes vs. no	1.56 (1.19 – 2.03)	<.001	1.46 (1.11 – 1.93)	0.007
Self-managed pain*				
Yes vs. no	2.43 (2.10 – 2.80)	<.001	2.25 (1.94 – 2.61)	<0.001
Requested pain medication*				
Yes vs. no	2.27 (1.94 – 2.66)	<.001	2.01 (1.69 – 2.38)	<0.001
Denied pain medication*				
Yes vs. no	2.01 (1.52 – 2.66)	<.001	1.10 (0.82 – 1.48)	0.524
Mental illness diagnosis[†]				
Yes vs. no	1.63 (1.20 – 2.22)	<.001	1.47 (1.11 – 1.94)	0.007
Attempted suicide*				
Yes vs. no	1.64 (0.88 – 3.07)	0.119		
CD4+ cell count (med, IQR)*	100 (100-100)	0.230		
Viral load*				
≥ 50 copies/mL vs. < 50 copies/mL	0.95 (0.79 – 1.15)	0.611		
ART*				
≥ 1 day vs. 0 days	0.99 (0.83 – 1.19)	0.922		

* Refers to the six-month period prior to interview

[†] Refers to ever

CI: confidence interval; MMT: methadone maintenance therapy; ART: antiretroviral therapy; AOR: adjusted odds ratio; IQR: interquartile range

Chapter 3: Prevalence and correlates of self-reporting being denied pain medication among people living with HIV who use drugs with moderate-to-extreme pain

3.1 INTRODUCTION

As described in previous chapters, pain has long been recognized as one of the most common symptoms of HIV infection, with PLWH reporting pain at rates significantly higher compared to the general population.^{183,186,275,276} Studies investigating pain among PLWH have identified numerous potential causes, ranging from damage to the central and nervous systems leading to conditions such as peripheral receptor hypersensitization and neuropathy to side-effects of medications, including ART, to opportunistic infections.^{213,214,277} Other studies have failed to identify a conclusive aetiology.^{75,185,190,213,214,278}

Similarly, many marginalized PWUD report pain; the association between pain among PWUD and high-intensity unregulated opioid use, in addition to higher risks of drug-related harms, including accidental overdose, have been well studied.^{73,231,255,279,280} For example, a cross-sectional study by Dahlman and colleagues found that almost 50% of PWUD reported pain.¹⁹⁹ Similarly, in a cohort study of PWUD, Alford *et al.* observed that 87% of participants reported pain, half of which described their pain as severe.²⁸¹ Prior research has shown that, compared to PWUD who do not report pain, those with pain tend to use more heroin and other opioids from unregulated sources, likely in an effort to self-manage their untreated pain.²²¹

Despite the elevated level of pain among PWUD, studies have also detailed how substantial barriers exist to accessing safe and effective prescription analgesia.^{153,255,279} The ongoing opioid

overdose crisis has been met in some jurisdictions with efforts to shorten the course and lower the dosages of prescriptions for opioid analgesics.^{282,283}

Preliminary studies, including the findings from the previous chapter, have detailed how PLWH who use unregulated drugs report high rates of pain, including experiencing more severe pain compared to PLWH from other key affected populations.^{185,284,43,228} However, the experience of pain among this marginalized and vulnerable population is not well characterized. In one early analysis among indigent individuals living with HIV in San Francisco, most (83%) reported severe or moderate pain and misuse of opioid analgesics was associated with lower rates of optimal adherence to prescribed ART.²⁷¹

Unfortunately, despite the important role denial of pain medication among PWUD has in the ongoing opioid crisis, studies investigating pain medication denial among PWUD living with HIV and detailed links to relevant sociodemographic, behavioral, social/structural, healthcare access, and clinical factors is largely absent from the literature. There is also a dearth of information on post-denial actions taken among PWUD living with HIV. Thus, to address these gaps in the literature, this study was undertaken to measure the prevalence, estimate the correlates, and detail actions taken after being denied pain medication among a community-recruited prospective cohort of PLWH who use drugs in Vancouver, Canada.

3.2 METHODS

3.2.1 Study design and population

To address these objectives, this study used data from the ACCESS study – an open, prospective cohort of PLWH who use unregulated drugs, described in detail in chapter 1, section 1.4. This study has been described at length elsewhere.²²³

3.2.2 Study sample and inclusion/exclusion criteria

All ACCESS participants who completed at least one interview between December 2011 and November 2018 were included in this analysis. The current study includes all participants who self-reported experiencing moderate-to-extreme pain or discomfort, ascertained through the same EuroQol EQ-5D measure used and described in chapter 2, section 2.2.2. This study was further restricted to ART-exposed participants by only including interviews after a participant's earliest dispensation of ART, if any. Individuals were excluded from the study if they had not completed ≥ 1 CD4+ cell count and ≥ 1 HIV VL test within 180 days of the baseline interview. Finally, to differentiate between participants who requested and were denied pain medication to those who requested pain medication and were not denied, the sample was further restricted to participants who reported they had requested pain medication from a healthcare provider at least once in the previous six months.

3.2.3 Outcome of interest and explanatory variables

The primary outcome of interest was pain medication denial from a healthcare provider in the previous six months, elicited by the following question: *Were you refused a prescription for pain medication in the last six months?* (Yes vs No). Various sociodemographic, behavioral,

social/structural and clinical variables hypothesized to be associated with denial of pain medication were then included. These were: age; sex (male vs. female); ethnicity (white vs. non-white); education status (\geq vs. $<$ high school diploma); homelessness (yes vs. no); and recent incarceration, defined as spending at least one night in a youth detention facility, municipal jail, provincial prison or federal penitentiary (yes vs. no). Substance use factors were: binge alcohol use, defined as at least one period of above average alcohol use (yes vs. no); binge injection drug use (yes vs. no); at least daily cannabis use (yes vs. no); at least daily crack use (yes vs. no); at least daily crystal methamphetamine use (yes vs. no); at least daily heroin injection (yes vs. no); at least daily cocaine injection (yes vs. no); and at least daily illicit prescription opioid use, defined as using pharmaceutical opioids not as prescribed (yes vs. no). Other characteristics considered were: engagement in MMT (yes vs. no); recent non-fatal overdose (yes vs. no); self-management of pain (yes vs. no); attempted suicide (yes vs. no); and ever having a mental illness diagnosis (yes vs. no). Through the confidential linkage to the local HIV treatment dispensary and clinical registry, the following clinical variables were included: HIV VL (defined as <50 vs. ≥ 50 copies/mL plasma); ART dispensed in the previous six months (0 vs. ≥ 1 day); and CD4+ cell count (per 100 cells/mL blood). For HIV VL and CD4+ cell count, the median of all test results in the previous six months was used or, if none, the most recent result at the time of the study interview.

Various aspects of healthcare access that may be associated with being denied pain medication within the greater context of the care environment were also examined. These were: accessed a family physician (yes vs. no); accessed a community clinic (yes vs. no); accessed a specialist (yes vs. no); accessed a methadone physician (yes vs. no); accessed a hospital emergency department (yes vs. no); accessed a hospital (yes vs. no); accessed a prison physician (yes vs. no); accessed outreach healthcare (yes vs. no); and accessed dental care (yes vs. no). All variables save

sex, education status, and ethnicity were time-updated and refer to behaviors or exposures that occurred in the six-month period prior to the interview.

3.2.4 Data analysis

First, descriptive baseline characteristics of the analytic sample, stratified by self-reported pain medication denial, were examined. Variables in each of the strata were analyzed using Wilcoxon rank sum tests (for continuous variables) and Pearson's Chi-Squared test (for categorical variables) to test for significant differences in the distribution of each explanatory variable. As a next step, and to account for the inherent correlation in observations gathered from each individual, generalized estimating equations (GEE) with logistic regression were used to estimate the relationship between each explanatory variable and being denied pain medication. Using an *a priori*-defined statistical method based on the Quasi-likelihood under Independence Model Criterion (QIC), a full model was constructed, followed by a step-wise procedure removing the secondary explanatory variable with the highest *p*-value, resulting in a reduced multivariable model. This process was continued until no explanatory variables remained and selected as the final multivariable model based lowest corresponding QIC score, as this was indicative of the best fit model with the optimal number of parameters.²²³

In a sub-analysis, the actions self-reported by participants after they were refused pain medication were analyzed. Participants who reported being refused a prescription for pain medication in the previous six months were then asked what they did after they were refused. Participants were able to select from six pre-defined responses (e.g., "Diversion to unregulated drugs", "went to a different doctor/clinic") developed by the study investigators and front-line interview/nursing staff, and could also provide other responses which were recorded in free text.

These free-text responses were analyzed (by JL and M-JM) and recategorized into one of the pre-defined categories or categorized into one of five additional categories: consumed alcohol; obtained unregulated non-opioid drugs (e.g., stimulants); used an over-the-counter medication (e.g., acetaminophen, ibuprofen); used cannabis; and other actions. Responses categorized as “Other actions” were those which did not fit into one of the structured categories, and represented a very small proportion of responses. A frequency table was then constructed using denial of pain medication as the outcome, stratified by each action following denial of pain medication. All statistical analyses were conducted using R, version 1.1.456 (R Foundation for Statistical Computing, Vienna, Austria). All p-values were two-sided, with a defined threshold for significance at $p < 0.05$.

3.3 RESULTS

Between December 2011 and November 2018, 575 study participants completed 2931 study interviews. Of these, 416 individuals contributing 1142 interviews had complete baseline clinical data. Of these, 506 interviews (from 416 participants) contained a report of pain. Among these interviews, 316 interviews (from 416 participants) included a report of requesting pain relief and were included in the final analytic sample. Among these participants, 84 (20.2%) people reported being denied pain medication.

Among the sample of 416 PLWH who use unregulated drugs that experience pain, 178 (42.3%) participants self-reported being denied pain medication at least once throughout the entire study period. The characteristics of the study sample at their earliest study interview, stratified by denial of pain medication, are reported in Table 3.1.

As shown in Table 3.1, study participants included 265 (63.7%) males, their median age was 49.1 years (IQR: 42.9–54.4), and 243 (58.4%) identified as white. The median number of follow-up interviews completed per study participant during the study period was 4 (IQR: 2–8).

At baseline, 279 (67.1%) participants reported self-management of pain and 301 (72.4%) reported ever being diagnosed with a mental illness. Of note, 16 (3.8%) individuals had attempted suicide in the previous six months. Among the clinical measures included in this analysis (i.e., CD4+ cell count, VL >50 copies/mL, and receiving ART in the L6M), none were found to be significantly associated with being denied pain medication. Table 3.2 presents the baseline healthcare utilization characteristics among the study sample, stratified by pain medication denial. At baseline, 308 (92.8%) participants who had not been denied medication had seen a family physician in the past six months.

The bivariable and multivariable analyses of the explanatory factors are presented in Table 3.3. In unadjusted GEE analyses, being denied pain medication was positively associated with several measures of high-intensity substance use (e.g., binge alcohol use, daily injection cocaine use, and daily crack use). In the multivariable model, being denied pain medication remained independently and positively associated with daily injection cocaine use (AOR = 1.95, 95% CI: 1.04–3.68) and incarceration (AOR = 2.35, 95% CI: 1.30–4.26). Notably, in the adjusted model, being denied pain medication was independently associated with approximately five times the odds of self-management of pain (AOR = 4.69; 95% CI: 2.98–7.40) and more than four times the odds of reporting a recent suicide attempt (AOR = 4.28; 95% CI: 1.87–9.81).

Table 3.4 presents the bivariable and multivariable logistic regression analysis of various healthcare utilization factors. At the bivariable level, denial of pain medication was significantly associated with accessing a general physician and accessing a prison physician. In the

multivariable GEE model, being denied pain medication remained independently and negatively associated with accessing a general physician (AOR = 0.32, 95% CI: 0.21–0.49).

The results from the sub-analysis of self-reported actions taken after being denied prescription medication are shown in Table 3.5. The most common action taken after being denied pain medication was diversion to unregulated drugs (181, 52.5%). This category contains responses from four subcategories: bought the requested medication off the street (79, 22.9%), obtained unregulated opioids (52, 15.1%), bought a different pain medication off the street (34, 9.9%), and obtained unregulated non-opioid drugs (16, 4.6%). The next most common actions reported were: no action taken (127, 36.8%), going to a different doctor/clinic/emergency room (28, 8.1%), other actions (13, 3.8%), using over-the-counter medications (10, 2.9%), consuming alcohol (8, 2.3%), using cannabis (6, 1.74%), and using medication from a friend/partner/acquaintance (2, 0.6%).

3.4 DISCUSSION

In this study of PLWH who use unregulated drugs living with moderate-to-extreme pain, being denied pain medications by a healthcare provider was a common experience, with approximately one-in-five participants at baseline reporting being denied in the previous six months. Being denied pain medication was also associated with pain self-management, often involving high-risk administration of unknown substances, including fentanyl being sold as heroin. Notably, the present study found that individuals who were denied pain medication were more likely to have reported attempting suicide in the same six-month period. In a sub-analysis examining the actions taken following being denied pain medication, approximately half of participant responses indicated diversion to unregulated opioids.

This study supports previous research findings that have found that undertreatment of pain is common and continues to persist among PWUD.^{136,286–288} One study found that 98% of PWUD had to self-manage their undertreated pain, most often with injection heroin and nonmedical use of prescription pain medication.¹³⁶ In another recent analysis, almost half of the study population reported chronic pain; three-quarters of which were not receiving adequate pain management and had to self-manage their pain.²⁸⁶

This study is among the first to explore denial of pain medication among PLWH who use drugs. In one early study of people with AIDS with and without a diagnosed substance use disorder, those who used drugs were less likely to receive adequate pain medications and reported lower levels of pain relief compared to those who did not use drugs.²⁸⁸ The finding from this study of a link between pain medication denial and use of diverted medications is consistent with a previous qualitative study of PLWH who use drugs who had their access to pain medication restricted or discontinued.²⁸⁹ Similar to this and other studies, the present study findings suggest that after being denied pain medication, turning to high-risk drug use (e.g., injecting heroin or unregulated prescription opioids) was common.^{136,255,290} However, research indicating the choice of diverted drugs has been mixed. In contrast to this study, and others, some studies found associations between undertreated pain and the use of heroin and unregulated prescription opioids, but not the use of stimulants (e.g., crystal methamphetamine, crack, cocaine) or cannabis.^{221,290,291} However, in one study of 462 PWUD, being denied pain medication was associated with two times the odds of cocaine injection, but not the use of cannabis, heroin, unregulated prescription opioids, or alcohol.¹³⁵ In yet another study, untreated pain was associated with risky alcohol use (defined as more than 14 drinks/week) among a cohort of HIV-positive drinkers in Russia.²⁹² These findings, though they suggest different routes of self-medication, collectively support that pain is

highly prevalent and undertreated among PLWH who use unregulated drugs, which in turn, influences and may contribute to high-risk substance use behaviors.

The current study findings are consistent with prior studies showing that individuals who are denied pain medication are more likely to self-manage pain, often by means that pose a higher health risk, such as obtaining substances from the unregulated drug market.^{136,153,255} For example, in a U.S.-based analysis of youth who used prescription opioids, Fibbi *et al.* found that participants who were denied pain medication were more likely to engage in more harmful drug use behaviors and patterns (e.g. taking higher doses of a drug and initiating injection heroin use) than those who were not denied pain medication.¹⁵³ The present analyses revealed that, after being denied pain medication, over half of the study responses indicated diversion to unregulated drugs. These findings emphasize the dangers of pain self-management as well as links to the ongoing opioid crisis. Despite the well-known risks associated with use of diverted medications, such as exposure to the fentanyl-contaminated unregulated drug supply, and ultimately, a higher risk of overdose, the findings from this analysis suggest that for many PLWH who use unregulated drugs, pain management is a higher priority than the risk of overdose.

In the present analyses, being denied pain medication was associated with approximately four times the odds of attempting suicide. This finding builds upon existing literature suggesting a relationship between inadequately managed pain and suicide.^{280,293,294} One study in the United States found that 9% of suicide decedents had documented evidence of severe pain, though the authors cautioned that this is likely an underrepresentation of the true rate given inconsistencies in diagnosing pain, barriers to accessing prescription medication (which would result in a lack of documented evidence of pain), and the sensitive nature of suicidality.²⁹³ Attempted suicide among PWUD is common, with some studies indicating 7% to 32% of PWUD having reported at least

one attempt.^{148,227,295–297} In a retrospective analysis of decedents with known drug use in Singapore, 64% had died by suicide, with more than 50% of the cohort having been diagnosed with depression.²⁹⁸ While many factors influence the risk of suicide among PWUD, including high rates of mental illness and increased exposure to perpetrated violence, the association between suicide and methadone use—most commonly used as a treatment for opioid use disorder and, to a lesser extent, as an analgesic—has more recently been explored in the literature.^{164,299–301} In a secondary exploration of data from a randomized control trial of opioid dependent patients with pain, methadone was found to be a successful agent in reducing pain, however, more than half of patients exhibiting significant pain at each follow up reported their current pain treatment dosage as insufficient, prompting diversion to unregulated drugs for pain relief.^{302,303}

Given the high risk of both pain and attempted suicide among PWUD, the present study findings support the need for improved preventative interventions, such as the incorporation of pain assessments in suicide screening and integrated, accessible pain management services for PLWH who use unregulated drugs. Further exploration of risk factors, as well as protective factors, of attempted suicide is critical to effectively develop these interventions. Although in this study, I did not collect data on why participants thought they were denied medication, two explanations from the recent literature to consider are stigma against so-called drug seeking PWUD and the unintended consequences of restrictive measures meant to reduce opioid over-prescribing in the context of the overdose crisis. Despite exhibiting higher prevalence of pain and other health challenges among PWUD, there still exist many barriers to adequate pain management and treatment programs. Stigma against PWUD presenting with pain, particularly in the form of being accused of drug seeking by healthcare providers, is a significant barrier to accessing adequate pain management treated reported among PWUD.^{169,304} Studies suggest that discrimination and stigma

against PWUD predicts lower health care utilization, decreased access to harm reduction services, and inadequate treatment of pain.^{225,257,305,306} Among PLWH who use drugs, these debilitating experiences are often compounded as patients face challenges with accessing timely HIV treatment, harm reduction services, and adequate pain management.^{307–310} The current study suggests that denial of effective analgesia or non-pharmacologic pain management for PWUD living with pain can also contribute to negative drug-related sequelae, including self-management of pain via substances from the unregulated drug supply.

Findings from the present study did not reveal any significant association between denial of pain medication with HIV clinical measures. However, previous studies have linked pain among PLWH with poorer HIV clinical status. For example, in a study of PLWH who use illicit drugs in Florida, those with untreated pain had a 42% lower odds of achieving VL suppression and were less likely to adhere to ART compared to those without pain.²⁶⁷ Similarly, PWUD with chronic pain are also more likely to request pain management healthcare utilization as well as demonstrate a lower likelihood of achieving optimal ART adherence.²⁶⁸ Pain plays a significant negative role on various aspects of QOL, which in itself is multidimensional; an interconnected web of physical, social, mental, spiritual, and psychological well-being. All of these aspects of QOL are vulnerable to a number of HIV-specific and drug related factors, including, but not limited to, direct effects from HIV itself, side effects from ART, complications associated with drug use, and the burden of stigma.^{186,190,208} Given the vulnerabilities independently associated with HIV infection, compounded with those associated with drug use, pain experienced by PLWH who use unregulated drugs should be addressed through evidence-based, tailored pain interventions and strategies that empower the individual. A recent systematic review by Merlin and colleagues found that, despite the high prevalence of pain among PLWH, there were only 11 studies investigating potential

avenues of treatment; of these, only one higher-quality investigation on the use of capsaicin showed promise.^{311,312} While a set of clinical guidelines for the use of opioid analgesics to treat pain is available, studies assessing adherence to these guidelines has indicated that many complementary therapies are underutilized, such as combination therapies.^{26,244,245} Moreover, there are currently no non-pharmacological guidelines tailored to address pain among PWUD, in particular behavioral, interventional, and alternative therapies. Further research exploring the efficacy of these other therapeutic approaches should be a priority.

PLWH who use unregulated drugs experience complex, intertwined co-morbid conditions that contribute to negative health outcomes and require unique, multidimensional interaction with the larger healthcare environment.^{150,313} A wealth of prior research has shown that despite experiencing higher rates of illness and co-infections, both PWUD and PLWH report poorer access to healthcare services, are more likely to be discharged from the hospital prematurely, experience stigma and discrimination in accessing care, and report receiving inferior care compared to non-PWUD and non-PLWH.^{155,288,308,314–316} The present study found that accessing a general physician in the past six months was a protective factor associated with being denied pain medication. Among those who had seen a physician in the past six months, a 68% reduced odds of having been denied pain medication was observed. However, there were no significant associations between denial of pain medication and accessing a healthcare clinic, specialist, hospital, methadone doctor, emergency room, outreach care, or dental care. One possible interpretation of the finding that accessing a general physician may serve as a protective factor on being denied pain medication is the association of positive, well-established patient-provider relationships on patient health outcomes. Past studies have shown that positive, trusting relationships between patients and their providers may increase patient satisfaction and encourage patients to participate in shared decision

making, ensuring they feel empowered and respected.³¹⁷⁻³¹⁹ Among PLWH, positive relationships with providers have been shown to positively influence ART initiation, adherence, and achieving VL suppression.^{319-322,322-326} Given the increasing recognition of the benefits of multidisciplinary care on health care utilization, retention, and outcomes, future research is needed to better understand the relationship between access to pain medication and access to elements of the broader healthcare environment.^{313,327-331}

Limitations shared across the studies in this thesis are presented in chapter 5, section 5.3. However, there are limitations specific to this chapter that merit discussion, First, in this study, the study population was restricted to only include people who had requested pain medication in the past six months. This restriction was imposed in order to make a more accurate assessment of the prevalence of being denied pain medication; however, it likely underestimates the prevalence of untreated pain in this sample, as it may fail to capture those had previously been denied and have since ceased asking their providers for analgesia. Another limitation of the present study is the reduced number of observations of the measurement for attempted suicide. Given the stigma attached to suicide and mental health, it is not surprising that the frequency of participant responses for this variable are lower than other variables as participants may be less likely to provide a response. Instead of omitting attempted suicide from the final model, this measure was included in order to examine the relationship between pain medication denial and attempted suicide. While this ultimately decreased the sample size from 416 participants in the initial model to 366 participants in the bivariable and multivariable analysis, it was decided by the candidate to include this measure given that PLWH and PWUD experience high rates of undertreated pain, stigma, and increased risk of suicide.

3.4.1 Conclusions

This is the first study to investigate associations of pain medication denial and actions taken after being denied pain medication among a cohort of PLWH who use unregulated drugs. The results from this study indicated that a substantial proportion of PLWH who use unregulated drugs are denied pain medication. In multivariable GEE analysis, it was found that pain medication denial was independently associated with pain self-management and attempted suicide. These findings indicate that provision of adequate pain management may reduce the risks associated with self-management of pain and improve the QOL for PLWH who use unregulated drugs, which, in turn, could reduce the risk of attempted suicide. These findings also support establishing comprehensive and accessible pain management approaches for PLWH who use unregulated drugs that address the wide range of unique health needs specific to this population.

Table 3.1 Sociodemographic, behavioral, social/structural, and clinical characteristics at baseline of PLWH that use unregulated drugs living with pain stratified by recent denial of pain medication (n = 416)

Characteristic	Total, n = 416 (100%)	Denied Pain Medication		p - value
		Yes, n = 84 (20.2%)	No, n = 332 (79.8%)	
Age (med, IQR)	49.1 (42.9-54.4)	48.2 (43.1-51.6)	49.4 (42.9-54.8)	0.058
Sex				
Male	265 (63.7)	59 (70.2)	206 (62.0)	0.237
Female	139 (33.4)	24 (28.6)	115 (34.6)	
Ethnicity				
White	243 (58.4)	58 (69.0)	185 (55.7)	0.03
Non-White	171 (41.1)	26 (31.0)	145 (43.7)	
Education status				
≥ High school	202 (48.6)	34 (40.5)	168 (50.6)	0.199
< High school	201 (48.3)	44 (52.4)	157 (47.3)	
Homelessness*				
Yes	35 (8.4)	8 (9.5)	27 (8.1)	0.682
No	381 (91.6)	76 (90.5)	305 (91.9)	
Incarceration*				
Yes	15 (3.6)	9 (10.7)	6 (1.8)	<.0001
No	398 (95.7)	73 (86.9)	325 (97.9)	
Binge alcohol use*				
Yes	98 (23.6)	25 (29.8)	73 (22)	0.149
No	314 (75.5)	59 (70.2)	255 (76.8)	
Binge injection drug use*				
Yes	70 (16.8)	23 (27.4)	47 (14.2)	0.003
No	344 (82.7)	59 (70.2)	285 (85.8)	
Daily cannabis use*				
Yes	94 (22.6)	20 (23.8)	74 (22.3)	0.776
No	321 (77.2)	64 (76.2)	257 (77.4)	
Daily crack use*				

Characteristic	Denied Pain Medication			p - value
	Total, n = 416 (100%)	Yes, n = 84 (20.2%)	No, n = 332 (79.8%)	
Yes	67 (16.1)	21 (25)	46 (13.9)	0.012
No	347 (83.4)	62 (73.8)	285 (85.8)	
Daily crystal meth use*				
Yes	15 (3.6)	3 (3.6)	12 (2.6)	0.985
No	399 (95.9)	79 (94)	320 (96.4)	
Daily heroin injection*				
Yes	36 (8.7)	11 (13.1)	25 (7.5)	0.090
No	378 (90.9)	71 (84.5)	307 (92.5)	
Daily cocaine injection*				
Yes	27 (6.5)	9 (10.7)	18 (5.4)	0.068
No	387 (93)	73 (86.9)	314 (94.6)	
Daily prescription opioid use*				
Yes	26 (6.3)	7 (8.3)	19 (5.7)	0.351
No	387 (93)	75 (89.3)	312 (94)	
Enrolled in MMT*				
Yes	204 (49)	49 (58.3)	155 (46.7)	0.057
No	212 (51)	35 (41.7)	177 (53.3)	
Non-fatal overdose*				
Yes	20 (4.8)	5 (6)	15 (4.5)	0.583
No	396 (95.2)	79 (94)	317 (95.5)	
Self-managed pain*				
Yes	279 (67.1)	79 (94.0)	200 (60.2)	<0.001
No	134 (32.2)	5 (6.0)	129 (38.9)	
Mental illness †				
Yes	301 (72.4)	62 (73.8)	239 (72)	0.739
No	115 (27.6)	22 (26.2)	93 (28)	
Attempted suicide*				
Yes	16 (3.8)	6 (7.1)	10 (3.0)	0.079
No	360 (86.5)	70 (83.3)	290 (87.3)	

Characteristic	Denied Pain Medication			<i>p</i> - value
	Total, <i>n</i> = 416 (100%)	Yes, <i>n</i> = 84 (20.2%)	No, <i>n</i> = 332 (79.8%)	
CD4+ cell count (med, IQR)*	390 (260 – 580)	370 (270 – 590)	390 (260 – 580)	0.677
Viral load*				
≥ 50 copies/mL	136 (32.7)	28 (33.3)	108 (32.5)	0.918
< 50 copies/mL	263 (63.2)	53 (63.1)	210 (63.3)	
ART*				
≥ 1 days	386 (92.8)	77 (91.7)	309 (93.1)	0.34
0 days	13 (3.1)	4 (4.8)	9 (2.7)	

* Refers to the six-month period prior to interview
† Refers to ever
CI: confidence interval; IQR: interquartile range; Med: median; DTES: downtown Eastside;
MMT: methadone maintenance therapy; ART: antiretroviral therapy

Table 3.2 Baseline healthcare utilization characteristics of PLWH that use unregulated drugs living with pain stratified by denial of pain medication (n = 416)

Characteristic	Total, <i>n</i> = 416 (100%)	Denied Pain Medication		<i>p</i> - value
		Yes, <i>n</i> = 84 (20.2%)	No, <i>n</i> = 332 (79.8%)	
Family physician*				
Yes	374 (89.9)	66 (78.6)	308 (92.8)	0.001
No	42 (10.1)	18 (21.4)	24 (7.20)	
Attended a community clinic*				
Yes	120 (28.8)	21 (25.0)	99 (29.8)	0.384
No	296 (71.2)	63 (75.0)	233 (70.2)	
Specialist physician*				
Yes	164 (39.4)	32 (38.1)	132 (39.8)	0.780
No	252 (60.6)	52 (61.9)	200 (60.2)	
Methadone physician*				
Yes	35 (8.40)	5.0 (6.0)	30 (9.0)	0.363
No	381 (91.6)	79 (94.0)	302 (91.0)	
Emergency room visit*				
Yes	159 (38.2)	36 (42.9)	123 (57.0)	0.328
No	257 (61.8)	48 (57.1)	209 (63.0)	
Hospital care*				
Yes	103 (24.8)	25 (29.8)	78 (23.5)	0.234
No	313 (75.2)	59 (70.2)	254 (76.5)	
Prison physician*				
Yes	21 (5.0)	11 (13.1)	10 (3.0)	0.002
No	395 (95.0)	73 (86.9)	322 (97.0)	
Outreach care*				
Yes	80 (19.2)	18 (21.4)	62 (18.7)	0.567
No	336 (80.8)	66 (78.6)	270 (81.3)	
Dental care*				
Yes	30 (7.20)	10 (11.9)	20 (6.0)	0.063
No	386 (92.8)	74 (88.1)	312 (94)	

* Refers to the six-month period prior to interview

Table 3.3 Bivariable and multivariable generalized estimating equations (GEE) analyses of factors associated with being denied pain medication among PLWH who use unregulated drugs with pain (n = 366)

Characteristic	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	<i>p</i> - value	Odds Ratio (95% CI)	<i>p</i> - value
Age				
Per year older	0.98 (0.96 – 1.00)	0.019	0.99 (0.97 – 1.01)	0.334
Sex				
Male vs. Female	1.29 (0.93 – 1.86)	0.161		
Ethnicity				
White vs. non-White	1.29 (0.93 – 1.78)	0.123		
Education Status				
≥ High school vs. < High school	0.98 (0.71 – 1.36)	0.905		
Homelessness*				
Yes vs. no	1.17 (0.73 – 1.89)	0.513		
Incarceration*				
Yes vs. no	2.45 (1.40 – 4.28)	0.002	2.35 (1.30 – 4.26)	0.047
Binge alcohol use*				
Yes vs. no	1.37 (1.01 – 1.85)	0.045	1.30 (0.90 – 1.87)	0.165
Binge injection drug use*				
Yes vs. no	1.35 (0.98 – 1.86)	0.063		
Daily cannabis use*				
Yes vs. no	1.33 (0.96 – 1.82)	0.082		
Daily crack use*				
Yes vs. no	1.58 (1.06 – 2.37)	0.025	1.32 (0.80 – 2.20)	0.282
Daily crystal meth use*				
Yes vs. no	0.99 (0.55 – 1.81)	0.986		
Daily heroin injection*				
Yes vs. no	1.85 (1.24 – 2.75)	0.002	1.21 (0.74 – 1.99)	0.444
Daily cocaine injection*				
Yes vs. no	1.88 (1.09 – 3.26)	0.024	1.95 (1.04 – 3.68)	0.038

Characteristic	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	<i>p</i> - value	Odds Ratio (95% CI)	<i>p</i> - value
Daily prescription opioid use*				
Yes vs. no	1.16 (0.76 – 1.79)	0.488		
Enrolled in MMT*				
Yes vs. no	1.48 (1.09 – 2.00)	0.012	1.29 (0.89 – 1.86)	0.179
Non-fatal overdose*				
Yes vs. no	1.43 (0.97 – 2.11)	0.067	1.11 (0.58 – 2.13)	0.747
Self-managed pain*				
Yes vs. no	3.14 (2.33 – 4.21)	<0.001	4.69 (2.98 – 7.40)	<0.001
Mental illness diagnosis[†]				
Yes vs. no	0.95 (0.67 – 1.35)	0.769		
Attempted suicide*				
Yes vs. no	4.04 (1.91 – 8.58)	<0.001	4.28 (1.87 – 9.81)	0.006
CD4+ cell count (med, IQR)*	98 (92 – 103)	0.407		
Viral load*				
≥ 50 copies/mL vs. < 50 copies/mL	1.09 (0.81 – 1.47)	0.560		
ART*				
≥ 1 day vs. 0 days	0.65 (0.27 – 1.52)	0.319		

* Refers to the six-month period prior to interview

† Refers to ever

CI: confidence interval; MMT: methadone maintenance therapy; ART: antiretroviral therapy; AOR: adjusted odds ratio; IQR: interquartile range

Table 3.4 Bivariable and multivariable generalized estimating equations (GEE) analyses of healthcare utilization factors associated with being denied pain medication among PLWH who use unregulated drugs with pain (n = 366)

Characteristic	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	<i>p</i> - value	Odds Ratio (95% CI)	<i>p</i> - value
Family physician*				
Yes vs. no	0.44 (0.30 – 0.63)	<0.001	0.32 (0.21 – 0.49)	<0.001
Attended a community clinic*				
Yes vs. no	1.00 (0.76 – 1.31)	0.999		
Specialist physician*				
Yes vs. no	0.89 (0.68 – 1.16)	0.385		
Methadone physician*				
Yes vs. no	0.80 (0.54 – 1.18)	0.255		
Emergency room visit*				
Yes vs. no	1.19 (0.93 – 1.53)	0.162		
Hospital care*				
Yes vs. no	1.11 (0.83 – 1.48)	0.476		
Prison physician*				
Yes vs. no	2.72 (1.59 – 4.68)	<0.001	1.42 (0.68 – 2.99)	0.354
Outreach care*				
Yes vs. no	1.01 (0.76 – 1.36)	0.923		
Dental care*				
Yes vs. no	0.99 (0.68 – 1.42)	0.941		

* Refers to the six-month period prior to interview
 CI: confidence interval

Table 3.5 Self-reported actions taken following being denied prescription medication among people living with HIV who use unregulated drugs in Vancouver, Canada (n = 345 reports)

Action taken after being denied prescription medication	Frequency † n (%), n = 345
Diversion to unregulated drugs	181 (52.5)
Bought the requested medication off the street	79 (22.9)
Obtained unregulated opioids	52 (15.1)
Bought a different pain medication off the street	34 (9.9)
Obtained unregulated non-opioid drugs	16 (4.6)
No action taken	127 (36.8)
Went to a different doctor/clinic/emergency room	28 (8.1)
Other actions	13 (3.8)
Used over-the-counter medication (e.g. ibuprofen, acetaminophen)	10 (2.9)
Consumed alcohol	8 (2.3)
Used cannabis	6 (1.7)
Used medication from a friend/partner/acquaintance	2 (0.6)

† Participants were able to provide more than one response

Chapter 4: Characterizing self-management of pain among people living with HIV who use unregulated drugs

4.1 INTRODUCTION

Chronic pain affects approximately one-third (33%) of the global adult population and is the worldwide leading cause of disability and burden of disease.^{65,66,332,333} As discussed in previous chapters, among marginalized communities managing other complex co-morbid conditions, such as PLWH and PWUD, studies have consistently documented higher levels of chronic pain compared to the general population, with prevalence estimates ranging between 36% to 90%.^{189,228,270,288,334–336}

Although current clinical pain management strategies vary considerably, the World Health Organizations' clinical guidelines for managing chronic cancer pain have generally been used as the primary platform for chronic non-cancer pain management protocols.³³⁷ According to these guidelines, first-line treatment of chronic pain is the use of opioid analgesics. However, a large body of research has raised concerns about the addictive properties and potential pharmaceutical contraindications of opioids being used as a first-line of treatment among PWUD and PLWH.^{26,65,120,229,259,335,338–347} In particular, concerns over the risk of patient substance use and dependence, in addition to increased oversight by regulators, have been cited by physicians as driving factors in limiting patient opioid access.^{348–351} This has contributed to a decline in overall opioid prescribing practices across many jurisdictions within North America, ultimately restricting access to pain medications and creating additional barriers for patients with pain, leading many to seek out alternative (high-risk) forms of pain relief elsewhere (e.g. seeking out heroin).^{121,135,153,255}

Especially concerning is the (albeit unintended) interaction between these structural restrictions and the contamination of the unregulated drug supply with highly potent drugs such as fentanyl. Together, these circumstances have further fueled the opioid crisis, resulting in unprecedented levels of opioid-related overdose morbidity and mortality.^{89,105}

Despite the abundance of evidence showing disproportionately higher rates of chronic pain among PWUD and PLWH, people in these populations continue to report challenges accessing and acquiring appropriate pain management from healthcare providers, particularly when requiring opioid-based medications.^{240,270,276,352,353} For example, a qualitative analysis exploring the healthcare experiences of PWUD living with HIV and/or HCV recounted patient challenges with accessing and navigating the healthcare system, as well as obtaining adequate and timely pain management from their providers.²²⁵ These negative interactions and patient-provider barriers, shaped by institutionalized stigma against PLWH and substance use, can be profoundly detrimental to the health of marginalized patients, in part because it negatively influences their future willingness to engage in hospital care.²²⁵ A number of studies highlight the importance of communication and positive interactions between patients and their healthcare providers on healthcare engagement, HIV disclosure, improved individual health outcomes, and substance use recovery.^{326,354–357}

One of the significant findings from the previous chapter (chapter 3) indicated that limiting pain medication access is associated with individuals self-medicating via higher risk methods, such as injecting heroin or using prescription opioids from unregulated sources, which are often diverted or counterfeit.^{135,136,153,230,255,358} In one study by Voon and colleagues, 68% of PWUD with extreme pain reported pain self-management via high-risk methods, including obtaining diverted prescriptions.³³⁶ Although some prior studies have identified the consequences of denial of pain

medication among PWUD and the effect of undertreated pain on clinical outcomes and QOL among PLWH, there is a limited body of evidence that has characterized pain self-management strategies among PLWH who use drugs. Understanding the correlates of pain self-management, as well as identifying common self-management methods, can provide a basis for development of pain-specific treatment guidelines for PLWH who use drugs. Thus, this study was undertaken to characterize the relationship between pain self-management and various socio-structural, clinical, and demographic variables, as well as to investigate common methods of pain self-management among PLWH who use unregulated drugs living with chronic pain.

4.2 METHODS

4.2.1 Study design and population

Data for this study were drawn from ACCESS study, which was described at length in chapter 1, section 1.4.

4.2.2 Study sample and inclusion/exclusion criteria

Participants were included in the present analysis if they had completed at least one interview between June 2014 and November 2017. The current study was further restricted to ART-exposed participants who had contributed ≥ 1 CD4+ cell count and ≥ 1 plasma HIV-1 RNA VL count within six months of their baseline interview, and who had self-reported moderate-to-extreme pain in the previous six months measured using the EuroQol EQ-5D, a previously validated health utility instrument used in the previous chapters of this thesis, and that has been used in other studies of PLWH, PWUD, and people living with pain.^{135,226,255,359,360}

4.2.3 Outcome of interest and explanatory variables

The primary outcome of interest for the present analyses was pain self-management in the previous six months, elicited by the following question: *What medications are you currently prescribed for your pain?* If they answered: not currently prescribed any medications for pain, the following question was asked: *In the last six months, have you managed your pain on your own?* (Yes vs No). For the purpose of this analysis, pain self-management was defined as using any method to manage one's pain, and was not restricted to include only substance-based methods. To investigate correlates of pain self-management, several demographic, behavioral, and socio-structural explanatory factors believed to be potential correlates of pain included: age (in years); sex (male vs. female); ethnicity (white vs. non-white); homelessness (yes vs. no); incarceration (yes vs. no); daily alcohol use (yes vs. no); daily cannabis use (yes vs. no); daily heroin injection (yes vs. no); daily non-medical prescription opioid injection (yes vs. no), and engagement in MMT (yes vs. no). All variables except sex and ethnicity were time-updated variables, referring to exposures that occurred in the six-months preceding each study interview. Time-updated variables assessing lifetime diagnosis with major pain conditions were also considered, including: neuropathic pain (yes vs. no); inflammatory pain (yes vs. no); musculoskeletal pain (yes vs. no); or never being diagnosed with a chronic pain condition (yes vs. no). Finally, the following HIV-related clinical measures from the DTP linkage were included: CD4+ cell count (per 100 cells/mL) and HIV-1 RNA VL (< 50 vs. ≥ 50 copies/mL plasma). For the clinical measures, the median of all observations collected via the study or in the course of regular clinical care within the previous six-month period were used, or, if unavailable, the most recent observation.

4.2.4 Data analysis

First, baseline characteristics of study sample were stratified by whether or not they reported pain self-management (Yes vs. No) and examined. Categorical variables were analyzed using Pearson's Chi squared test and Fisher's exact test (if one or more cells contained frequencies less than or equal to five) whereas continuous variables were analyzed using Wilcoxon rank-sum test. Descriptive statistics were calculated to describe characteristics of the study sample at baseline. Next, GLMM were used to conduct bivariable and multivariable analyses of explanatory variables and the outcome. To construct a multivariable model, an *a-priori* defined modelling procedure was used. Using a backwards selection approach with Likelihood Ratio Tests, reduced models were fit by removing one variable at a time from the full model and comparing the coefficients from each reduced model to the full model. This iterative process was continued until the minimum change in the coefficient of the independent variable of interest from the full model exceeded 5%. All p-values were two-sided and set at $p < 0.05$.

The same procedure used to observe baseline descriptive statistics (described above) was used to analyze self-reported pain management methods employed in the previous six months. Participants who reported pain self-management in the past six months were then asked to indicate how they self-managed their pain. They were able to select from pre-defined categories (e.g., "used cannabis", "used opioids", "without any type of drug") or provide their own response which were recorded in free text. All free-text responses were analyzed and were either manually redistributed into one of the pre-defined subcategories or, for those which did not fall into one of the predefined categories and represented a notable proportion of responses, additional subcategories were created (e.g., "used hot and cold hydrotherapy"). All subcategories were categorized as either

“Medication/Substance-based Pain Management Methods” or “Non-pharmacologic Pain Management Methods”. Participants were able to provide more than one response.

An additional sub-analysis was conducted to investigate the specific type of unregulated drugs/medications used to self-manage pain within the past 24-hour period. All responses were recorded in free text and manually analyzed and recategorized by JL into six categories (e.g., “opioids”, “cannabis”, “amphetamines”, “over-the-counter medications”, “non-opioid based prescription medications”, and “alcohol”). Categories were not restricted by method of use (e.g., ingestion, injection, smoking) and participants were able to provide more than one response.

All statistical analyses were performed using R version 1.1.456 (R Foundation for Statistical Computing, Vienna, Austria).

4.3 RESULTS

Between June 2014 and November 2017, a total of 588 participants completed ≥ 1 study interview and had ≥ 1 CD4 and ≥ 1 VL measurement within 180 days of their baseline interview. Among these, 486 (82.7%) participants reported chronic pain, were not currently receiving pain medication prescriptions from their doctors, and were included in the final analytic sample; of these, 342 (70.4%) reported pain self-management at baseline. A total of 1,649 observations were contributed over the entire study period; of these, 1137 (69.0%) reported pain self-management. At baseline, study participants included 306 males (63.0%), with a median age of 44.2 years (IQR: 38.2–48.9). The full list of baseline characteristics, stratified by pain self-management (Yes vs. No), are shown in Table 4.1.

Table 4.2 presents the results of the bivariable and multivariable GLMM analyses examining the relationship between the explanatory variables of interest and pain self-

management. As shown, variables that were significant in the bivariable analysis that remained significantly and independently associated with pain self-management were: age (AOR = 0.98 per year older, 95% CI: 0.96–1.00); homelessness (AOR = 1.72, 95% CI: 1.06–2.79); daily injection heroin use (AOR = 2.30, 95% CI: 1.42–3.71); daily non-medical prescription opioid injection (AOR = 2.70, 95% CI: 1.28–5.71); never being diagnosed with a pain condition (AOR = 0.70, 95% CI: 0.51–0.95); and CD4+ cell count (AOR = 1.08 per 100 cells/mL, 95% CI: 1.02–1.14).

The sub-analysis of various pain self-management methods used in the last six months contained 555 responses. Most (367, 66.0%) indicated using medication or substance-based pain management methods while 34% (188) reported non-pharmacologic methods. The full list of responses is summarized in Table 4.3. The most commonly reported substance-based pain management method was opioid use (108, 19.5%), followed by using prescription medication prescribed to someone else (97, 17.5%), using cannabis (69, 12.4%), using stimulants (42, 7.6%), using over the counter medications (33, 5.9%), and using alcohol (18, 3.2%). Among the responses in the non-pharmacologic pain management methods category, the most commonly reported method was exercise (42, 7.6%). Hot and cold hydrotherapy (e.g., using steam rooms, hot showers, or ice packs) was also common (32, 5.8%), followed by mindfulness and meditation (31, 5.6%) and sleeping/resting (18, 3.2%). Integrative pain management therapies (e.g., physiotherapy, massage therapy, acupuncture) were less common (11, 2.0%).

The self-reported types of illicitly-obtained substances or medications used to manage pain in the previous 24 hours are shown in Table 4.4. Among 384 reports, almost 60% (229) indicated opioids as the most commonly used substance. Cannabis was reported as the second most commonly used substance (66, 17.2%), followed by amphetamines (55, 14.3%). Less common responses included: over the counter medications, such as acetaminophen and ibuprofen (15,

3.9%), non-opioid based prescription medications, such as lorazepam and gabapentin (10, 2.6%), and alcohol (9, 2.3%).

4.4 DISCUSSION

In this study of PLWH who use unregulated drugs living with chronic pain, pain self-management was widespread: almost three-quarters of participants at baseline reported self-managing their pain in the past six months (342, 70.4%). Pain self-management was positively associated with periods of homelessness, daily injection heroin use, daily non-medical prescription opioid injection, and a higher CD4+ cell count. Older age and never being diagnosed with a chronic pain condition were both independently and negatively associated with pain self-management. In a sub-analysis, participants revealed various medication/substance-based methods commonly used to self-manage their pain, with opioids reported as the most common (19.5%). Additionally, participants revealed various non-pharmacologic strategies to self-manage their pain, with 7.6% of responses indicating exercise as a form of pain management.

While prior research has described pain self-management strategies among PLWH and PWUD independently, this study is among the first to examine pain self-management strategies among PLWH who use unregulated drugs.^{136,230} The finding of widespread self-management builds upon the results from chapter 2 and chapter 3, and also adds to prior research indicating the high prevalence of untreated pain among both PLWH and PWUD, which often leads to high-risk pain self-management strategies.^{75,187,198,361}

In the present analysis, those who self-managed pain had 1.72 times greater odds of being homeless in the previous six months. Chronic pain is often left untreated among people experiencing homelessness due to substantial barriers in pain management, such as high levels of

substance use and challenges with accessing appropriate care.^{150,362,363} In one study of a random sample of homeless individuals in Toronto, Canada, 50% of respondents reported using unregulated drugs to self-manage their pain, while 29% reported using alcohol.³⁶² Only 40% of participants with pain were currently receiving treatment.³⁶² The challenges of managing pain among homeless populations occur along a continuum; compared to the general population, people without secure housing face multiple overlapping barriers to retention in care and often report inability to access appropriate therapies and treatment options.^{270,362–365} The present study findings further substantiate the lack of appropriate access to pain management among homeless individuals; future research could explore holistic interventions that incorporate HIV care, drug treatment, and pharmacologic and non-pharmacologic pain management options.

Strong positive associations between pain self-management and high-intensity injection of both heroin and unregulated prescription opioids were seen in this study. Consistent with findings from chapter 3, these findings build upon existing evidence suggesting that limiting access to pain medications may lead PWUD to self-medicate via high risk alternatives, including initiating injecting or transitioning to more potent substances.^{136,153,169,230,255} This is especially concerning given the ongoing national opioid crisis fueled by the adulteration of illicitly-obtained opioids with highly potent fentanyl, contributing to rising opioid-related death rates across Canada.¹⁰⁵ Of note, pain self-management was not found to be significantly associated with daily alcohol consumption nor daily cannabis use in the past six months. This is in contrast to previous studies that suggest alcohol and cannabis are commonly used as pain self-management strategies among both PLWH and PWUD.^{281,291,345,358,366–368} Given the potential benefits of cannabis as an analgesic, further research could investigate the possible use of cannabis as a pain management strategy among PLWH who use drugs.³⁶⁹

In the present study, age and pain self-management were negatively associated. This finding is in line with a previous study among a randomly selected cohort of adults in Paris, France, that found that self-medication was more common among younger adults, with 44% of their cohort between the ages of 18 and 39 years.³⁷⁰ Despite the well-known association between chronic pain and older age that has been well described in the existing literature, the present findings indicate that, although chronic pain is more common among older adults, pain self-management may be higher among younger adults.^{281,332,371} Given that, in general, older adults are prescribed more pain medications compared to younger adults, these results suggest that younger people face greater barriers to accessing pain medication, prompting self-medication in ways that are unregulated and pose a higher health risk.³⁷² As the association between pain self-management and age among PWUD—especially PLWH who use drugs—is not well documented in the literature, future research in this area is needed.

While prior studies have not reached consensus on the relationships between HIV infection and chronic pain, this is the first study to estimate the relationship between HIV clinical parameters and pain self-management among PLWH who use unregulated drugs.^{265,271,276,373,374} In this analysis of ART-exposed individuals including comprehensive repeated measures of CD4+ cell counts and HIV VL, pain self-management was positively associated with higher CD4+ cell count, suggesting that pain self-management was more common among individuals with less compromised immune systems. However, pain self-management was not significantly associated with HIV VL suppression. Prior research in this area is conflicting; some studies have observed significant associations between pain and decreased odds of achieving VL suppression, while others have found no association.^{265–271} Based on the findings from the present study, it is

reassuring that periods of self-management—and widespread substance use to address pain—do not appear to threaten virologic control through non-adherence to prescribed ART.

In the sub-analysis of self-reported pain management, strategies were grouped into one of two categories: medication/substance-based or non-pharmacologic pain management methods. The findings from this analysis echo previous studies documenting how individuals with untreated pain may seek out higher-risk substances from unregulated sources to address their pain. However, prior research has shown conflicting results on the most commonly sought after substances, with some studies indicating stimulants as the most frequently diverted drug, and others indicating different opioids.^{135,290,291} In the current study sub analysis of strategies employed in the previous 24 hours prior to each study interview, approximately 60% of responses indicated pain self-management via opioids, with cannabis as the second most frequently reported substance (17%). While the efficacy and risks of using opioids as analgesics for long-term non-cancer pain are increasingly well appreciated, the use of cannabis as a pain management tool has more recently been studied in greater detail, especially within the context of marginalized populations.^{58,96,124,256,343,367,368,375,376} For example, a previous study among PWUD with chronic pain found that individuals who reported daily cannabis use had 50% lower odds of using unregulated opioids.²⁵⁶ As future controlled research investigates the risks and possible benefits of cannabinoids as analgesics, more individuals might incorporate cannabis in their pain self-management strategies and reduce unregulated opioid use, especially given the lower likelihood of fatal overdose risk associated with cannabis use.^{33,256,367,368,377,378}

Prior research has demonstrated the effectiveness of non-pharmacological pain management methods, such as CBT and physical activity, in reducing self-reported pain and improving treatment outcomes.^{53,379–382} One prior study investigating self-management methods

among PLWH reporting pain due to HIV neuropathy identified several effective and frequently reported non-pharmacologic pain management methods, such as exercise, rest, hot bath, and massage.³⁸³ Similarly, a randomized control trial comparing the effectiveness of CBT used singly versus in combination with acceptance-based approaches (e.g. mindfulness, self-talk) among PWUD engaged in substance use treatment found that the combined psychotherapeutic intervention yielded significantly greater improvements in pain and functionality compared to CBT alone.³⁸⁴ In the present study, 34% of responses in the past six months indicated use of non-pharmacologic based pain management strategies, such as exercise (8%), hot and cold hydrotherapy (6%), and sleep/rest (3%). There are key advantages to non-pharmacologically based pain self-management strategies, especially within the context of the overdose crisis in the United States and Canada. In a qualitative study of PLWH with chronic pain, many of the reported non-substance based strategies (e.g. massage therapy, pain education, positive self-talk) listed were already part of existing pain management programs.²³⁰ Developing these programs to be readily accessible and available to PLWH who use unregulated drugs, possibly in the form of multimodal care, would better utilize pre-existing tools in place and provide patients with pain management strategies that do not solely rely on unregulated substances.

This study is bound by some limitations. Shared limitations with chapter 2 and chapter 3 are discussed in chapter 5, section 5.3. This analysis sought to explore commonly used pain self-management strategies among people who reported pain who were not receiving prescription medication from their physicians. While restricting to people who were not using physician provided prescription medication would exclude participants who were self-managing pain to supplement provider-assisted pharmaceutical management methods, there is potential for misclassification bias, as participants could be receiving non-pharmaceutical treatments, such as

exercise programs or acupuncture, while also having to self-manage their pain through other means. Therefore, the true prevalence of pain self-management may be underestimated in this study, as the analyses were unable to differentiate these participants. Additionally, this analysis was unable to assess perceived or actual effectiveness of the pain management methods described.

4.4.1 Conclusions

In conclusion, more than 70% of PLWH who use unregulated drugs with pain reported pain self-management, often through use of opioids from unregulated sources. This finding highlights that current pain treatment options are insufficiently provided to PLWH who use unregulated drugs, and that this in turn motivates diversion to high risk pain self-management alternatives. The results from this study have important implications regarding the availability and accessibility of both pharmacologic and non-pharmacologic pain management treatments among this population. These findings indicate a need for development of innovative, comprehensive interventions that incorporate a variety of accessible pharmacologically and non-pharmacologically-based pain management strategies tailored specifically within the context of HIV care, substance use, and pain management.

Table 4.1 Baseline characteristics of PLWH that use unregulated drugs with pain in Vancouver, Canada, stratified by pain self-management in the previous six months (n = 486)

Characteristic	Total, (100%) <i>n</i> = 486	Pain Self-Management		<i>p</i> - value
		Yes (70.4%) <i>n</i> = 342	No (29.6%) <i>n</i> = 144	
Age (med, IQR)	44 (38 – 49)	44 (37 – 49)	45 (40 – 50)	0.074
Sex				
Male	306 (63.0)	212 (62.0)	94 (65.3)	0.446
Female	168 (34.6)	122 (35.7)	46 (31.9)	
Ethnicity				
White	260 (53.5)	174 (50.9)	86 (59.7)	0.076
Non-White	222 (45.7)	165 (48.2)	57 (39.6)	
Homelessness*				
Yes	58 (11.9)	46 (13.5)	12 (8.3)	0.112
No	428 (88.1)	296 (86.5)	132 (91.7)	
Daily alcohol use*				
Yes	41 (8.4)	38 (11.1)	3.0 (2.1)	<0.001
No	445 (91.6)	304 (88.9)	141 (97.9)	
Daily cannabis use*				
Yes	108 (22.2)	75 (21.9)	33 (22.9)	0.811
No	378 (77.8)	267 (78.1)	111 (77.1)	
Daily injection heroin use*				
Yes	69 (14.2)	61 (17.8)	8.0 (5.6)	<0.001
No	417 (85.8)	281 (82.2)	136 (94.4)	
Daily injection non-medical prescription opioid use*				
Yes	22 (4.5)	17 (5.0)	5.0 (3.5)	0.634
No	464 (95.5)	325 (95.0)	139 (96.5)	
Enrolled in MMT*				
Yes	227 (46.7)	162 (47.4)	65 (45.1)	0.680
No	257 (52.9)	179 (52.3)	78 (54.2)	

Characteristic	Pain Self-Management			<i>p</i> - value
	Total, (100%)	Yes (70.4%)	No (29.6%)	
	<i>n</i> = 486	<i>n</i> = 342	<i>n</i> = 144	
Diagnosed with musculoskeletal pain condition†				
Yes	158 (32.5)	113 (33.0)	45 (31.3)	0.757
No	325 (66.9)	228 (66.7)	97 (67.4)	
Diagnosed with a neuropathic pain condition†				
Yes	82 (16.9)	64 (18.7)	18 (12.5)	0.104
No	401 (82.5)	277 (81.0)	124 (86.1)	
Diagnosed with an inflammatory pain condition†				
Yes	117 (24.1)	88 (25.7)	29 (20.1)	0.208
No	366 (75.3)	253 (74.0)	113 (78.5)	
Never diagnosed with a pain condition†				
Yes	152 (31.3)	97 (28.4)	55 (38.2)	0.027
No	331 (68.1)	244 (71.3)	87 (60.4)	
CD4+ cell count (med, IQR)*	440 (280 – 600)	460 (290 – 640)	380 (230 – 570)	0.012
HIV viral load*				
≥ 50 copies/mL plasma	326 (67.1)	225 (65.8)	101 (70.1)	0.351
< 50 copies/mL plasma	160 (32.9)	117 (34.2)	43 (29.9)	

* Refers to the six-month period prior to interview
† Refers to ever
IQR: interquartile range; Med: median; MMT: methadone maintenance therapy

Table 4.2 Bivariable and multivariable GLMM analysis of factors associated with pain self-management among a cohort of PLWH who use unregulated drugs (n = 1649 observations)

Characteristic	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	p - value	Odds Ratio (95% CI)	p - value
Age				
Per year older	0.97 (0.95 – 0.99)	0.007	0.98 (0.96 – 1.00)	0.023
Sex				
Male vs. Female	0.79 (0.57 – 1.11)	0.175		
Ethnicity				
White vs. non-White	0.87 (0.64 – 1.19)	0.387		
Homelessness*				
Yes vs. no	1.85 (1.14 – 2.98)	0.012	1.72 (1.06 – 2.79)	0.028
Incarceration*				
Yes vs. no	1.71 (0.75 – 3.90)	0.200		
Daily alcohol use*				
Yes vs. no	1.33 (0.81 – 2.19)	0.264		
Daily cannabis use*				
Yes vs. no	1.26 (0.90 – 1.75)	0.182		
Daily injection heroin use*				
Yes vs. no	2.60 (1.62 – 4.18)	<0.001	2.30 (1.42 – 3.71)	<0.001
Daily injection non-medical prescription opioid use*				
Yes vs. no	2.65 (1.26 – 5.61)	0.011	2.70 (1.28 – 5.71)	0.009
Enrolled in MMT*				
Yes vs. no	1.18 (0.87 – 1.59)	0.278		
Diagnosed with musculoskeletal pain condition†				
Yes vs. no	1.05 (0.80 – 1.36)	0.739		
Diagnosed with a neuropathic pain condition†				

Characteristic	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	<i>p</i> - value	Odds Ratio (95% CI)	<i>p</i> - value
Yes vs. no	1.31 (0.94 – 1.83)	0.116		
Diagnosed with an inflammatory pain condition†				
Yes vs. no	1.07 (0.81 – 1.40)	0.640		
Never diagnosed with a pain condition†				
Yes vs. no	0.74 (0.54 – 1.00)	0.053	0.70 (0.51 – 0.95)	0.021
CD4+ cell count (per 100 cells/ μ L)	1.08 (1.02 – 1.15)	0.007	1.08 (1.02 – 1.14)	0.007
Viral load*				
≥ 50 copies/mL vs. < 50 copies/mL	0.84 (0.62 – 1.14)	0.255		

* Refers to the six-month period prior to interview

† Refers to ever

CI: confidence interval; MMT: methadone maintenance therapy; AOR: adjusted odds ratio; GLMM: generalized linear mixed-effects modelling

Table 4.3 Self-reported pain self-management strategies employed in the last six months among PLWH who use unregulated drugs with pain in Vancouver, Canada (n = 555 reports)

Pain Management Method	n (%), n = 555*
<i>Pharmacologic / Substance-based</i>	
Used opioids (e.g., heroin, fentanyl)**	108 (19.5)
Used prescription medication prescribed to someone else**	97 (17.5)
Used cannabis**	69 (12.4)
Used amphetamines (e.g., cocaine, crystal methamphetamine, crack)**	42 (7.6)
Over-the-counter medications (e.g., ibuprofen, acetaminophen)	33 (5.9)
Alcohol	18 (3.2)
	367 (66.0)
<i>Non-pharmacologic</i>	
Without any type of drug †	54 (9.7)
Exercise †	42 (7.6)
Hot and cold therapy (e.g., steam rooms, hot showers, ice packs)	32 (5.8)
Mindfulness or meditation	31 (5.6)
Sleep/rest	18 (3.2)
Integrative therapies (e.g., physiotherapy, massage, acupuncture)	11 (2.0)
	188 (34.0)
* Participants were able to provide more than one response	
** Indicates various routes of use (e.g., snorting, smoking, injecting, ingesting etc.)	
† Individual methods unspecified	

Table 4.4 Self-reported use of illicitly-obtained substances or medications to manage pain within the past 24 hours among PLWH who use unregulated drugs with pain in Vancouver, Canada (n = 384 reports)

Medication/Substance Used	<i>n</i> (%), <i>n</i> = 384*
Opioids (e.g., heroin, fentanyl)**	229 (59.6)
Cannabis	66 (17.2)
Amphetamines (e.g., cocaine, crystal methamphetamine, crack)**	55 (14.3)
Over-the-counter medications (e.g., ibuprofen, acetaminophen)	15 (3.90)
Non-opioid based prescription medications (e.g., lorazepam, gabapentin)	10 (2.60)
Alcohol	9.0 (2.30)

* Participants were able to provide more than one response
 ** Indicates various routes of use (e.g., snorting, smoking, injecting, ingesting etc.)

Chapter 5: Summary of Findings, Implications for Policy and Research, and Future Directions

5.1 SUMMARY OF FINDINGS

As morbidity and mortality rates continue to climb as a result of unregulated opioid use, a greater understanding of the consequences of the opioid crisis and its links to opioid analgesics in the treatment of chronic pain among key populations, such as PLWH, is critical.^{100,385} However, despite being a population with high levels of concurrent unregulated drug use and chronic pain, much of the existing research in this area has largely excluded PLWH.^{182,191,286,386} To fill this gap, I sought to empirically characterize and investigate various aspects of chronic pain among PLWH who use unregulated drugs—including denial of pain medications and pain management strategies—among the ACCESS cohort, an open prospective cohort study of PLWH who use drugs in Vancouver, Canada. The findings from this work will strengthen our current understanding of socio-structural, clinical, and behavioral associations of chronic pain among marginalized populations. This research aims to provide insight into the complex relationships between chronic pain, living with HIV, and unregulated drug use. Further, these findings seek to guide development of policies and interventions that incorporate both pharmacologic and non-pharmacologic pain management strategies that address and manage chronic pain among PLWH who use unregulated drugs.

5.1.1 Estimating prevalence and correlates of pain among people living with HIV who use unregulated drugs

In chapter 2, I sought to estimate the prevalence of chronic pain in this community-recruited cohort of PWUD both in and out of clinical care and, using multivariable generalized linear mixed-effects modelling (GLMM), identify significant relationships between chronic pain and sociodemographic characteristics, substance use patterns, social/structural exposures, and clinical diagnoses of chronic pain. To my knowledge, this chapter is the first to assess the prevalence of, and associations with, pain among PLWH who use unregulated drugs.

I found that just over half (53%) of participants reported moderate-to-extreme chronic pain within the previous six months, supporting previous studies suggesting that chronic pain is common and undertreated among PLWH and PWUD.^{73,75,140,142,182,186,228,387} The multivariable associations identified in this study were consistent with prior research—in particular, the strong association between pain and both non-medical prescription opioid use and pain self-management, both of which are linked with overdose. This study demonstrates that chronic pain among PLWH who use unregulated drugs is undertreated and points to several high-risk substance use patterns and factors associated with pain. Findings from this study will serve as a foundation upon which clinical interventions and large-scale policies tailored to minimize these harms could be developed. The findings from chapter 2 provided the platform for which the research questions addressed in chapters 3 and 4 were based upon.

5.1.2 Assessing the prevalence and correlates of being denied pain medication among people living with HIV who use unregulated drugs

In light of the relationship identified in chapter 2 of a strong association between pain and self-management, in addition to non-medical prescription opioid use, I sought to further explore access to licit analgesia in chapter 3. In chapter 3, I estimated the frequency of being denied pain medication among this population, and, using generalized estimating equations (GEE), identified various factors associated with being denied. Among participants reporting pain, 20.2% of the population who requested pain medication from a healthcare provider in the last six months reported being denied pain medication.

In the multivariable GEE model, those who had recently been denied pain medication had approximately five times the odds of pain self-management and four times the odds of a recent suicide attempt. Several healthcare access factors were considered in the model, and in line with prior research indicating improved health outcomes associated with positive, consistent relationships between patients and their providers, I observed a protective effect of accessing a family physician on being denied pain medication.^{317,319,320,322} In a sub-analysis of self-reported actions taken after being denied pain medication, diversion to unregulated drugs was the most commonly reported action. Taken together, the results from the primary- and sub-analyses support the hypothesis stated in chapter 1, section 1.3, that, among PLWH who use unregulated drugs, restricting access to pain medications leads to sub-optimal health outcomes, such as increased risk of suicide, and higher-risk exposures, such as riskier substance use patterns.

5.1.3 Characterizing self-management of pain among people living with HIV who use unregulated drugs

Chapter 4—the final empirical analysis in my thesis—sought to build on the results from chapter 3. As stated in chapter 1, section 1.3, chapter 4 tested the hypothesis that pain self-management is common among PLWH who use unregulated drugs, and that self-managing pain is linked with increased exposure to higher risk substance use patterns and health vulnerabilities; the findings from this chapter support this hypothesis. This analysis found that pain self-management was highly prevalent—occurring among 70% of the study population—and revealed that homelessness, daily heroin injection, and daily non-medical prescription opioid injection were significantly and positively associated with pain self-management. In a sub-analysis characterizing common self-management methods, 66% of responses indicated self-management via pharmacologically-based strategies, while 34% of responses revealed non-pharmacologic (e.g., exercise, hot and cold hydrotherapy) methods.

Also, a sub-analysis of the most commonly used substances to self-manage pain within the past 24-hour period found 60% of reports indicated unregulated opioid use. The high prevalence of pain self-management in this study demonstrates the ongoing undertreatment of pain among PLWH who use unregulated drugs and the health vulnerabilities associated with self-managing. This analysis revealed a number of commonly used pharmacologic and non-pharmacologically-based pain management strategies; future research is needed to explore and quantify the potential of multimodal interventions that combine both pharmacologic and non-pharmacologic pain management strategies.

5.2 IMPLICATIONS FOR HEALTH POLICY AND RESEARCH

The high prevalence of chronic pain among PLWH who use unregulated drugs (chapter 2) sheds light on the undertreatment of pain and inaccessibility of adequate pain management interventions; in the context of the ongoing opioid overdose crisis, this is especially relevant. Following the initial increase of opioid deaths in 1999 as a result of a surge in opioid prescriptions, several legislative motions were instituted to decrease the number of active opioid prescriptions and ultimately, prevent nonmedical use. Some of these regulatory measures included heightened surveillance of existing and new opioid prescriptions, strict opioid prescribing guidelines for providers, and institution of legal repercussions against physicians for inappropriate prescribing.^{117,130–132} These reforms and increased scrutiny have contributed to physician reluctance to prescribe opioids, resulting in many people living with pain being denied access to critical pain management drugs.^{117,255} As demonstrated in chapter 3, this discrimination was especially evident among marginalized and stigmatized populations, including PWUD and PLWH. While these legislative strategies effectively reduced the rate of legal opioid analgesic prescriptions, a number of unintended substance use and health-related consequences followed the growing inaccessibility of prescription opioid analgesics, including an increase in use of heroin and other unregulated opioids that contributed to another spike in opioid overdose deaths beginning in 2010, followed by another distinct surge of overdose deaths involving synthetic opioids (e.g., fentanyl).^{108,113,117,118,131,385}

Taken together, these trends and findings from chapter 2 demonstrate policy changes aimed at reducing the number of opioid prescriptions, as opposed to reducing the number of people living with pain. Current pain management recommendations for PLWH are based upon the CDC guidelines for management of chronic cancer pain, however, the efficacy of these guidelines as an

appropriate pain management tool specifically among PLWH who use unregulated drugs has not been validated.²⁵ In addition to the complexity in identifying the source of pain (which can be attributed to a number of HIV-infection or HIV-treatment consequences, as well as various substance-related issues such as abscesses or cellulitis), PLWH who use unregulated drugs often have an increased prevalence of other comorbidities such as mental illness, an association which was observed in chapter 2.^{185,217,268,352,388} The results from chapter 2 highlight the current lack of adequate pain management guidelines tailored towards PLWH who use unregulated drugs and the consequences stemming from this gap – in particular, a high prevalence of undertreated chronic pain. To my knowledge, chapter 2 is the first study to measure the prevalence of and associations with chronic pain among PLWH who use unregulated drugs. In addition to reinforcing findings from prior studies on PLWH and PWUD, this analysis provides a foundation for future research on chronic pain among PLWH who use unregulated drugs.^{185,229,279,373}

The findings from chapter 3 illustrate the unintended consequences of legislative reform drawn from an abstinence-based approach, as opposed to the harm reduction model. Briefly, while the goal of abstinence-based treatments is absolute abstinence from using substances, the harm reduction model is centered on minimizing the risks and negative impacts of substance use.^{389,390} Due in part to the implementation of abstinence-focused measures that sought to decrease the rate of opioid prescriptions by denying patients access to pain medication, in addition to failing to institute alternative interventions geared towards providing effective pain management services, denial of pain medication (especially among those who experience multiple layers of stigma or discrimination, such as PWUD and PLWH) has become increasingly prevalent, leading patients to seek out pain relief from the unregulated drug market, such as injecting heroin or using diverted/counterfeit prescription opioids.^{135,255} Given the findings in this analysis of a high

prevalence of pain medication denial and its alarming association with various suboptimal health outcomes—in particular, an increased odds of attempting suicide—evidence from chapter 3 calls for rigorous evaluation and design of accessible, integrative pain-management interventions built upon a harm reduction and client centered approach. The aim of these interventions should focus on reducing the harms associated with substance use, moving away from the morally-implicated abstinence-based model of treatment and towards a focus on appropriate pain management strategies tailored towards PLWH who use unregulated drugs.

In chapter 4, I observed a high prevalence of pain self-management, often via high-risk substance use methods, among PLWH who use unregulated drugs. This chapter revealed positive associations between self-managing pain and various structural and substance use factors, including homelessness, daily injection heroin use, and daily non-medical prescription injection. While substance-based pain self-management methods, such as heroin injection, were most commonly reported as self-management strategies, the findings from this analysis also revealed a number of non-pharmacological approaches, such as hydrotherapy and exercise. These findings support prior research indicating the efficacy of non-pharmacologic pain management strategies on improving health outcomes, and have important implications on alternative pain management strategies within the context of the ongoing opioid crisis.^{53,381,382,391,392} Research funding to design and evaluate multimodal pain-management interventions incorporating both pharmacologic (e.g., analgesia, non-narcotic medications) and non-pharmacologically (e.g., massage therapy, exercise) sourced approaches, tailored specifically to PLWH who use unregulated drugs, is critical. Within the context of HIV care, this is especially imperative given the high comorbidity between substance use, pain, and HIV infection. Despite the limited number of studies that have evaluated integrated care on HIV clinical outcomes, existing studies have demonstrated its benefits,

including improved HIV clinical outcomes (e.g., increased odds of achieving VL suppression), mental well-being (e.g., increase in activities to encourage neuroplasticity and brain health) and improved pain and symptom control.^{313,330,393–395} The findings from my thesis support multimodal pain-management interventions designed to address the range of prevalent co-occurring conditions experienced by PLWH, including substance use and mental health disorders. Given the high prevalence of multiple, interacting health diagnoses among PLWH, future research to inform these interventions is needed to effectively and appropriately manage chronic pain among PLWH.

5.3 STRENGTHS AND LIMITATIONS

5.3.1 Study Strengths

The data from each empirically driven chapter of my research were drawn from the AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS) study—a prospective cohort of PLWH who use unregulated drugs in Vancouver, Canada. First, the ACCESS study is situated in a setting with universal, no-cost healthcare including HIV medication and treatments. While the results produced in this thesis are less likely to be confounded by socio-economic/financial status, it is important to note that there may remain costs associated with accessing care (e.g., transportation). A major strength of the ACCESS study is its longitudinal nature, as this allowed for inclusion of repeated measurements over a number of time points, which allowed for a more reliable analysis and interpretation of factors associated with the outcome of interest. While much of the current literature on chronic pain among PLWH and PWUD utilizes cross-sectional modelling, all of the chapters in my thesis utilized longitudinal statistical modelling (e.g., GEE and GLMM analysis), which afforded the ability to take several observations of the same study population over an extended period of time (chapters 2 and 3 analyzed seven years of data,

chapter 4 contained measures from three-and a half years' worth of data) contributing to the strength of the study.

Across all the chapters, I utilized the EuroQol EQ-5D utility instrument—a validated tool using a Likert scale—to measure pain. This instrument has been previously validated, and affords participants to describe their pain in one of three response categories (no pain/discomfort, moderate pain/discomfort, and extreme pain/discomfort).²²⁶ Therefore, regardless of the subjectivity involved in the definition of pain, utilizing this survey is inclusive of the different experiences and understandings of pain that vary person-to-person. However, it is important to note that, while the EuroQol EQ-5D instrument assesses current pain and discomfort, it does not measure pain experienced at any other point in time in the prior six-month follow up period.

Lastly, the data used in this thesis was augmented by confidential clinical information on HIV treatment and care from the DTP, the centralized HIV/AIDS registry in British Columbia. Combining data on socio-structural, behavioral, and drug use factors with clinical data (e.g., CD4+ cell counts, HIV-1 plasma VL), strengthening the subsequent results.

5.3.2 Study Limitations

Each study in my thesis has unique, study-specific limitations that have been discussed in each corresponding chapter. However, there are notable limitations shared across data driven that I will present here. First, participant recruitment into the ACCESS study is conducted through various community-based sampling methods. As this recruitment method is not random, generalizability is limited as the study population may not be representative of PLWH who use unregulated drugs (or other populations) in other settings. Moreover, as is with all observational studies, the temporal relationships analyzed in each chapter cannot be established, and therefore,

cannot be used to attribute causation. Second, the data used in this research were obtained through self-report. Although various studies assessing the reliability of self-report among PWUD have determined self-report to be largely accurate and valid, it is possible that some responses may have introduced some form of recall or social desirability bias.^{227,396} However, in each of the studies, I utilized non-self-reported data where possible, linking HIV-related responses with confidential HIV-clinical measures data from the DTP.

My thesis sought to measure and analyze different dimensions of chronic pain among PLWH who use unregulated drugs. Due to the lack of an objective and consistent measure of chronic pain across the literature, as well as a lack of a quantitative clinical measure of pain, it is possible that some participant responses may be misclassified.^{1,2,397-399} To minimize potential misclassification, I utilized the EuroQol EQ-5D, a standardized tool to measure pain described in detail in section 5.3.1. Another potential limitation in my thesis is the use of the term ‘ethnicity’ in the sociodemographic portion of the ACCESS questionnaire. In these analyses, the term ‘ethnicity’ is used to describe self-identified ancestry (eg., white, non-white), however, due to the evolving language around race and ethnicity, there is potential for misclassification due to the use of the term ‘ethnicity’ as opposed to ‘race’. However, as ACCESS interviewers receive up-to-date cultural sensitivity training and that the ‘ethnicity’ variable is a self-identified indicator, misclassification is likely to be minimal.

Finally, one of the aims of my thesis was to assess various substance use patterns on associations of chronic pain. Given the ongoing opioid overdose crisis that has spanned from the early 1990s to the present day, it is expected that the associations identified in my studies would relate to the trends and patterns observed throughout the overdose crisis. In chapter 2 and chapter 3, I utilized data from December 2011 to November 2018, while chapter 4 contained data from

June 2014 to November 2017—time periods with patterns and differences that would likely reflect the parallel ongoing overdose crisis. In particular, changes in the unregulated opioid market—in particular the replacement of heroin and heroin-like substances—has been a considerable force that has shaped the opioid overdose crisis. Beginning in approximately 2013, the unregulated opioid supply, known commonly as ‘down’, began to become adulterated with fentanyl and other novel opioids. Although these preparations of down were still labelled and marketed as heroin, the percentage of heroin began to decrease as down became increasingly composed of various potent drugs, contaminants, and cutting agents – in particular, fentanyl. Since then, the labels *heroin*, *down*, and *fentanyl* have become mixed in the unregulated market. Recent studies have shown that the increasing presence of fentanyl in the unregulated drug supply has shifted many PWUDs’ interpretation of the term *heroin*, with many PWUD’s using opioids marketed as *heroin* under the assumption that their drugs contain a portion, or are entirely made up of, fentanyl.^{400,401} While ACCESS study interviewers are up-to-date with the evolving language used to describe unregulated drugs, and longstanding rapport to ensure the accuracy of responses is well-established with the study participants, it is possible that some participants who injected what they believed to be heroin may have injected fentanyl (and vice versa).

5.4 FUTURE DIRECTIONS

The findings from my thesis highlight the complex, intersecting relationships between chronic pain, HIV, and drug use. While the existing literature on chronic pain, HIV, and drug use investigated singly is plentiful, investigation of the intersections and relationships between them is limited. In the context of future avenues for policy on multimodal HIV, drug, and chronic pain care, future research is needed to evaluate optimal recommendations to guide these interventions.

As shown in chapter 2, a high rate of PLWH who use unregulated drugs live with chronic pain and are at significantly higher risk of adverse health outcomes. Similarly, chapter 3 suggested a potential benefit of consistent patient-provider relationships on pain outcomes. Future research on effective multimodal pain-management treatments, and how to increase their accessibility, is a crucial first step in addressing optimal pain management strategies for people with multidimensional, complex healthcare needs. In the context of HIV management, integrated harm reduction-based models of care that offer various services (e.g., trauma and violence care, counselling) in addition to HIV care have been implemented and evaluated in a number of studies with promising implications, including increased adherence to ART, improved virologic outcomes, and increased uptake of harm reduction strategies.^{330,402} Therefore, integrated healthcare, which would provide a variety of services for HIV, substance use, and chronic pain at a single facility may be a promising approach that requires further investigation.

An important finding from chapter 3 was the significantly increased odds of attempted suicide associated with being denied pain medication. Prior research has shown high rates of suicide and attempted suicide among people with a history of chronic pain; given the association that also exists between suicide and mental illness, and the high prevalence of mental illness among PWUD, the need for preventative pain management services is critical.^{280,294,295} Future studies on effective pain assessments in suicide screening, and understanding of the relationship between chronic pain and suicide should be explored.

The high rate of pain self-management found in chapter 4 echoes the findings from previous chapters that chronic pain among this population is severely undertreated and has led to severe health outcomes closely tied to the opioid crisis. PLWH who use unregulated drugs experience disproportionately high rates of pain (chapter 2), are consistently faced with

discrimination and denied access to pain medication (chapter 3), which leads to increased rates of pain self-management, often via high-risk methods, such as injection heroin use (chapter 4). The common self-management strategies identified in chapter 4 are promising, and should serve as a basis for future research to investigate the benefits of multidisciplinary, multimodal pain management services that incorporate pharmacological and non-pharmacologically based interventions. In addition, future exploration of the different sources of chronic pain among PLWH who use unregulated drugs are important for development of preventative policies and interventions.

My thesis sought to fill a gap in the literature on chronic pain among PLWH who use drugs. While much of the existing literature in this area largely focuses on populations of PLWH or PWUD separately, the high rate of co-existing HIV infection and drug use is a critical component in further understanding chronic pain among these groups. My thesis found that chronic pain is highly prevalent among PLWH who use unregulated drugs; that chronic pain is significantly and positively associated with high risk substance use factors and lower health outcomes; and that chronic pain is largely undertreated, leading people to self-manage their pain via high risk, illicit methods. The studies included in my thesis are among the first analyses to empirically investigate chronic pain among PLWH who use unregulated drugs. In particular, my work demonstrates the potential benefits of integrated, multimodal care for PLWH who use unregulated drugs that minimizes high risk behaviors, improves HIV clinical outcomes, and provides long term non-pharmacologic and pharmacologic pain management methods.

References

1. Classification of Chronic Pain, Second Edition (Revised) - IASP [Internet]. [cited 2020 Jul 17]. Available from: <https://www.iasp-pain.org/PublicationsNews/Content.aspx?ItemNumber=1673&navItemNumber=677>
2. Ruysen-Witrand A, Tubach F, Ravaud P. Systematic review reveals heterogeneity in definition of a clinically relevant difference in pain. *Journal of Clinical Epidemiology*. 2011 May;64(5):463–70.
3. Edwards RR, Doleys DM, Fillingim RB, Lowery D. Ethnic Differences in Pain Tolerance: Clinical Implications in a Chronic Pain Population. *Psychosomatic Medicine*. 2001 Apr;63(2):316–323.
4. Rahim-Williams B, Riley JL, Williams AKK, Fillingim RB. A quantitative review of ethnic group differences in experimental pain response: do biology, psychology, and culture matter? *Pain Med*. 2012 Apr;13(4):522–40.
5. Fillingim RB. Individual Differences in Pain: Understanding the Mosaic that Makes Pain Personal. *Pain*. 2017 Apr;158(Suppl 1):S11–8.
6. Berkley KJ. Sex differences in pain. *Behav Brain Sci*. 1997 Sep;20(3):371–80; discussion 435-513.
7. Green CR, Hart-Johnson T. The Association Between Race and Neighborhood Socioeconomic Status in Younger Black and White Adults With Chronic Pain. *The Journal of Pain*. 2012 Feb 1;13(2):176–86.
8. Sorge RE, Totsch SK. Sex Differences in Pain. *Journal of Neuroscience Research*. 2017;95(6):1271–81.
9. Pillay T, Zyl HA van, Blackbeard D. Chronic Pain Perception and Cultural Experience. *Procedia - Social and Behavioral Sciences*. 2014 Feb 7;113:151–60.
10. Coghill RC. Individual Differences in the Subjective Experience of Pain: New Insights into Mechanisms and Models. *Headache*. 2010 Oct;50(9):1531–5.
11. Fong A, Schug SA. Pathophysiology of Pain: A Practical Primer. *Plastic and Reconstructive Surgery*. 2014 Oct;134(4S-2):8S.
12. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. *Pain*. 2015 Jun;156(6):1003–7.
13. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. *Nat Rev Dis Primers*. 2017 Feb 16;3:17002.

14. Simons L, Elman I, Borsook D. Psychological Processing in Chronic Pain: A Neural Systems Approach. *Neurosci Biobehav Rev*. 2014 Feb;0:61–78.
15. Eisenberger NI. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. *Nature Reviews Neuroscience*. 2012 Jun;13(6):421–34.
16. Eisenberger NI. The neural bases of social pain: Evidence for shared representations with physical pain. *Psychosom Med*. 2012 Feb;74(2):126–35.
17. Holm AL, Bégat I, Severinsson E. Emotional pain: surviving mental health problems related to childhood experiences. *Journal of Psychiatric and Mental Health Nursing*. 2009;16(7):636–45.
18. Sachs-Ericsson NJ, Sheffler JL, Stanley IH, Piazza JR, Preacher KJ. When Emotional Pain Becomes Physical: Adverse Childhood Experiences, Pain, and the Role of Mood and Anxiety Disorders. *Journal of Clinical Psychology*. 2017;73(10):1403–28.
19. Sharp TJ. The prevalence of post-traumatic stress disorder in chronic pain patients. *Current Science Inc*. 2004 Apr 1;8(2):111–5.
20. Kross E, Berman MG, Mischel W, Smith EE, Wager TD. Social rejection shares somatosensory representations with physical pain. *PNAS*. 2011 Apr 12;108(15):6270–5.
21. Strang P. Cancer Pain - A Provoker of Emotional, Social and Existential Distress. *Acta Oncologica*. 1998 Jan 1;37(7–8):641–4.
22. Koyyalagunta D, Bruera E, Solanki DR, Nouri KH, Burton AW, Toro MP, et al. A systematic review of randomized trials on the effectiveness of opioids for cancer pain. *Pain Physician*. 2012 Jul;15(3 Suppl):ES39-58.
23. Nersesyan H, Slavin KV. Current approach to cancer pain management: Availability and implications of different treatment options. *Ther Clin Risk Manag*. 2007 Jun;3(3):381–400.
24. Tassinari D, Drudi F, Rosati M, Tombesi P, Sartori S, Maltoni M. The second step of the analgesic ladder and oral tramadol in the treatment of mild to moderate cancer pain: A systematic review. *Palliat Med*. 2011 Jul 1;25(5):410–23.
25. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep*. 2016 Mar 18;65(1):1–49.
26. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin M, Boswell MV, et al. American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part I – Evidence Assessment. *Pain Physician*. (2012):66.

27. Kahan M, Srivastava A, Wilson L, Mailis-Gagnon A, Midmer D. Opioids for managing chronic non-malignant pain. *Can Fam Physician*. 2006 Sep 10;52(9):1091–6.
28. Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A. Canadian guideline for safe and effective use of opioids for chronic noncancer pain. *Can Fam Physician*. 2011 Nov;57(11):1257–66.
29. Sansone RA, Sansone LA. Pain, Pain, Go Away. *Psychiatry (Edgmont)*. 2008 Dec;5(12):16–9.
30. Ho KY, Gwee KA, Cheng YK, Yoon KH, Hee HT, Omar AR. Nonsteroidal anti-inflammatory drugs in chronic pain: implications of new data for clinical practice. *J Pain Res*. 2018 Sep 20;11:1937–48.
31. Vyvey M. Steroids as pain relief adjuvants. *Can Fam Physician*. 2010 Dec;56(12):1295–7.
32. Meng H, Dai T, Hanlon JG, Downar J, Alibhai SMH, Clarke H. Cannabis and cannabinoids in cancer pain management. *Current Opinion in Supportive and Palliative Care*. 2020 Jun;14(2):87–93.
33. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al. The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. *The Clinical Journal of Pain*. 2016 Dec;32(12):1036–1043.
34. Dobson JL, McMillan J, Li L. Benefits of exercise intervention in reducing neuropathic pain. *Front Cell Neurosci* [Internet]. 2014 Apr 4 [cited 2020 Nov 6];8. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3983517/>
35. Iacovides A, Siamouli M. Comorbid mental and somatic disorders: an epidemiological perspective. *Curr Opin Psychiatry*. 2008 Jul;21(4):417–21.
36. Kong LJ, Lauche R, Klose P, Bu JH, Yang XC, Guo CQ, et al. Tai Chi for Chronic Pain Conditions: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Scientific Reports*. 2016 Apr 29;6(1):25325.
37. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD007912.
38. Chang DG, Holt JA, Sklar M, Groessl EJ. Yoga as a treatment for chronic low back pain: A systematic review of the literature. *J Orthop Rheumatol*. 2016 Jan 1;3(1):1–8.
39. Cherkin DC, Sherman KJ, Avins AL, Erro JH, Ichikawa L, Barlow WE, et al. A Randomized Trial Comparing Acupuncture, Simulated Acupuncture, and Usual Care for Chronic Low Back Pain. *Arch Intern Med*. 2009 May 11;169(9):858–66.
40. Witt CM, Jena S, Brinkhaus B, Liecker B, Wegscheider K, Willich SN. Acupuncture for patients with chronic neck pain. *Pain*. 2006 Nov;125(1–2):98–106.

41. Angioni MM, Denotti A, Pinna S, Sanna C, Montisci F, Dessole G, et al. Spa therapy induces clinical improvement and protein changes in patients with chronic back pain. *Reumatismo* [Internet]. 2019 Oct 1 [cited 2020 Nov 6];71(3). Available from: <https://doaj.org>
42. Waller B, Lambeck J, Daly D. Therapeutic aquatic exercise in the treatment of low back pain: a systematic review. *Clin Rehabil*. 2009 Jan 1;23(1):3–14.
43. Silva LE, Valim V, Pessanha APC, Oliveira LM, Myamoto S, Jones A, et al. Hydrotherapy versus conventional land-based exercise for the management of patients with osteoarthritis of the knee: a randomized clinical trial. *Physical therapy*. 2008 Jan;88(1):12–21.
44. McCracken LM, Vowles KE. Acceptance and commitment therapy and mindfulness for chronic pain: Model, process, and progress. *American Psychologist*. 2014;69(2):178–87.
45. Wetherell JL, Afari N, Rutledge T, Sorrell JT, Stoddard JA, Petkus AJ, et al. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain*. 2011 Sep;152(9):2098–107.
46. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. *Am Psychol*. 2014 Mar;69(2):153–66.
47. Knoerl R, Lavoie Smith EM, Weisberg J. Chronic Pain and Cognitive Behavioral Therapy: An Integrative Review. *West J Nurs Res*. 2016 May;38(5):596–628.
48. Zis P, Daskalaki A, Bountouni I, Sykioti P, Varrassi G, Paladini A. Depression and chronic pain in the elderly: links and management challenges. *Clin Interv Aging*. 2017;12:709–20.
49. Lima EN. Chronic pain and mental health: moving beyond the conceptualization of pain as the fifth vital sign. *N C Med J*. 2013 Jun;74(3):229–31.
50. Kohrt BA, Griffith JL, Patel V. Chronic pain and mental health: integrated solutions for global problems. *Pain*. 2018 Sep;159 Suppl 1:S85–90.
51. Goesling J, Lin LA, Clauw DJ. Psychiatry and Pain Management: at the Intersection of Chronic Pain and Mental Health. *Curr Psychiatry Rep*. 2018 05;20(2):12.
52. Van Damme S, Crombez G, Eccleston C. Disengagement from pain: the role of catastrophic thinking about pain. *Pain*. 2004 Jan 1;107(1):70–6.
53. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain*. 1999 Mar;80(1–2):1–13.

54. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognit Ther Res.* 2012 Oct 1;36(5):427–40.
55. Hechler T, Dobe M, Kosfelder J, Damschen U, Hübner B, Blankenburg M, et al. Effectiveness of a 3-week Multimodal Inpatient Pain Treatment for Adolescents Suffering From Chronic Pain: Statistical and Clinical Significance. *The Clinical Journal of Pain.* 2009 Feb;25(2):156–166.
56. Lee C, Crawford C, Swann S, Active Self-Care Therapies for Pain (PACT) Working Group. Multimodal, integrative therapies for the self-management of chronic pain symptoms. *Pain Med.* 2014 Apr;15 Suppl 1:S76-85.
57. Kehlet H, Dahl JB. The Value of “Multimodal” or “Balanced Analgesia” in Postoperative Pain Treatment. *Anesthesia & Analgesia.* 1993 Nov;77(5):1048–1056.
58. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ.* 2006 May 23;174(11):1589–94.
59. Cuomo A, Bimonte S, Forte CA, Botti G, Cascella M. <p>Multimodal approaches and tailored therapies for pain management: the trolley analgesic model</p> [Internet]. Vol. 12, *Journal of Pain Research.* Dove Press; 2019 [cited 2020 Nov 6]. p. 711–4. Available from: <https://www.dovepress.com/multimodal-approaches-and-tailored-therapies-for-pain-management-the-t-peer-reviewed-fulltext-article-JPR>
60. Elvir-Lazo OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. *Current Opinion in Anesthesiology.* 2010 Dec;23(6):697–703.
61. Jackson TP, Stabile VS, McQueen KAK. The Global Burden Of Chronic Pain. *ASA Newsletter.* 2014 Jun 1;78(6):24–7.
62. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017 Sep 16;390(10100):1211–59.
63. WHO | International Classification of Diseases, 11th Revision (ICD-11) [Internet]. WHO. [cited 2019 Aug 27]. Available from: <http://www.who.int/classifications/icd/en/>
64. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet.* 2020 Oct;396(10258):1204–22.
65. Moulin DE, Clark AJ, Speechley M, Morley-Forster PK. Chronic Pain in Canada - Prevalence, Treatment, Impact and the Role of Opioid Analgesia [Internet]. *Pain Research and Management.* 2002 [cited 2019 Aug 14]. Available from: <https://www.hindawi.com/journals/prm/2002/323085/abs/>

66. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. *Pain Res Manag.* 2011;16(6):445–50.
67. Canada H. Canadian Pain Task Force Report: June 2019 [Internet]. aem. 2019 [cited 2019 Aug 27]. Available from: <https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/canadian-pain-task-force/report-2019.html>
68. Van Den Kerkhof EG, Hopman WM, Towheed TE, Anastassiades TP, Goldstein DH. The Impact of Sampling and Measurement on the Prevalence of Self-Reported Pain in Canada. *Pain Research and Management.* 2003;8(3):157–63.
69. Cragg JJ. Prevalence of chronic pain among individuals with neurological conditions. *Health Reports.* 2018;29(82):8.
70. Docking RE, Fleming J, Brayne C, Zhao J, Macfarlane GJ, Jones GT, et al. Epidemiology of back pain in older adults: prevalence and risk factors for back pain onset. *Rheumatology (Oxford).* 2011 Sep;50(9):1645–53.
71. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth.* 2013 Jul;111(1):52–8.
72. Eachus J, Chan P, Pearson N, Propper C, Davey S. An additional dimension to health inequalities: disease severity and socioeconomic position. *J Epidemiol Community Health.* 1999 Oct;53(10):603–11.
73. Heimer R, Zhan W, Grau LE. Prevalence and experience of chronic pain in suburban drug injectors. *Drug Alcohol Depend.* 2015 Jun 1;151:92–100.
74. Dobalian A, Tsao JCI, Duncan RP. Pain and the Use of Outpatient Services among Persons with HIV: Results from a Nationally Representative Survey. *Medical Care.* 2004;42(2):129–38.
75. Azagew AW, Woreta HK, Tilahun AD, Anlay DZ. High prevalence of pain among adult HIV-infected patients at University of Gondar Hospital, Northwest Ethiopia. *J Pain Res.* 2017 Oct 13;10:2461–9.
76. Lebovits AH, Smith G, Maignan M, Lefkowitz M. Pain in hospitalized patients with AIDS: analgesic and psychotropic medications. *Clin J Pain.* 1994 Jun;10(2):156–61.
77. McCarberg B, Nicholson B, Todd K, Palmer T, Penles L. The Impact of Pain on Quality of Life and the Unmet Needs of Pain Management: Results From Pain Sufferers and Physicians Participating in an Internet Survey. *American Journal of Therapeutics.* 2008 Aug;15(4):312–20.

78. Hogan M-E, Taddio A, Katz J, Shah V, Krahn M. Incremental health care costs for chronic pain in Ontario, Canada: a population-based matched cohort study of adolescents and adults using administrative data. *Pain*. 2016 Aug;157(8):1626–33.
79. Canada PHA of. Economic Burden of Illness in Canada, 2010 [Internet]. aem. 2018 [cited 2019 Sep 6]. Available from: https://www.canada.ca/en/public-health/services/publications/science-research-data/economic-burden-illness-canada-2010.html#res1_1
80. Gaskin DJ, Richard P. The Economic Costs of Pain in the United States. *The Journal of Pain*. 2012 Aug 1;13(8):715–24.
81. Poleshuck EL, Green CR. Socioeconomic Disadvantage and Pain. *Pain*. 2008 Jun;136(3):235–8.
82. Feldman CH, Dong Y, Katz JN, Donnell-Fink LA, Losina E. Association between socioeconomic status and pain, function and pain catastrophizing at presentation for total knee arthroplasty. *BMC Musculoskeletal Disorders*. 2015 Feb 7;16(1):18.
83. Yu T, Wei Z, Xu T, Gamber M, Han J, Jiang Y, et al. The association between the socioeconomic status and body pain. *Medicine (Baltimore)* [Internet]. 2020 Mar 20 [cited 2020 Nov 9];99(12). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7220486/>
84. Fuentes M, Hart-Johnson T, Green CR. The association among neighborhood socioeconomic status, race and chronic pain in black and white older adults. *J Natl Med Assoc*. 2007 Oct;99(10):1160–9.
85. Baumeister H, Knecht A, Hutter N. Direct and indirect costs in persons with chronic back pain and comorbid mental disorders--a systematic review. *J Psychosom Res*. 2012 Aug;73(2):79–85.
86. Zhu TY, Tam L-S, Leung Y-Y, Kwok L-W, Wong K-C, Yu T, et al. Socioeconomic burden of psoriatic arthritis in Hong Kong: direct and indirect costs and the influence of disease pattern. *J Rheumatol*. 2010 Jun;37(6):1214–20.
87. Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. *Proc Natl Acad Sci U S A*. 1993 Jun 15;90(12):5391–3.
88. Booth M. *Opium: A History*. First edition. New York: St. Martin's Griffin; 1999. 400 p.
89. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. *Pain Ther*. 2018 Jun;7(1):13–21.
90. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions. *Exp Clin Psychopharmacol*. 2008 Oct;16(5):405–16.

91. Hosztafi S. [The history of heroin]. *Acta Pharm Hung*. 2001 Aug;71(2):233–42.
92. Williams J. Basic Opioid Pharmacology. *Rev Pain*. 2008 Mar;1(2):2–5.
93. Pathan H, Williams J. Basic opioid pharmacology: an update. *Br J Pain*. 2012 Feb;6(1):11–6.
94. Duarte DF. Opium and opioids: a brief history. *Revista Brasileira de Anestesiologia*. 2005 Feb;55(1):135–46.
95. Degenhardt L, Larance B, Mathers B, Azim T, Kamarulzaman A, Mattick R, et al. Benefits and risks of pharmaceutical opioids: Essential treatment and diverted medication. :114.
96. Manchikanti L, Benyamin R, Datta S, Vallejo R, Smith H. Opioids in chronic noncancer pain. *Expert Review of Neurotherapeutics*. 2010 May 1;10(5):775–89.
97. *A Nation in Pain: Healing our Biggest Health Problem*. Oxford, New York: Oxford University Press; 2014. 464 p.
98. Nicholson B, Passik SD. Management of Chronic Noncancer Pain in the Primary Care Setting: *Southern Medical Journal*. 2007 Oct;100(10):1028–36.
99. Macy B. *Dopesick: Dealers, Doctors, and the Drug Company that Addicted America*. New York: Little, Brown and Company; 2018. 384 p.
100. McGreal C. *American Overdose: The Opioid Tragedy in Three Acts*. 1 edition. New York: PublicAffairs; 2018. 336 p.
101. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008 Mar;11(2 Suppl):S63-88.
102. Canadian Institute for Health Information. *Opioid Prescribing in Canada: How Are Practices Changing?* 2019;42.
103. United Nations Office on Drugs and Crime. *Report of the international narcotics control board for 2016*. Place of publication not identified: UNITED NATIONS; 2017.
104. Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. *CMAJ*. 2016 Dec 6;188(17–18):1240–4.
105. Lisa B, Jessica H. Evidence synthesis - The opioid crisis in Canada: a national perspective. *Health Promot Chronic Dis Prev Can*. 2018 Jun;38(6):224–33.
106. Centers for Disease Control and Prevention. *Annual Surveillance Report Of Drug-related Risks And Outcomes*. 2019 Nov 1;United States Surveillance Special Report:128.

107. Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data [Internet]. 2020 [cited 2020 Nov 9]. Available from: <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>
108. Warner M, Chen L-H. Trends in Drug-poisoning Deaths Involving Opioid Analgesics and Heroin: United States, 1999–2012. :5.
109. Morgan JP. American opiophobia: customary underutilization of opioid analgesics. *Adv Alcohol Subst Abuse*. 1985 Fall-1986 Winter;5(1–2):163–73.
110. Zenz M, Willweber-Strumpf A. Opiophobia and cancer pain in Europe. *Lancet*. 1993 Apr 24;341(8852):1075–6.
111. Max MB. Improving outcomes of analgesic treatment: is education enough? *Ann Intern Med*. 1990 Dec 1;113(11):885–9.
112. Porter J, Jick H. Addiction rare in patients treated with narcotics. *The New England journal of medicine*. 1980 Jan;302(2):123.
113. Joranson DE, Gilson AM, Dahl JL, Haddox JD. Pain management, controlled substances, and state medical board policy: a decade of change. *J Pain Symptom Manage*. 2002 Feb;23(2):138–47.
114. Van Zee A. The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy. *Am J Public Health*. 2009 Feb;99(2):221–7.
115. Evans WN, Lieber EMJ, Power P. How the Reformulation of OxyContin Ignited the Heroin Epidemic. *The Review of Economics and Statistics*. 2019 Mar;101(1):1–15.
116. Perry S, Heidrich G. Management of pain during debridement: a survey of U.S. burn units. *Pain*. 1982 Jul;13(3):267–80.
117. Fischer B, Jones W, Rehm J. Trends and changes in prescription opioid analgesic dispensing in Canada 2005–2012: an update with a focus on recent interventions. *BMC Health Services Research*. 2014 Feb 26;14(1):90.
118. Gomes T, Juurlink D, Yao Z, Camacho X, Paterson JM, Singh S, et al. Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: a time series analysis. *CMAJ Open*. 2014 Oct 1;2(4):E256–61.
119. Dhalla IA, Persaud N, Juurlink DN. Facing up to the prescription opioid crisis. *BMJ*. 2011 Aug 23;343(aug23 1):d5142–d5142.
120. Dineen KK, DuBois JM. Between a Rock and a Hard Place: Can Physicians Prescribe Opioids to Treat Pain Adequately While Avoiding Legal Sanction? *Am J Law Med*. 2016;42(1):7–52.

121. U.S. Opioid Prescribing Rate Maps | Drug Overdose | CDC Injury Center [Internet]. 2020 [cited 2020 Oct 9]. Available from: <https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>
122. Gomes T, Mastorakos A, Paterson JM, Sketris I, Caetano P, Greaves S, et al. Changes in the dispensing of opioid medications in Canada following the introduction of a tamper-deterrent formulation of long-acting oxycodone: a time series analysis. *cmajo*. 2017 Nov 22;5(4):E800–7.
123. Comer S, Cunningham C, Fishman MJ, Gordon A, Kampman K, Langleben D, et al. National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. 2015;66.
124. Furlan AD, Reardon R, Wepler C, National Opioid Use Guideline Group. Opioids for chronic noncancer pain: a new Canadian practice guideline. *CMAJ*. 2010 Jun 15;182(9):923–30.
125. Furlan AD, MacDougall P, Pellerin D, Shaw K, Spitzig D, Wilson G, et al. Overview of four prescription monitoring/review programs in Canada. *Pain Res Manag*. 2014;19(2):102–6.
126. Nordmann S, Vilotitch A, Lions C, Michel L, Mora M, Spire B, et al. Pain in methadone patients: Time to address undertreatment and suicide risk (ANRS-Methaville trial). *PLOS ONE*. 2017 May 17;12(5):e0176288.
127. Socias ME, Wood E, McNeil R, Kerr T, Dong H, Shoveller J, et al. Unintended impacts of regulatory changes to British Columbia Methadone Maintenance Program on addiction and HIV-related outcomes: An interrupted time series analysis. *Int J Drug Policy*. 2017 Jul;45:1–8.
128. Cicero TJ, Ellis MS, Harney J. Shifting Patterns of Prescription Opioid and Heroin Abuse in the United States. *N Engl J Med*. 2015 Oct 29;373(18):1789–90.
129. Cicero TJ, Ellis MS. Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned From OxyContin. *JAMA Psychiatry*. 2015 May 1;72(5):424–30.
130. Kertesz SG. Outcomes after opioid dose reductions and stoppage: It’s time to start counting. *Journal of Substance Abuse Treatment*. 2019 Aug;103:64–5.
131. Mark TL, Parish W. Opioid medication discontinuation and risk of adverse opioid-related health care events. *J Subst Abuse Treat*. 2019;103:58–63.
132. Davis CS, Lieberman AJ, Hernandez-Delgado H, Suba C. Laws limiting the prescribing or dispensing of opioids for acute pain in the United States: A national systematic legal review. *Drug Alcohol Depend*. 2019 01;194:166–72.

133. Chua K-P, Brummett CM, Waljee JF. Opioid Prescribing Limits for Acute Pain: Potential Problems With Design and Implementation. *JAMA*. 2019 19;321(7):643–4.
134. Alpert A, Powell D, Pacula RL. Supply-Side Drug Policy in the Presence of Substitutes: Evidence from the Introduction of Abuse-Deterrent Opioids. *American Economic Journal Economic Policy*. 2018 Nov;10(4):1–35.
135. Voon P, Callon C, Nguyen P, Dobrer S, Montaner JSG, Wood E, et al. Denial of Prescription Analgesia Among People Who Inject Drugs in a Canadian Setting. *Drug Alcohol Rev*. 2015 Mar;34(2):221–8.
136. Voon P, Callon C, Nguyen P, Dobrer S, Montaner J, Wood E, et al. Self-management of pain among people who inject drugs in Vancouver. *Pain Manag*. 2014 Jan;4(1):27–35.
137. World Drug Report 2019 [Internet]. United Nations : World Drug Report 2019. [cited 2020 Nov 10]. Available from: [//wdr.unodc.org/wdr2019/en/index.html](http://wdr.unodc.org/wdr2019/en/index.html)
138. World Drug Report 2020 [Internet]. United Nations : World Drug Report 2020. [cited 2020 Nov 10]. Available from: [//wdr.unodc.org/wdr2020/en/index.html](http://wdr.unodc.org/wdr2020/en/index.html)
139. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alcohol Depend*. 2003 Apr 1;69(3):215–32.
140. Morasco BJ, Gritzner S, Lewis L, Oldham R, Turk DC, Dobscha SK. Systematic review of prevalence, correlates, and treatment outcomes for chronic non-cancer pain in patients with comorbid substance use disorder. *Pain*. 2011 Mar;152(3):488–97.
141. Tsui JI, Herman DS, Kettavong M, Anderson BJ, Stein MD. Chronic pain and hepatitis C virus infection in opioid dependent injection drug users. *J Addict Dis*. 2011 Apr;30(2):91–7.
142. Heimer R, Dasgupta N, Irwin KS, Kinzly M, Harvey AP, Givens A, et al. Chronic pain, Addiction severity, and misuse of opioids in Cumberland County, Maine. *Addictive Behaviors*. 2012 Mar;37(3):346–9.
143. Athanasos P, Ling W, Bochner F, White JM, Somogyi AA. Buprenorphine Maintenance Subjects Are Hyperalgesic and Have No Antinociceptive Response to a Very High Morphine Dose. *Pain Med*. 2019 01;20(1):119–28.
144. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. *J Pain*. 2009 Mar;10(3):316–22.
145. Compton P, Canamar CP, Hillhouse M, Ling W. Hyperalgesia in Heroin Dependent Patients and the Effects of Opioid Substitution Therapy. *J Pain*. 2012 Apr;13(4):401–9.

146. Cunningham JL. Opioid induced hyperalgesia: A focus on opioid use in chronic pain. *Mental Health Clinician*. 2013 Jun 1;2(12):395–7.
147. Walton G, Co SJ, Milloy M-J, Qi J, Kerr T, Wood E. High prevalence of childhood emotional, physical and sexual trauma among a Canadian cohort of HIV-seropositive illicit drug users. *AIDS Care*. 2011 Jun;23(6):714–21.
148. Marshall BDL, Fairbairn N, Li K, Wood E, Kerr T. Physical Violence Among a Prospective Cohort of Injection Drug Users: A Gender-Focused Approach. *Drug Alcohol Depend*. 2008 Oct 1;97(3):237–46.
149. Milloy M-J, Wood E, Small W, Tyndall M, Lai C, Montaner J, et al. Incarceration experiences in a cohort of active injection drug users. *Drug Alcohol Rev*. 2008 Nov;27(6):693–9.
150. Galea S, Vlahov D. Social determinants and the health of drug users: socioeconomic status, homelessness, and incarceration. *Public Health Rep*. 2002;117(Suppl 1):S135–45.
151. Ahern J, Stuber J, Galea S. Stigma, discrimination and the health of illicit drug users. *Drug and Alcohol Dependence*. 2007 May 11;88(2):188–96.
152. Bondesson E, Larrosa Pardo F, Stigmar K, Ringqvist Å, Petersson IF, Jöud A, et al. Comorbidity between pain and mental illness - Evidence of a bidirectional relationship. *Eur J Pain*. 2018;22(7):1304–11.
153. Fibbi M, Silva K, Johnson K, Langer D, Lankenau SE. Denial of prescription opioids among young adults with histories of opioid misuse. *Pain Med*. 2012 Aug;13(8):1040–8.
154. Palepu A, Patterson M, Strehlau V, Moniruzzamen A, de Bibiana JT, Frankish J, et al. Daily Substance Use and Mental Health Symptoms among a Cohort of Homeless Adults in Vancouver, British Columbia. *J Urban Health*. 2013 Aug 1;90(4):740–6.
155. Milloy M-JS, Kerr T, Zhang R, Tyndall M, Montaner J, Wood E. Inability to access addiction treatment and risk of HIV infection among injection drug users recruited from a supervised injection facility. *J Public Health (Oxf)*. 2010 Sep;32(3):342–9.
156. Tempalski B, Cleland CM, Pouget ER, Chatterjee S, Friedman SR. Persistence of low drug treatment coverage for injection drug users in large US metropolitan areas. *Substance Abuse Treatment, Prevention, and Policy*. 2010 Sep 21;5(1):23.
157. Room R. Stigma, social inequality and alcohol and drug use. *Drug and Alcohol Review*. 2005;24(2):143–55.
158. Kerr T, Fairbairn N, Tyndall M, Marsh D, Li K, Montaner J, et al. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug and Alcohol Dependence*. 2007 Feb 23;87(1):39–45.

159. Bombardier CH, Rimmele CT, Zintel H. The magnitude and correlates of alcohol and drug use before traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*. 2002 Dec 1;83(12):1765–73.
160. Corrigan JD. Substance abuse as a mediating factor in outcome from traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*. 1995 Apr 1;76(4):302–9.
161. Tomolillo CM, Crothers LJ, Aberson CL. The Damage Done: A Study of Injection Drug Use, Injection Related Abscesses and Needle Exchange Regulation. *Substance Use & Misuse*. 2007 Sep 21;42(10):1603–11.
162. Kinner SA, George J, Campbell G, Degenhardt L. Crime, drugs and distress: patterns of drug use and harm among criminally involved injecting drug users in Australia. *Aust N Z J Public Health*. 2009 Jun;33(3):223–7.
163. Khoury L, Tang YL, Bradley B, Cubells JF, Ressler KJ. Substance use, childhood traumatic experience, and Posttraumatic Stress Disorder in an urban civilian population. *Depress Anxiety*. 2010 Dec;27(12):1077–86.
164. Lipari RN, Hedden SL, Hughes A. Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings. In: *The CBHSQ Report [Internet]*. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2013 [cited 2020 May 6]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK385055/>
165. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association Between Mental Health Disorders, Problem Drug Use, and Regular Prescription Opioid Use. *Arch Intern Med*. 2006 Oct 23;166(19):2087–93.
166. Matsuzaki M, Vu QM, Gwadz M, Delaney JAC, Kuo I, Trejo MEP, et al. Perceived access and barriers to care among illicit drug users and hazardous drinkers: findings from the Seek, Test, Treat, and Retain data harmonization initiative (STTR). *BMC Public Health*. 2018 Mar 20;18(1):366.
167. Hogue A, Dauber S, Dasaro C, Morgenstern J. Predictors of Employment in Substance-Using Male and Female Welfare Recipients. *J Subst Abuse Treat*. 2010 Mar;38(2):108.
168. Laudet AB. Rate and Predictors of Employment among Formerly Polysubstance Dependent Urban Individuals in Recovery. *J Addict Dis*. 2012 Jul;31(3):288–302.
169. Voon P, Greer AM, Amlani A, Newman C, Burmeister C, Buxton JA. Pain as a risk factor for substance use: a qualitative study of people who use drugs in British Columbia, Canada. *Harm Reduct J*. 2018 Dec;15(1):35.
170. People who inject drugs, HIV and AIDS [Internet]. AVERT. 2015 [cited 2018 Dec 10]. Available from: <https://www.avert.org/professionals/hiv-social-issues/key-affected-populations/people-inject-drugs>

171. Public Health Agency of Canada. Summary: Estimates of HIV incidence, prevalence and Canada's progress on meeting the 90-90-90 HIV targets, 2016 [Internet]. aem. 2018 [cited 2020 May 6]. Available from: <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/summary-estimates-hiv-incidence-prevalence-canadas-progress-90-90-90.html>
172. Wood E, Montaner JSG, Yip B, Tyndall MW, Schechter MT, O'Shaughnessy MV, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. *CMAJ*. 2003 Sep 30;169(7):656–61.
173. Milloy M-J, Wood E, Kerr T, Hogg B, Guillemi S, Harrigan PR, et al. Increased Prevalence of Controlled Viremia and Decreased Rates of HIV Drug Resistance Among HIV-Positive People Who Use Illicit Drugs During a Community-wide Treatment-as-Prevention Initiative. *Clin Infect Dis*. 2016 Mar 1;62(5):640–7.
174. McNeil R, Kerr T, Coleman B, Maher L, Milloy MJ, Small W. Antiretroviral Therapy Interruption Among HIV Positive People Who Use Drugs in a Setting with a Community-Wide HIV Treatment-as-Prevention Initiative. *AIDS Behav*. 2017 Feb;21(2):402–9.
175. Kwan CK, Ernst JD. HIV and Tuberculosis: a Deadly Human Syndemic. *Clinical Microbiology Reviews*. 2011 Apr 1;24(2):351–76.
176. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV Co-Infection. *PLOS Pathogens*. 2012 Feb 16;8(2):e1002464.
177. Tien PC, Veterans Affairs Hepatitis C Resource Center Program, National Hepatitis C Program Office. Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. *Am J Gastroenterol*. 2005 Oct;100(10):2338–54.
178. Soriano V, Rodríguez-Rosado R, García-Samaniego J. Management of chronic hepatitis C in HIV-infected patients. *AIDS*. 1999 Apr 1;13(5):539–46.
179. Goulet JL, Fultz SL, McGinnis KA, Justice AC. Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV/HCV-co-infected veterans. *AIDS*. 2005 Oct;19:S99.
180. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. *The Lancet*. 2010 Jul 31;376(9738):367–87.
181. Milloy M-J, Kerr T, Buxton J, Rhodes T, Krusi A, Guillemi S, et al. Social and environmental predictors of plasma HIV RNA rebound among injection drug users treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2012 Apr 1;59(4):393–9.

182. Marcus KS, Kerns RD, Rosenfeld B, Breitbart W. HIV/AIDS-related Pain as a Chronic Pain Condition: Implications of a Biopsychosocial Model for Comprehensive Assessment and Effective Management. *Pain Med.* 2000 Sep 1;1(3):260–73.
183. Norval DA. Symptoms and sites of pain experienced by AIDS patients. *S Afr Med J.* 2004 Jun;94(6):450–4.
184. McCormack JPBS (PHARM), Li RBS (PHARM), Zarowny DMS, Singer JPD. Inadequate Treatment of Pain in Ambulatory HIV Patients. [Editorial]. *Journal of Pain.* 1993 Dec;9(4):279–83.
185. Del Borgo C, Izzi I, Chiarotti F, Del Forno A, Moscati AM, Cornacchione E, et al. Multidimensional aspects of pain in HIV-infected individuals. *AIDS Patient Care STDS.* 2001 Feb;15(2):95–102.
186. Breitbart W, McDonald M, Rosenfeld B, Passik S, Hewitt D, Thaler H, et al. Pain in ambulatory AIDS patients. I: Pain characteristics and medical correlates. *Pain.* 1996 Dec;68(2–3):315–21.
187. Bernard N, Spira R, Ybanez S, Chêne G, Morlat P, Lacoste D, et al. Prevalence and underestimation of pain in HIV-infected patients by physicians: a cross-sectional study in a day care hospital. *AIDS.* 1999 Feb 4;13(2):293.
188. Tsao JCI, Stein JA, Dobalian A. Sex Differences in Pain and Misuse of Prescription Analgesics Among Persons with HIV. *Pain Med.* 2010 Jun 1;11(6):815–24.
189. Richardson JL, Heikes B, Karim R, Weber K, Anastos K, Young M. Experience of Pain among Women with Advanced HIV Disease. *AIDS Patient Care STDS.* 2009 Jul;23(7):503–11.
190. Hewitt D, McDonald M, Portenoy R, Rosenfeld B, Passik S, Breitbart W. Pain syndromes and etiologies in ambulatory AIDS patients. *Pain.* 1997 Apr;70(2–3):117–23.
191. Meera P. Epidemiology of chronic pain in HIV-infected individuals. In: *Chronic Pain and HIV* [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2020 May 7]. p. 1–6. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118777374.ch1>
192. Max B, Sherer R. Management of the Adverse Effects of Antiretroviral Therapy and Medication Adherence. *Clin Infect Dis.* 2000 Jun 1;30(Supplement_2):S96–116.
193. Schiller DS. Identification, management, and prevention of adverse effects associated with highly active antiretroviral therapy. *American Journal of Health-System Pharmacy.* 2004 Dec 1;61(23):2507–22.
194. Florence E, Schrooten W, Verdonck K, Dreezen C, Colebunders R. Rheumatological complications associated with the use of indinavir and other protease inhibitors. *Annals of the Rheumatic Diseases.* 2002 Jan 1;61(1):82–4.

195. Calza L, Magistrelli E, Colangeli V, Borderi M, Contadini I, Bon I, et al. Significant association between statin-associated myalgia and vitamin D deficiency among treated HIV-infected patients. *AIDS*. 2017 Mar;31(5):681–8.
196. Mansueto P, Seidita A, Vitale G, Gangemi S, Iaria C, Cascio A. Vitamin D Deficiency in HIV Infection: Not Only a Bone Disorder. *Biomed Res Int* [Internet]. 2015 [cited 2019 Aug 21];2015. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4426898/>
197. Harding R, Molloy T, Easterbrook P, Frame K, Higginson IJ. Is antiretroviral therapy associated with symptom prevalence and burden? *Int J STD AIDS*. 2006 Jun;17(6):400–5.
198. Martin C, Pehrsson P, Österberg A, Sönnerborg A, Hansson P. Pain in ambulatory HIV-infected patients with and without intravenous drug use. *European Journal of Pain*. 1999;3(2):157–64.
199. Dahlman D, Kral AH, Wenger L, Hakansson A, Novak SP. Physical pain is common and associated with nonmedical prescription opioid use among people who inject drugs. *Subst Abuse Treat Prev Policy*. 2017 Dec;12(1):29.
200. Djiaideu P, Nguemo J, Mukandoli C, Odhiambo AJ, Lightfoot D, Mbuagbaw L, et al. Barriers to HIV care among Francophone African, Caribbean and Black immigrant people living with HIV in Canada: a protocol for a scoping systematic review. *BMJ Open*. 2019 Jan;9(1):e027440.
201. Strathdee SA, Palepu A, Cornelisse PGA, Yip B, O’Shaughnessy MV, Montaner JSG, et al. Barriers to Use of Free Antiretroviral Therapy in Injection Drug Users. *JAMA*. 1998 Aug 12;280(6):547–9.
202. Wolfe D, Carrieri MP, Shepard D. Treatment and care for injecting drug users with HIV infection: a review of barriers and ways forward. *The Lancet*. 2010 Jul 31;376(9738):355–66.
203. Mimiaga MJ, Safren SA, Dvoryak S, Reisner SL, Needle R, Woody G. “We fear the police, and the police fear us”: structural and individual barriers and facilitators to HIV medication adherence among injection drug users in Kiev, Ukraine. *AIDS care*. 2010 Nov;22(11):1305–13.
204. Milloy M-J, Montaner J, Wood E. Barriers to HIV treatment among people who use injection drugs: implications for ‘treatment as prevention.’ *Current Opinion in HIV and AIDS*. 2012 Jul;7(4):332–338.
205. Kalichman SC, Kalichman MO, Cherry C. Forget about forgetting: structural barriers and severe non-adherence to antiretroviral therapy. *AIDS Care*. 2017 Apr;29(4):418–22.
206. Kazanowski MK, Laccetti MS. *Pain*. Jones & Bartlett Learning; 2002. 214 p.

207. Larue F, Fontaine A, Colleau SM. Underestimation and undertreatment of pain in HIV disease: multicentre study. *BMJ*. 1997 Jan 4;314(7073):23.
208. Krashin DL, Merrill JO, Trescot AM. Opioids in the management of HIV-related pain. *Pain Physician*. 2012 Jul;15(3 Suppl):ES157-168.
209. Bruce RD, Merlin J, Lum PJ, Ahmed E, Alexander C, Corbett AH, et al. 2017 HIV Medicine Association of Infectious Diseases Society of America Clinical Practice Guideline for the Management of Chronic Pain in Patients Living With Human Immunodeficiency Virus. *Clin Infect Dis*. 2017 Oct 30;65(10):1601–6.
210. AIDS Education and Training Center Program. General Guidelines for Chronic Pain Management | AIDS Education and Training Centers National Coordinating Resource Center (AETC NCRC) [Internet]. [cited 2020 Nov 13]. Available from: <https://aidsetc.org/resource/general-guidelines-chronic-pain-management>
211. Mack KA, Ory MG. AIDS and older Americans at the end of the Twentieth Century. *J Acquir Immune Defic Syndr*. 2003 Jun 1;33 Suppl 2:S68-75.
212. Shippy RA, Karpiak SE. The aging HIV/AIDS population: Fragile social networks. *Aging & Mental Health*. 2005 May;9(3):246–54.
213. Stavros K, Simpson DM. Understanding the etiology and management of HIV-associated peripheral neuropathy. *Curr HIV/AIDS Rep*. 2014 Sep;11(3):195–201.
214. Pettersen JA, Jones G, Worthington C, Krentz HB, Keppler OT, Hoke A, et al. Sensory neuropathy in human immunodeficiency virus/acquired immunodeficiency syndrome patients: protease inhibitor-mediated neurotoxicity. *Ann Neurol*. 2006 May;59(5):816–24.
215. Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res*. 2006 Apr 4;6:46.
216. Canada PHA of. Summary: Estimates of HIV incidence, prevalence and Canada’s progress on meeting the 90-90-90 HIV targets, 2016 [Internet]. *aem*. 2018 [cited 2020 Jul 17]. Available from: <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/summary-estimates-hiv-incidence-prevalence-canadas-progress-90-90-90.html>
217. RachBeisel J, Scott J, Dixon L. Co-Occurring Severe Mental Illness and Substance Use Disorders: A Review of Recent Research. *PS*. 1999 Nov 1;50(11):1427–34.
218. Voon P, Karamouzian M, Kerr T. Chronic pain and opioid misuse: a review of reviews. *Subst Abuse Treat Prev Policy*. 2017 15;12(1):36.
219. Larson MJ, Paasche-Orlow M, Cheng DM, Lloyd-Travaglini C, Saitz R, Samet JH. Persistent pain is associated with substance use after detoxification: a prospective cohort analysis. *Addiction*. 2007;102(5):752–60.

220. Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. *J Clin Psychiatry*. 2009 Sep;70(9):1213–8.
221. Potter JS, Prather K, Weiss RD. Physical pain and associated clinical characteristics in treatment-seeking patients in four substance use disorder treatment modalities. *Am J Addict*. 2008 Apr;17(2):121–5.
222. Linton SJ. A Transdiagnostic Approach to Pain and Emotion. *Journal of Applied Biobehavioral Research*. 2013;18(2):82–103.
223. Milloy MJ, Kerr T, Buxton J, Rhodes T, Guillemi S, Hogg R, et al. Dose-response Effect of Incarceration Events on Nonadherence to HIV Antiretroviral Therapy Among Injection Drug Users. *J Infect Dis*. 2011 May 1;203(9):1215–21.
224. Merrill JO, Rhodes LA, Deyo RA, Marlatt GA, Bradley KA. Mutual Mistrust in the Medical Care of Drug Users. *J Gen Intern Med*. 2002 May;17(5):327–33.
225. Chan Carusone S, Guta A, Robinson S, Tan DH, Cooper C, O’Leary B, et al. “Maybe if I stop the drugs, then maybe they’d care?”—hospital care experiences of people who use drugs. *Harm Reduction Journal*. 2019 Feb 13;16(1):16.
226. Obradovic M, Lal A, Liedgens H. Validity and responsiveness of EuroQol-5 dimension (EQ-5D) versus Short Form-6 dimension (SF-6D) questionnaire in chronic pain. *Health Qual Life Outcomes*. 2013 Jul 1;11:110.
227. Darke S. Self-report among injecting drug users: a review. *Drug Alcohol Depend*. 1998 Aug 1;51(3):253–63; discussion 267–268.
228. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and Characteristics of Chronic Pain Among Chemically Dependent Patients in Methadone Maintenance and Residential Treatment Facilities. *JAMA*. 2003 May 14;289(18):2370–8.
229. Manchikanti L, Damron KS, McManus CD, Barnhill RC. Patterns of Illicit Drug Use and Opioid Abuse in Patients with Chronic Pain at Initial Evaluation: A Prospective, Observational Study. 2004;7(4):8.
230. Merlin JS, Walcott M, Kerns R, Bair MJ, Burgio KL, Turan JM. Pain Self-Management in HIV-Infected Individuals with Chronic Pain: A Qualitative Study. *Pain Med*. 2015 Apr 1;16(4):706–14.
231. Karasz A, Zallman L, Berg K, Gourevitch M, Selwyn P, Arnstein J. The experience of chronic severe pain in patients undergoing methadone maintenance treatment. *Journal of Pain and Symptom Management*. 2004 Nov 1;28(5):517–25.
232. Blay N, Glover S, Bothe J, Lee S, Lamont F. Substance users’ perspective of pain management in the acute care environment. *Contemp Nurse*. 2012 Oct;42(2):289–97.

233. Baldacchino A, Gilchrist G, Fleming R, Bannister J. Guilty until proven innocent: a qualitative study of the management of chronic non-cancer pain among patients with a history of substance abuse. *Addict Behav.* 2010 Mar;35(3):270–2.
234. Cavalieri TA. Management of Pain in Older Adults. *J Am Osteopath Assoc.* 2005 Mar 1;105(3_suppl):12S-17S.
235. Schofield P. Pain in Older Adults: Epidemiology, Impact and Barriers to Management. *Rev Pain.* 2007 Aug;1(1):12–4.
236. Wu L-T, Blazer DG. Illicit and Nonmedical Drug Use Among Older Adults: A Review. *J Aging Health.* 2011 Apr 1;23(3):481–504.
237. Arndt S, Clayton R, Schultz SK. Trends in substance abuse treatment 1998-2008: increasing older adult first-time admissions for illicit drugs. *Am J Geriatr Psychiatry.* 2011 Aug;19(8):704–11.
238. Balderson BH, Grothaus L, Harrison RG, McCoy K, Mahoney C, Catz S. Chronic illness burden and quality of life in an aging HIV population. *AIDS Care.* 2013 Apr 1;25(4):451–8.
239. Susser E, Betne P, Valencia E, Goldfinger SM, Lehman AF. Injection drug use among homeless adults with severe mental illness. *American Journal of Public Health.* 1997 May;87(5):854–6.
240. Aouizerat BE, Miaskowski CA, Gay C, Portillo CJ, Coggins T, Davis H, et al. Risk Factors and Symptoms Associated With Pain in HIV-Infected Adults. *Journal of the Association of Nurses in AIDS Care.* 2010 Mar 1;21(2):125–33.
241. Hooten WM. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. *Mayo Clinic Proceedings.* 2016 Jul 1;91(7):955–70.
242. Gureje O, Von Korff M, Kola L, Demyttenaere K, He Y, Posada-Villa J, et al. The relation between multiple pains and mental disorders: Results from the World Mental Health Surveys. *PAIN®.* 2008 Mar 1;135(1):82–91.
243. Spithoff S, Leece P, Sullivan F, Persaud N, Belesiotis P, Steiner L. Drivers of the opioid crisis: An appraisal of financial conflicts of interest in clinical practice guideline panels at the peak of opioid prescribing. *Lexchin J, editor. PLoS ONE.* 2020 Jan 24;15(1):e0227045.
244. Rasu RS, Sohraby R, Cunningham L, Knell ME. Assessing Chronic Pain Treatment Practices and Evaluating Adherence to Chronic Pain Clinical Guidelines in Outpatient Practices in the United States. *The Journal of Pain.* 2013 Jun 1;14(6):568–78.
245. Morasco BJ, Duckart JP, Dobscha SK. Adherence to Clinical Guidelines for Opioid Therapy for Chronic Pain in Patients with Substance Use Disorder. *J GEN INTERN MED.* 2011 May 12;26(9):965.

246. Colasanti J, Lira MC, Cheng DM, Liebschutz JM, Tsui JI, Forman LS, et al. Chronic Opioid Therapy in People Living With Human Immunodeficiency Virus: Patients' Perspectives on Risks, Monitoring, and Guidelines. *Clin Infect Dis*. 2019 Jan 7;68(2):291–7.
247. Reyes-Gibby CC, Anderson KO, Shete S, Bruera E, Yennurajalingam S. Early Referral to Supportive Care Specialists for Symptom Burden in Lung Cancer Patients: A Comparison of Non-Hispanic Whites, Hispanics, and Non-Hispanic Blacks. *Cancer*. 2012 Feb 1;118(3):856–63.
248. Kwok W, Bhuvanakrishna T. The Relationship Between Ethnicity and the Pain Experience of Cancer Patients: A Systematic Review. *Indian J Palliat Care*. 2014;20(3):194–200.
249. Barnabe C, Elias B, Bartlett J, Roos L, Peschken C. Arthritis in Aboriginal Manitobans: evidence for a high burden of disease. *J Rheumatol*. 2008 Jun;35(6):1145–50.
250. Latimer M, Sylliboy JR, Francis J, Amey S, Rudderham S, Finley GA, et al. Co-creating better healthcare experiences for First Nations children and youth: The FIRST approach emerges from Two-Eyed seeing. *Paediatric and Neonatal Pain* [Internet]. [cited 2020 Jul 15];n/a(n/a). Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/pne2.12024>
251. Latimer M, Rudderham S, Lethbridge L, MacLeod E, Harman K, Sylliboy JR, et al. Occurrence of and referral to specialists for pain-related diagnoses in First Nations and non-First Nations children and youth. *CMAJ*. 2018 Dec 10;190(49):E1434–40.
252. Lin IB, Bunzli S, Mak DB, Green C, Goucke R, Coffin J, et al. Unmet Needs of Aboriginal Australians With Musculoskeletal Pain: A Mixed-Method Systematic Review. *Arthritis Care & Research*. 2018;70(9):1335–47.
253. Vindigni D, Perkins J. Identifying Musculoskeletal Conditions Among Rural Indigenous Peoples. *Australian Journal of Rural Health*. 2003;11(4):187–93.
254. Ranasinghe I, Chew D, Aroney C, Coverdale S, Allen R, Walters D, et al. Differences in Treatment and Management of Indigenous and Non-Indigenous Patients Presenting with Chest Pain: Results of the Heart Protection Partnership (HPP) Study. *Heart, Lung and Circulation*. 2009 Feb 1;18(1):32–7.
255. Ti L, Voon P, Dobrer S, Montaner J, Wood E, Kerr T. Denial of Pain Medication by Health Care Providers Predicts In-Hospital Illicit Drug Use among Individuals who Use Illicit Drugs. *Pain Research and Management*. 2015;20(2):84–8.
256. Lake S, Walsh Z, Kerr T, Cooper ZD, Buxton J, Wood E, et al. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: A longitudinal analysis. *PLoS Medicine*. 2019 Nov 1;16(11):e1002967.
257. Lan C-W, Lin C, Thanh DC, Li L. Drug-related stigma and access to care among people who inject drugs in Vietnam. *Drug and Alcohol Review*. 2018;37(3):333–9.

258. Mars SG, Fessel JN, Bourgois P, Montero F, Karandinos G, Ciccarone D. Heroin-related overdose: The unexplored influences of markets, marketing and source-types in the United States. *Soc Sci Med*. 2015 Sep;140:44–53.
259. Rummans TA, Burton MC, Dawson NL. How Good Intentions Contributed to Bad Outcomes: The Opioid Crisis. *Mayo Clin Proc*. 2018;93(3):344–50.
260. Yarborough BJH, Stumbo SP, Janoff SL, Yarborough MT, McCarty D, Chilcoat HD, et al. Understanding opioid overdose characteristics involving prescription and illicit opioids: A mixed methods analysis. *Drug Alcohol Depend*. 2016 Oct 1;167:49–56.
261. Gwira Baumblatt JA, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, Jones TF. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. *JAMA Intern Med*. 2014 May;174(5):796–801.
262. Cepeda MS, Fife D, Vo L, Mastrogiovanni G, Yuan Y. Comparison of Opioid Doctor Shopping for Tapentadol and Oxycodone: A Cohort Study. *The Journal of Pain*. 2013 Feb 1;14(2):158–64.
263. Martyres RF, Clode D, Burns JM. Seeking drugs or seeking help? Escalating “doctor shopping” by young heroin users before fatal overdose. *The Medical Journal of Australia*. 2004 Mar 1;180(5):211–4.
264. Simeone R. Doctor Shopping Behavior and the Diversion of Prescription Opioids. *Subst Abuse [Internet]*. 2017 Apr 11 [cited 2020 Jul 28];11. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5398712/>
265. Lucey BP, Clifford DB, Creighton J, Edwards RR, McArthur JC, Haythornthwaite J. Relationship of Depression and Catastrophizing to Pain, Disability, and Medication Adherence in Patients with HIV-Associated Sensory Neuropathy. *AIDS Care*. 2011 Aug;23(8):921–8.
266. Berg KM, Cooperman NA, Newville H, Arnsten JH. Self-Efficacy and Depression as Mediators of the Relationship between Pain and Antiretroviral Adherence. *AIDS Care*. 2009 Feb;21(2):244–8.
267. Surratt HL, Kurtz SP, Levi-Minzi MA, Cicero TJ, Tsuyuki K, O’Grady CL. Pain Treatment and Antiretroviral Medication Adherence Among Vulnerable HIV-Positive Patients. *AIDS Patient Care STDS*. 2015 Apr 1;29(4):186–92.
268. Denis CM, Morales KH, Wu Q, Metzger DS, Cheatle MD. Association Between Diagnoses of Chronic Noncancer Pain, Substance Use Disorder, and HIV-Related Outcomes in People Living With HIV. *J Acquir Immune Defic Syndr*. 2019 01;82 Suppl 2:S142–7.
269. Cervia LD, McGowan JP, Weseley AJ. Clinical and Demographic Variables Related to Pain in HIV-Infected Individuals Treated with Effective, Combination Antiretroviral Therapy (cART). *Pain Medicine*. 2010;11(4):498–503.

270. Miaskowski C, Penko JM, Guzman D, Mattson JE, Bangsberg DR, Kushel MB. Occurrence and Characteristics of Chronic Pain in a Community-Based Cohort of Indigent Adults Living With HIV Infection. *J Pain*. 2011 Sep;12(9):1004–16.
271. Jeevanjee S, Penko J, Guzman D, Miaskowski C, Bangsberg DR, Kushel MB. Opioid analgesic misuse is associated with incomplete antiretroviral adherence in a cohort of HIV-infected indigent adults in San Francisco. *AIDS Behav*. 2014 Jul;18(7):1352–8.
272. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL. Sex, Gender, and Pain: A Review of Recent Clinical and Experimental Findings. *J Pain*. 2009 May;10(5):447–85.
273. Peacock S, Patel S. Cultural Influences on Pain. *Rev Pain*. 2008 Mar;1(2):6–9.
274. Tremblay J, Hamet P. Genetics of pain, opioids, and opioid responsiveness. *Metabolism*. 2010 Oct 1;59:S5–8.
275. Sabin CA a, Harding R b, Bagkeris E a, Nkhoma K b, Post FA c, Sachikonye M d, et al. Pain in people living with HIV and its association with healthcare resource use, well being and functional status. *AIDS*. 2018 Nov;32(18):2697–706.
276. Parker R, Stein DJ, Jelsma J. Pain in people living with HIV/AIDS: a systematic review. *J Int AIDS Soc* [Internet]. 2014 Feb 18 [cited 2020 Mar 28];17(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3929991/>
277. Merlin JS. Chronic Pain in Patients With HIV Infection: What Clinicians Need To Know. *Top Antivir Med*. 2016 Nov 28;23(3):120–4.
278. Jiao JM, So E, Jebakumar J, George MC, Simpson DM, Robinson-Papp J. Chronic pain disorders in HIV primary care: clinical characteristics and association with healthcare utilization. *Pain*. 2016 Apr;157(4):931–7.
279. Dassieu L, Kaboré J-L, Choinière M, Arruda N, Roy É. Chronic pain management among people who use drugs: A health policy challenge in the context of the opioid crisis. *International Journal of Drug Policy*. 2019 Sep 1;71:150–6.
280. Cheatle MD. Depression, Chronic Pain, and Suicide by Overdose: On the Edge. *Pain Med*. 2011 Jun;12(Suppl 2):S43–8.
281. Alford DP, German JS, Samet JH, Cheng DM, Lloyd-Travaglini CA, Saitz R. Primary Care Patients with Drug Use Report Chronic Pain and Self-Medicating with Alcohol and Other Drugs. *J Gen Intern Med*. 2016 May;31(5):486–91.
282. Morasco BJ, Cavanagh R, Gritzner S, Dobscha SK. Care management practices for chronic pain in veterans prescribed high doses of opioid medications. *Fam Pract*. 2013 Dec;30(6):671–8.

283. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med*. 2015 Jan 15;372(3):241–8.
284. Fantoni M, Ricci F, Del Borgo C, Izzi I, Damiano F, Moscati AM, et al. Multicentre study on the prevalence of symptoms and symptomatic treatment in HIV infection. Central Italy PRESINT Group. *J Palliat Care*. 1997;13(2):9–13.
285. Mitchell MM, Maragh-Bass AC, Nguyen TQ, Isenberg S, Knowlton AR. The role of chronic pain and current substance use in predicting negative social support among disadvantaged persons living with HIV/AIDS. *AIDS Care*. 2016;28(10):1280–6.
286. Bicket MC, Park JN, Torrie A, Allen ST, Weir BW, Sherman SG. Factors associated with chronic pain and non-medical opioid use among people who inject drugs. *Addictive Behaviors*. 2020 Mar 1;102:106172.
287. Prater CD, Zylstra RG, Miller KE. Successful Pain Management for the Recovering Addicted Patient. *Prim Care Companion J Clin Psychiatry*. 2002;4(4):125–31.
288. Breitbart W, Rosenfeld B, Passik S, Kaim M, Funesti-Esch J, Stein K. A comparison of pain report and adequacy of analgesic therapy in ambulatory AIDS patients with and without a history of substance abuse. *PAIN*. 1997 Aug 1;72(1):235–43.
289. Behar E, Bagnulo R, Knight K, Santos G-M, Coffin PO. “Chasing the pain relief, not the high”: Experiences managing pain after opioid reductions among patients with HIV and a history of substance use. *PLoS ONE*. 2020;15(3):e0230408.
290. Knowlton AR, Nguyen TQ, Robinson AC, Harrell PT, Mitchell MM. Pain Symptoms Associated with Opioid Use among Vulnerable Persons with HIV: An Exploratory Study with Implications for Palliative Care and Opioid Abuse Prevention. *J Palliat Care*. 2015 Dec;31(4):228–33.
291. Tsui JI, Cheng DM, Coleman SM, Blokhina E, Bridden C, Krupitsky E, et al. Pain is Associated with Heroin Use over Time in HIV-Infected Russian Drinkers. *Addiction*. 2013 Oct;108(10):1779–87.
292. Tsui JI, Cheng DM, Coleman SM, Lira MC, Blokhina E, Bridden C, et al. Pain is Associated with Risky Drinking over Time among HIV-Infected Persons in St. Petersburg, Russia. *Drug Alcohol Depend*. 2014 Nov 1;144:87–92.
293. Petrosky E, Harpaz R, Fowler KA, Bohm MK, Helmick CG, Yuan K, et al. Chronic Pain Among Suicide Decedents, 2003 to 2014: Findings From the National Violent Death Reporting System. *Annals of internal medicine*. 2018 Oct 2;169(7):448–55.
294. Ashrafioun L, Kane C, Bishop TM, Britton PC, Pigeon WR. The Association of Pain Intensity and Suicide Attempts Among Patients Initiating Pain Specialty Services. *The Journal of Pain*. 2019 Jul 1;20(7):852–9.

295. Backmund M, Meyer K, Schütz C, Reimer J. Factors associated with suicide attempts among injection drug users. *Subst Use Misuse*. 2011;46(12):1553–9.
296. Wines JD, Saitz R, Horton NJ, Lloyd-Travaglini C, Samet JH. Suicidal behavior, drug use and depressive symptoms after detoxification: a 2-year prospective study. *Drug Alcohol Depend*. 2004 Dec 7;76 Suppl:S21-29.
297. Zullig KJ, Divin AL, Weiler RM, Haddox JD, Pealer LN. Adolescent Nonmedical Use of Prescription Pain Relievers, Stimulants, and Depressants, and Suicide Risk. *Substance Use & Misuse*. 2015 Nov 10;50(13):1678–89.
298. PV A, Jun Wen T, Karuvetil MZ, Cheong A, Cheok C, Kandasami G. Unnatural Death among Treatment Seeking Substance Users in Singapore: A Retrospective Study. *Int J Environ Res Public Health* [Internet]. 2019 Aug [cited 2020 Jul 30];16(15). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6695629/>
299. Darke S, Ross J. Suicide among heroin users: rates, risk factors and methods. *Addiction*. 2002 Nov;97(11):1383–94.
300. Darke S, Torok M, Kaye S, Ross J. Attempted suicide, self-harm, and violent victimization among regular illicit drug users. *Suicide Life Threat Behav*. 2010 Dec;40(6):587–96.
301. Shand FL, Degenhardt L, Slade T, Nelson EC. Sex differences amongst dependent heroin users: Histories, clinical characteristics and predictors of other substance dependence. *Addictive Behaviors*. 2011 Jan;36(1–2):27–36.
302. Nordmann S, Vilotitch A, Lions C, Michel L, Mora M, Spire B, et al. Pain in methadone patients: Time to address undertreatment and suicide risk (ANRS-Methaville trial). DeLuca V, editor. *PLoS ONE*. 2017 May 17;12(5):e0176288.
303. St. Marie B. Health Care Experiences when Pain and Substance Use Disorder Coexist: “Just Because I’m an Addict Doesn’t Mean I Don’t Have Pain.” *Pain Med*. 2014 Dec 1;15(12):2075–86.
304. McNeil R, Small W, Wood E, Kerr T. Hospitals as a “risk environment”: an ethno-epidemiological study of voluntary and involuntary discharge from hospital against medical advice among people who inject drugs. *Soc Sci Med*. 2014 Mar;105:59–66.
305. Grover CA, Close RJH, Wiele ED, Villarreal K, Goldman LM. Quantifying Drug-seeking Behavior: A Case Control Study. *Journal of Emergency Medicine*. 2012 Jan 1;42(1):15–21.
306. Biancarelli DL, Biello KB, Childs E, Drainoni M, Salhaney P, Edeza A, et al. Strategies used by people who inject drugs to avoid stigma in healthcare settings. *Drug and Alcohol Dependence*. 2019 May;198:80–6.
307. Chesney MA, SMITH AW. Critical Delays in HIV Testing and Care: The Potential Role of Stigma. *American Behavioral Scientist*. 1999 Apr 1;42(7):1162–74.

308. Levi-Minzi MA, Surratt HL. HIV Stigma Among Substance Abusing People Living with HIV/AIDS: Implications for HIV Treatment. *AIDS Patient Care STDS*. 2014 Aug 1;28(8):442–51.
309. Nyblade LC. Measuring HIV stigma: existing knowledge and gaps. *Psychol Health Med*. 2006 Aug;11(3):335–45.
310. Van Nguyen H, Nguyen HLT, Mai HT, Le HQ, Tran BX, Hoang CD, et al. Stigmatization among methadone maintenance treatment patients in mountainous areas in northern Vietnam. *Harm Reduct J* [Internet]. 2017 Jan 6 [cited 2020 Jul 22];14. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5217586/>
311. Merlin JS, Bulls HW, Vucovich LA, Edelman EJ, Starrels JL. Pharmacologic and non-pharmacologic treatments for chronic pain in individuals with HIV: a systematic review. *AIDS Care*. 2016 Dec;28(12):1506–15.
312. Simpson DM, Brown S, Tobias J, NGX-4010 C107 Study Group. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology*. 2008 Jun 10;70(24):2305–13.
313. Collins AB, Parashar S, Hogg RS, Fernando S, Worthington C, McDougall P, et al. Integrated HIV care and service engagement among people living with HIV who use drugs in a setting with a community-wide treatment as prevention initiative: a qualitative study in Vancouver, Canada. *J Int AIDS Soc*. 2017 Mar 3;20(1):21407.
314. Palepu A, Gadermann A, Hubley AM, Farrell S, Gogosis E, Aubry T, et al. Substance Use and Access to Health Care and Addiction Treatment among Homeless and Vulnerably Housed Persons in Three Canadian Cities. *PLoS One* [Internet]. 2013 Oct 4 [cited 2020 May 6];8(10). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3790780/>
315. Ti L, Ti L. Leaving the Hospital Against Medical Advice Among People Who Use Illicit Drugs: A Systematic Review. *Am J Public Health*. 2015 Dec;105(12):e53-59.
316. Skinner N, Feather NT, Freeman T, Roche A. Stigma and Discrimination in Health-Care Provision to Drug Users: The Role of Values, Affect, and Deservingness Judgments. *Journal of Applied Social Psychology*. 2007;37(1):163–86.
317. Frantsve LME, Kerns RD. Patient-provider interactions in the management of chronic pain: current findings within the context of shared medical decision making. *Pain Med*. 2007 Feb;8(1):25–35.
318. Schoenthaler A, Rosenthal DM, Butler M, Jacobowitz L. Medication Adherence Improvement Similar for Shared Decision-Making Preference or Longer Patient-Provider Relationship. *J Am Board Fam Med*. 2018 Sep 1;31(5):752–60.

319. Schneider J, Kaplan SH, Greenfield S, Li W, Wilson IB. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *J Gen Intern Med.* 2004 Nov;19(11):1096–103.
320. McCoy L. HIV-Positive Patients and the Doctor-Patient Relationship: Perspectives From the Margins. *Qual Health Res.* 2005 Jul 1;15(6):791–806.
321. Riedl D, Schüßler G. The Influence of Doctor-Patient Communication on Health Outcomes: A Systematic Review. *Zeitschrift für Psychosomatische Medizin und Psychotherapie.* 2017 Jun 1;63(2):131–50.
322. Beach MC, Keruly J, Moore RD. Is the Quality of the Patient-Provider Relationship Associated with Better Adherence and Health Outcomes for Patients with HIV? *Journal of General Internal Medicine.* 2006;21(6):661–5.
323. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000 Jul 4;133(1):21–30.
324. Zhang C, McMahon J, Leblanc N, Braksmajer A, Crean HF, Alcena-Stiner D. Association of Medical Mistrust and Poor Communication with HIV-Related Health Outcomes and Psychosocial Wellbeing Among Heterosexual Men Living with HIV. *AIDS Patient Care STDS.* 2020;34(1):27–37.
325. Murri R, Antinori A, Ammassari A, Nappa S, Orofino G, Abrescia N, et al. Physician estimates of adherence and the patient-physician relationship as a setting to improve adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2002 Dec 15;31 Suppl 3:S158-162.
326. Dorflinger L, Kerns RD, Auerbach SM. Providers' roles in enhancing patients' adherence to pain self management. *Transl Behav Med.* 2013 Mar;3(1):39–46.
327. Westergaard RP, Ambrose BK, Mehta SH, Kirk GD. Provider and clinic-level correlates of deferring antiretroviral therapy for people who inject drugs: a survey of North American HIV providers. *Journal of the International AIDS Society.* 2012;15(1):10–10.
328. Bachireddy C, Soule MC, Izenberg JM, Dvoryak S, Dumchev K, Altice FL. Integration of health services improves multiple healthcare outcomes among HIV-infected people who inject drugs in Ukraine. *Drug Alcohol Depend.* 2014 Jan 1;134:106–14.
329. Wood RA, Zettel P, Stewart W. The Dr. Peter Centre. Harm reduction nursing. *Can Nurse.* 2003 May;99(5):20–4.
330. Ti L, Dong H, Kerr T, Turje RB, Parashar S, Min JE, et al. The effect of engagement in an HIV/AIDS integrated health programme on plasma HIV-1 RNA suppression among HIV-positive people who use illicit drugs: a marginal structural modelling analysis. *HIV Med.* 2017;18(8):580–6.

331. Ti L, Milloy M-J, Turje RB, Montaner J, Wood E, Kerr T. The impact of an HIV/AIDS adult integrated health program on leaving hospital against medical advice among HIV-positive people who use illicit drugs. *J Public Health (Oxf)*. 2017 01;39(2):e33–9.
332. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017 Sep;390(10100):1211–59.
333. Jackson T, Thomas S, Stabile V, Han X, Shotwell M, McQueen K. Prevalence of chronic pain in low-income and middle-income countries: a systematic review and meta-analysis. *The Lancet*. 2015 Apr 27;385:S10.
334. Lebovits AH, Lefkowitz M, McCarthy D, Simon R, Wilpon H, Jung R, et al. The Prevalence and Management of Pain in Patients with AIDS: A Review of 134 Cases. [Editorial]. *Journal of Pain*. 1989 Sep;5(3):245–8.
335. Barry DT, Savant JD, Beitel M, Cutter CJ, Moore BA, Schottenfeld RS, et al. Pain and Associated Substance Use among Opioid Dependent Individuals Seeking Office-Based Treatment with Buprenorphine-Naloxone: A Needs Assessment Study. *Am J Addict*. 2013 May;22(3):212–7.
336. Voon P, Hayashi K, Milloy M-J, Nguyen P, Wood E, Montaner J, et al. Pain among high-risk patients on methadone maintenance treatment. *J Pain*. 2015 Sep;16(9):887–94.
337. Pan American Health Organization. Cancer pain relief: a guide to opioid availability. 1996 [cited 2020 Oct 9]; Available from: <https://iris.paho.org/handle/10665.2/43140>
338. Katz MH. Opioid prescriptions for chronic nonmalignant pain: driving on a dangerous road. *JAMA internal medicine*. 2013 Feb 11;173(3):178.
339. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Archives of Internal Medicine*. 2011 Apr 11;171(7):686–91.
340. Braden JB, Russo J, Fan M-Y, Edlund MJ, Martin BC, DeVries A, et al. Emergency Department Visits Among Recipients of Chronic Opioid Therapy. *Arch Intern Med*. 2010 Sep 13;170(16):1425–32.
341. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. *Ann Intern Med*. 2010 Jan 19;152(2):85–92.
342. Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989 Mar;36(3):363–6.

343. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev* [Internet]. 2010 Jan 20 [cited 2020 Oct 9];2010(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6494200/>
344. Clark JD. Chronic pain prevalence and analgesic prescribing in a general medical population. *Journal of Pain and Symptom Management*. 2002 Feb;23(2):131–7.
345. Potter JS, Chakrabarti A, Domier CP, Hillhouse MP, Weiss RD, Ling W. Pain and Continued Opioid Use in Individuals Receiving Buprenorphine-Naloxone for Opioid Detoxification: Secondary Analyses from the Clinical Trials Network. *J Subst Abuse Treat*. 2010 Jun;38(Suppl 1):S80–6.
346. Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006 Nov;125(1–2):172–9.
347. Baca C, Grant K. Mortality from opioid analgesics must not be ignored. *Pain*. 2007 Apr;128(3):288; author reply 288-289.
348. Turk DC, Brody MC, Okifuji EA. Physicians' attitudes and practices regarding the long-term prescribing of opioids for non-cancer pain. *Pain*. 1994 Nov;59(2):201–8.
349. Morley-Forster PK, Clark AJ, Speechley M, Moulin DE. Attitudes Toward Opioid Use for Chronic Pain: A Canadian Physician Survey [Internet]. Vol. 8, *Pain Research and Management*. Hindawi; 2003 [cited 2020 Sep 22]. p. 189–94. Available from: <https://www.hindawi.com/journals/prm/2003/184247/>
350. Jamison RN, Sheehan KA, Scanlan E, Matthews M, Ross EL. Beliefs and attitudes about opioid prescribing and chronic pain management: survey of primary care providers. *J Opioid Manag*. 2014 Dec;10(6):375–82.
351. Weinstein SM, Laux LF, Thornby JI, Lorimor RJ, Hill CS, Thorpe DM, et al. Physicians' attitudes toward pain and the use of opioid analgesics: results of a survey from the Texas Cancer Pain Initiative. *South Med J*. 2000 May;93(5):479–87.
352. Lawson E, Sabin C, Perry N, Richardson D, Gilleece Y, Churchill D, et al. Is HIV Painful? An Epidemiologic Study of the Prevalence and Risk Factors for Pain in HIV-Infected Patients. *Clin J Pain*. 2015 Sep;31(9):813–9.
353. Mphahlele NR, Mitchell D, Kamerman PR. Pain in ambulatory HIV-positive South Africans. *Eur J Pain*. 2012 Mar;16(3):447–58.
354. Kiesler DJ, Auerbach SM. Integrating measurement of control and affiliation in studies of physician-patient interaction: the interpersonal circumplex. *Social Science & Medicine* (1982). 2003 Nov;57(9):1707–22.

355. Zallman L, Rubens SL, Saitz R, Samet JH, Lloyd-Travaglini C, Liebschutz J. Attitudinal Barriers to Analgesic Use among Patients with Substance Use Disorders. *Pain Res Treat* [Internet]. 2012 [cited 2020 Oct 8];2012. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3352625/>
356. Mitchell MM, Nguyen TQ, Maragh-Bass AC, Isenberg SR, Beach MC, Knowlton AR. Patient-Provider Engagement and Chronic Pain in Drug-Using, Primarily African American Persons Living with HIV/AIDS. *AIDS Behav*. 2017 Jun;21(6):1768–74.
357. Roter D, Hall JA. *Doctors Talking with Patients/patients Talking with Doctors: Improving Communication in Medical Visits*. Greenwood Publishing Group; 2006. 256 p.
358. Nicholas PK, Voss JG, Corless IB, Lindgren TG, Wantland DJ, Kempainen JK, et al. Unhealthy behaviours for self-management of HIV-related peripheral neuropathy. *AIDS Care*. 2007 Nov 1;19(10):1266–73.
359. Surah S, Adams R, Townsend L, Reynolds I, Kinahan JC, Keating S, et al. Health-related quality of life of HIV-infected intravenous drug users: *International Journal of STD & AIDS* [Internet]. 2013 Jul 23 [cited 2020 Sep 18]; Available from: <https://journals.sagepub.com/doi/10.1177/0956462413486454>
360. Tran BX, Dang AK, Truong NT, Ha GH, Nguyen HLT, Do HN, et al. Depression and Quality of Life among Patients Living with HIV/AIDS in the Era of Universal Treatment Access in Vietnam. *Int J Environ Res Public Health* [Internet]. 2018 Dec [cited 2020 Sep 18];15(12). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313339/>
361. Heimer R, Zhan W, Grau LE. Prevalence and experience of chronic pain in suburban drug injectors. *Drug and Alcohol Dependence*. 2015 Jun 1;151:92–100.
362. Hwang SW, Wilkins E, Chambers C, Estrabillo E, Berends J, MacDonald A. Chronic pain among homeless persons: characteristics, treatment, and barriers to management. *BMC Fam Pract*. 2011 Dec;12(1):73.
363. Turnbull J, Muckle W, Masters C. Homelessness and health. *CMAJ*. 2007 Oct 23;177(9):1065–6.
364. Stafford A, Wood L. Tackling Health Disparities for People Who Are Homeless? Start with Social Determinants. *Int J Environ Res Public Health* [Internet]. 2017 Dec [cited 2020 Sep 24];14(12). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5750953/>
365. Wise C, Phillips K. Hearing the Silent Voices: Narratives of Health Care and Homelessness. *Issues in Mental Health Nursing*. 2013 May 1;34(5):359–67.
366. Potter JS, Prather K, Weiss RD. Physical Pain and Associated Clinical Characteristics in Treatment-Seeking Patients in Four Substance Use Disorder Treatment Modalities. *The American Journal on Addictions*. 2008;17(2):121–5.

367. Sohler NL, Starrels J, Khalid L, Bachhuber M, Arnsten J, Nahvi S, et al. Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-infected individuals with chronic pain. *Subst Use Misuse*. 2018 Aug 24;53(10):1602–7.
368. Woolridge E, Barton S, Samuel J, Osorio J, Dougherty A, Holdcroft A. Cannabis Use in HIV for Pain and Other Medical Symptoms. *Journal of Pain and Symptom Management*. 2005 Apr 1;29(4):358–67.
369. National Academies of Sciences. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research [Internet]. 2017 [cited 2020 Oct 20]. Available from: <https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state>
370. Vanhaesebrouck A, Vuillermoz C, Robert S, Parizot I, Chauvin P. Who self-medicates? Results from structural equation modeling in the Greater Paris area, France. *PLOS ONE*. 2018 Dec 17;13(12):e0208632.
371. Kennedy J, Roll JM, Schraudner T, Murphy S, McPherson S. Prevalence of Persistent Pain in the U.S. Adult Population: New Data From the 2010 National Health Interview Survey. *The Journal of Pain*. 2014 Oct 1;15(10):979–84.
372. Herr K. Chronic pain in the older patient: management strategies. 2. *J Gerontol Nurs*. 2002 Feb;28(2):28–34; quiz 54–5.
373. Merlin JS, Long D, Becker WC, Cachay ER, Christopoulos KA, Claborn K, et al. The association of chronic pain and long-term opioid therapy with hiv treatment outcomes. *J Acquir Immune Defic Syndr*. 2018 Sep 1;79(1):77–82.
374. Konrad S, Skinner S, Kazadi GB, Gartner K, Lim HJ. HIV disease progression to CD4 count <200 cells/ μ L and death in Saskatoon, Saskatchewan. *Can J Infect Dis Med Microbiol*. 2013;24(2):97–101.
375. Safakish R, Ko G, Salimpour V, Hendin B, Sohanpal I, Loheswaran G, et al. Medical Cannabis for the Management of Pain and Quality of Life in Chronic Pain Patients: A Prospective Observational Study. *Pain Med* [Internet]. [cited 2020 Nov 6]; Available from: <https://academic.oup.com/painmedicine/advance-article/doi/10.1093/pm/pnaa163/5859722>
376. Vigil JM, Stith SS, Adams IM, Reeve AP. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. Vrana KE, editor. *PLoS ONE*. 2017 Nov 16;12(11):e0187795.
377. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. *JAMA Intern Med*. 2014 Oct;174(10):1668–73.

378. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *J Pain*. 2016;17(6):739–44.
379. McMahon S, Koltzenburg M, Tracey I, Turk D. *Wall and Melzack's Textbook of Pain: Expert Consult - Online and Print*. Philadelphia, PA: Elsevier Canada; 2013. 1184 p.
380. Gallagher RM. Biopsychosocial pain medicine and mind-brain-body science. *Phys Med Rehabil Clin N Am*. 2004 Nov;15(4):855–82, vii.
381. McCracken LM, Turk DC. Behavioral and cognitive-behavioral treatment for chronic pain: outcome, predictors of outcome, and treatment process. *Spine (Phila Pa 1976)*. 2002 Nov 15;27(22):2564–73.
382. Cheatle MD, Gallagher RM. Chronic pain and comorbid mood and substance use disorders: A biopsychosocial treatment approach. *Curr Psychiatry Rep*. 2006 Oct 1;8(5):371–6.
383. Nicholas PK, Kemppainen JK, Canaval GE, Corless IB, Sefcik EF, Nokes KM, et al. Symptom management and self-care for peripheral neuropathy in HIV/AIDS. *AIDS Care*. 2007 Feb 1;19(2):179–89.
384. Ilgen MA, Bohnert ASB, Chermack S, Conran C, Jannausch M, Trafton J, et al. A randomized trial of a pain management intervention for adults receiving substance use disorder treatment. *Addiction*. 2016;111(8):1385–93.
385. CDC. Drug Overdose Deaths | Drug Overdose | CDC Injury Center [Internet]. 2020 [cited 2020 Sep 25]. Available from: <https://www.cdc.gov/drugoverdose/data/statedeaths.html>
386. De Boni RB, Shepherd BE, Grinsztejn B, Cesar C, Cortes C, Padgett D, et al. Substance Use and Adherence Among People Living with HIV/AIDS Receiving cART in Latin America. *AIDS Behav*. 2016 Nov;20(11):2692–9.
387. Sheu R, Lussier D, Rosenblum A, Fong C, Portenoy J, Joseph H, et al. Prevalence and Characteristics of Chronic Pain in Patients Admitted to an Outpatient Drug and Alcohol Treatment Program. *Pain Med*. 2008 Oct 1;9(7):911–7.
388. Binswanger IA, Kral AH, Bluthenthal RN, Rybold DJ, Edlin BR. High Prevalence of Abscesses and Cellulitis Among Community-Recruited Injection Drug Users in San Francisco. *Clin Infect Dis*. 2000 Mar 1;30(3):579–81.
389. Lenton S, Single E. The definition of harm reduction. *Drug and Alcohol Review*. 1998;17(2):213–20.
390. MacMaster SA. Harm Reduction: A New Perspective on Substance Abuse Services. *Social Work*. 2004;49(3):8.

391. Nahin RL, Boineau R, Khalsa PS, Stussman BJ, Weber WJ. Evidence-Based Evaluation of Complementary Health Approaches for Pain Management in the United States. *Mayo Clinic Proceedings*. 2016 Sep 1;91(9):1292–306.
392. Schulenburg J. Considerations for Complementary and Alternative Interventions for Pain. *AORN Journal*. 2015 Mar 1;101(3):319–26.
393. Krakauer EL, Ngoc NTM, Green K, Van Kham L, Khue LN. Vietnam: Integrating Palliative Care Into HIV/AIDS and Cancer Care. *Journal of Pain and Symptom Management*. 2007 May 1;33(5):578–83.
394. Vance DE, Gakumo CA, Childs GD, Enah C, Fazeli PL. Feedback on a Multimodal Cognitive Intervention for Adults Aging With HIV: A Focus Group Study. *Journal of the Association of Nurses in AIDS Care*. 2017 Sep 1;28(5):685–97.
395. Hoang T, Goetz MB, Yano EM, Rossman B, Anaya HD, Knapp H, et al. The Impact of Integrated HIV Care on Patient Health Outcomes. *Med Care*. 2009 May;47(5):560–7.
396. Napper LE, Fisher DG, Johnson ME, Wood MM. The Reliability and Validity of Drug Users' Self Reports of Amphetamine Use Among Primarily Heroin and Cocaine Users. *Addict Behav*. 2010 Apr;35(4):350.
397. Narayan MC. Culture's effects on pain assessment and management. *Am J Nurs*. 2010 Apr;110(4):38–47; quiz 48–9.
398. Bates MS, Rankin-Hill L, Sanchez-Ayendez M. The effects of the cultural context of health care on treatment of and response to chronic pain and illness. *Soc Sci Med*. 1997 Nov;45(9):1433–47.
399. Becker S, Fuchs X, Schakib-Ekbatan K, Schweiker M. What does “moderate pain” mean? Subgroups holding different conceptions of rating scales evaluate experimental pain differently. *European Journal of Pain*. 2020;24(3):625–38.
400. Ciccarone D, Ondocsin J, Mars SG. Heroin uncertainties: Exploring users' perceptions of fentanyl-adulterated and -substituted 'heroin.' *International Journal of Drug Policy*. 2017 Aug 1;46:146–55.
401. McLean K, Monnat SM, Rigg K, Sterner GE, Verdery A. “You Never Know What You're Getting”: Opioid Users' Perceptions of Fentanyl in Southwest Pennsylvania. *Substance use & misuse*. 2019 May 12;54(6):955–66.
402. Barker B, Adams E, Wood E, Kerr T, DeBeck K, Dong H, et al. Engagement in Maximally-Assisted Therapy and Adherence to Antiretroviral Therapy Among a Cohort of Indigenous People Who Use Illicit Drugs. *AIDS Behav*. 2019 May;23(5):1258–66.