Université de Montréal

Examining the impact of healthcare and harm reduction services on drug use and hepatitis C virus infection risk among people who inject drugs

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Thèse présentée en vue de l'obtention du grade de Philosophiae Doctor (Ph. D.)
en santé publique, option épidémiologie

Octobre 2019

Université de Montréal

Département de médecine sociale et préventive, École de santé publique

Cette thèse intitulée

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RÉSUMÉ

L'infection par le virus de l'hépatite C (VHC) est l'un des principaux problèmes de santé publique chez les utilisateurs de drogues injectables (UDI). Actuellement, plusieurs outils sont disponibles pour réduire le fardeau du VHC dans cette population. Ceux-ci incluent des programmes de réduction des méfaits, tels que le traitement par un opioïde agoniste (TAO), pouvant réduire le risque d'infection par le VHC, ainsi que des traitements antiviraux extrêmement efficaces pour éradiquer le virus parmi les infectés. Plus récemment, il y a eu un intérêt national et international à éliminer le VHC en tant que menace pour la santé publique d'ici 2030, tout en priorisant les UDI dans les efforts de prévention et traitement. Parallèlement à ce mouvement, plus globalement, le fardeau des méfaits liés aux pratiques d'injection chez les UDI, tels que la surdose, soulignent la nécessité d'adopter une vision plus large sur leur santé. Dans l'ensemble, cette thèse vise à combler certaines lacunes dans les connaissances vis-à-vis de l'élimination du VHC chez les UDI.

Premièrement, puisque le lien entre l'adéquation du dosage des TAO et le risque d'infection au VHC est peu connu, j'examine cette relation dans un échantillon d'UDI suivis dans la cohorte HEPCO à Montréal. Les résultats indiquent que le risque d'infection par le VHC ne serait pas systématiquement réduit chez toutes les personnes recevant des TAO, mais plutôt que ce risque varie en fonction de la dose prescrite et de l'adéquation du dosage telle que perçue par le patient. Ces résultats soulignent qu'un élargissement de l'accès aux TAO ne serait pas suffisant pour atteindre les objectifs de prévention et d'élimination du VHC, et que l'adéquation du dosage devrait être prise en compte dans le cadre de nos efforts de prévention.

Deuxièmement, l'accès aux traitements antiviraux est faible chez les UDI, en partie à cause des préoccupations des prestataires et des décideurs politiques qui craignent une augmentation de la consommation de drogues et des comportements à risque après le traitement. En capitalisant sur deux études différentes - la cohorte IMPACT à Montréal et les essais SIMPLIFY / D3FEAT menés dans plusieurs pays - je montre que les comportements liés à la drogue diminuent ou restent stables après le traitement du VHC. Ensemble, ces deux études suggèrent que les

préoccupations liées à une consommation élevée de drogue ou à une hausse des comportements à risque après le traitement ne seraient pas fondées. Ainsi, ces résultats appuient davantage une augmentation de l'accès au traitement chez les UDI.

Troisièmement, allant au-delà du VHC en tant que problématique principale, en capitalisant une fois de plus sur les données collectées dans HEPCO, j'examine les associations entre trois facteurs - le TAO, le logement et le revenu - et la fréquence d'injection chez les UDI. Puisque la consommation de drogues est dynamique dans le temps, j'examine dans quelle mesure ces trois facteurs sont liés à la fréquence d'injection chez des UDI ayant des trajectoires d'injection variées. Nos résultats indiquent que la stabilité socioéconomique et le TAO seraient systématiquement liés à une fréquence d'injection inférieure chez les UDI, quelles que soit leurs trajectoires d'injection sous-jacentes. Globalement, ces résultats suggèrent qu'il y aurait des moyens de soutenir tous les UDI à atteindre de petits changements comportementaux qui pourraient réduire les risques liés aux pratiques d'injection, qu'ils soient ou non en mesure d'arrêter l'injection de drogues.

En conclusion, alors que presque tous les pays ont lancé un effort mondial pour éliminer le VHC, des efforts sont nécessaires pour optimiser les programmes de réduction des méfaits bien établis afin de réduire la transmission du VHC, et d'accroître l'accès au traitement chez ceux qui sont infectés, tout en considérant les besoins et les préoccupations des communautés touchées. Cette thèse a fourni des données permettant d'éclairer (i) l'optimisation des TAO dans la prévention de la transmission du VHC, (ii) l'élargissement de l'accès au traitement du VHC et (iii) l'accès à des logements et revenus stables afin de réduire plus globalement les risques liés aux pratiques d'injection chez les UDI. Ainsi, ces résultats pourraient aider à réduire le fardeau du VHC chez les UDI et à soutenir le progrès vers l'élimination du VHC.

Mots-clés : hépatite C, utilisation des drogues par injection, traitement par un opioïde agoniste, traitement antiviral, trajectoire d'injection

ABSTRACT

Infection with hepatitis C virus (HCV) is one of the main public health concerns affecting people who inject drugs (PWID). Although no effective prophylactic vaccine currently exists to prevent acquisition of HCV, a number of other tools are available to curb the HCV burden among PWID. These include harm-reduction programs, such as opioid agonist treatment (OAT), which can reduce the risk of HCV infection among those susceptible, and highly effective antiviral therapies to eradicate the virus among those who are infected. In recent years, there has been national and international interest in eliminating HCV as a public health threat by 2030, prioritising PWID in prevention and treatment efforts given that they are the population most affected. In parallel to this global effort, the high prevalence of injection-related harms among PWID that are unrelated to HCV, such as overdose, highlight a need to adopt a broader view on drug user health. Overall, this thesis is concerned with addressing some of the knowledge gaps and barriers that remain to achieving HCV elimination in PWID.

First, because little is known about the importance of OAT dosage in influencing the risk of HCV acquisition, I examine this relationship in a sample of PWID followed in the Hepatitis Cohort (HEPCO) in Montreal. Findings indicate that the risk of HCV infection may not be systematically reduced for everyone receiving OAT and rather, that the risk of infection varies considerably according to the level of the prescribed OAT dosage and patient-perceived dosage adequacy. These findings suggest that simply scaling-up OAT access may not be sufficient to achieving the HCV elimination goals, and that the dosage of treatment should be considered as part of prevention efforts.

Second, uptake of HCV treatment is low among PWID, partly due to concerns among providers and policymakers that drug use and injection risk behaviours may increase following treatment, thereby negating the benefits of therapy. Capitalising on two different studies - the IMPACT Cohort in Montreal and the SIMPLIFY/D3FEAT trials conducted in several countries - I illustrate that drug-related behaviours decrease or remain stable following HCV treatment. Together,

these two studies suggest that concerns of escalating drug use or risk behaviours following HCV treatment are unfounded, further supporting the importance of expanding access to therapy among PWID.

Third, moving beyond HCV as the primary focus of research, and capitalising once more on data collected in HEPCO, I examine the associations between three factors- OAT, housing and income, and patterns of injection frequency among PWID. Recognizing that injection patterns are dynamic over time, I examine the extent to which these three factors relate to injection frequencies among PWID with diverse trajectories of injection drug use, followed over a period of 7.5 years. Our findings indicate that socioeconomic stability and OAT are consistently associated with a lower injection frequency among all PWID, irrespective of their underlying injection trajectory and whether or not they are on a path to cessation. These findings suggest that there may be ways to support PWID in making small behavioral changes that could reduce their risks of injection-related harms, irrespective of whether or not they are in a position to stop injecting.

In conclusion, at a time when many countries have embarked onto a global effort to eliminate HCV, efforts are needed to ensure that well-evidenced harm-reduction programs are optimised to reduce transmission of HCV, treatment for HCV infection is scaled-up among those who are infected ,and efforts do not overlook the basic needs and concerns of affected communities. This thesis provided data to help inform (i) optimisation of OAT provision for the prevention of HCV transmission, (ii) expanded access to HCV treatment, and (iii) access to stable housing and income to reduce the risk of injection-related harms among PWID. Ultimately, findings could contribute to reducing the HCV burden among PWID, helping move towards HCV elimination and, more broadly, improving the overall health of this marginalised group.

Keywords: hepatitis C, injection drug use, opioid agonist treatment, hepatitis C treatment, drug use trajectory, direct-acting antiviral

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LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
AOR	Adjusted odds ratio
AUDIT-C	Alcohol Use Disorders Identification Test–Consumption
CHUM	Centre Hospitalier de l'Université de Montréal
CI	Confidence internal
CIT	Contra-indication to treatment
DAA	Direct-acting antivirals
HCV	Hepatitis C virus
HEPCO	Hepatitis Cohort
HIV	Human immunodeficiency virus
HR	Hazard ratio
GEE	Generalised estimating equations
IQR	Interquartile range
NE	Not engaged (in hepatitis C treatment)
OAT	Opioid agonist treatment
OR	Odds ratio
PWID	People who inject drugs
RT	Received treatment
SR	Spontaneous resolution
SVR	Sustained viral response
SD	Standard deviation
WHO	World health organisation

LIST OF PUBLICATIONS OVER THE COURSE OF THIS TRAINING

First-author publications

1. Artenie AA, Minoyan N, Jacka B, Høj S, Jutras-Aswad D, Roy É, Gauvin L, Zang G, Bruneau J. Opioid agonist treatment dosage and patient-perceived dosage adequacy, and risk of hepatitis C infection among people who inject drugs. CMAJ **2019**; 191(17): E462-e8.

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ACKNOWLEDGEMENTS

First and foremost, I would like to express my greatest appreciation to my primary supervisor, Professor Julie Bruneau, whose exceptional mentorship has made my experience as a doctoral student as rewarding as it can be. Her guidance, support and encouragement have contributed in the most positive way to my learning experience. She has been an inspirational role model, and I consider myself very fortunate to have been her student.

I am extremely grateful to my co-supervisor, Professor Lise Gauvin and mentors, Professor Didier Jutras-Aswad and Élise Roy, for having played pivotal roles in the creation of a rich and stimulating learning environment for the past four years. Thank you for the fruitful discussions, instructive feedback and unconditional support, all of which have been paramount in helping me shape the direction of this work and completing the project.

I would like to acknowledge the work of Geng Zang, whose programming and statistical advice has been invaluable throughout all stages of this work. To my colleagues, Emmanuel Fortier, Nanor Minoyan, Stine Hoj, Brendan Jacka, Iuliia Makarenko - thank you for your continuous help and cooperation. I am also very grateful to the Saint-Luc Cohort personnel, in particular Rachel Bouchard, Maryse Beaulieu, Marie-Eve Turcotte, for welcoming me in their team, and for all the time and efforts they have put into helping me complete this thesis. I also thank Valeria Saavedra and Aissata Sako for their unconditional support throughout.

I would like to extend my gratitude to the Department of Social and Preventive Medicine at the School of Public Health - to all the professors, for having set a strong foundation in epidemiology and public health research, thereby providing me with the necessary tools to complete this project. I could not have made a better choice than to pursue my doctoral degree here, and I am grateful for having been offered this opportunity.

Thank you also to Professors Jason Grebely and Greg Dore working at the University of Kirby in Sydney, Australia. The time spent working in their team as part of a traineeship has been an opportunity to experience a new training environment that is highly dynamic and enjoyable. It has been an invaluable learning experience that I will carry forward.

I would like to thank the Canadian Institute for Health Research (CIHR) and the Canadian Network on Hepatitis C (CanHepC) for generously funding my training. Similarly, the travel awards received through CIHR, CanHepC, the Research Centre of the Centre Hospitalier de l'Université de Montréal, the International Network on Hepatitis in Substance Users and the Institut Universitaire sur les Dependences have allowed me to present my research findings and exchange with other researchers at several national and international conferences. I am very grateful for these opportunities, as they have been invaluable to the progress of my project.

A special "thank you" goes to my family – my husband, my parents and my brother - for their unconditional love and support, and for having instilled in me a strong drive to pursue my goals. I dedicate this thesis to them.

CHAPTER 1: INTRODUCTION

People who inject drugs (PWID) are one of the most vulnerable populations in our society, with a mortality rate estimated to be 15 times greater compared to the general population [1]. In high-income countries, including Canada, infection with hepatitis C virus (HCV) is the primary blood-borne viral transmission and one of the main public health concerns among PWID [2, 3]. Discovered in 1989, HCV quickly emerged as a leading cause of liver disease and liver transplantation [2, 3]. HCV causes more years of life lost than any other infectious disease in the country and PWID are, by far, the population most affected; the majority of new (~85%) and existing (~60%) infections are reported in this group [2, 3].

Fortunately, a number of tools are available to curb the HCV burden among PWID. Although a vaccine conferring protection against HCV infection is not yet available [4], a strong foundation of harm reduction interventions to reduce injection-related risks among those susceptible to infection combined with broad access to HCV treatment among those infected can considerably reduce HCV incidence and prevalence [5, 6]. Key harm-reduction programs for the prevention of HCV include needle and syringe programmes and opioid agonist treatment (OAT), which in combination, can reduce the risk of HCV infection by 50-70% [7]. Unlike other chronic viral infections, hepatitis C is curable. Prior to 2014, standard therapy for HCV infection involved interferon-based therapies, which carried modest efficacy and significant side-effects [5, 8]. In recent years, however, the HCV treatment landscape has been transformed by the development of interferon-free direct-acting antiviral (DAA) agents. These short-course and all-oral regimens are curative in >95% of treated persons, with few or no side effects [5, 9].

In addition to delivering cure in nearly all patients, HCV treatment may carry population-level benefits. The remarkable efficacy, tolerability and simplicity of the novel DAA-based antiviral regimens sparked global interest in the potential of HCV treatment-as-prevention in driving HCV prevalence and incidence to negligible levels (i.e. towards elimination) [10, 11]. Treatment-as-prevention refers to the control of the HCV epidemic at the population level using large-scale

treatment to diminish the pool of circulating virus and subsequent likelihood of viral transmission [10, 11]. Although empirical research demonstrating the benefit of this approach is still ongoing [12, 13], numerous mathematical modeling studies support its potential, particularly when delivered in combination with harm-reduction interventions [14-19]. In this context, in 2016, the World Health Organization (WHO) called on the elimination of viral hepatitis as a public health threat by 2030, promoting a number of targets to mobilize global efforts towards this goal [20]. These targets include an 80% reduction in new HCV infections, 65% reduction in HCV-related mortality, and treatment of 80% of persons with HCV infection by 2030, relative to 2015 levels. In addition to having signed onto this ambitious global strategy, in 2019, Canada put forward a national blueprint to inform HCV elimination efforts through outlying specific objectives, targets and best practices [2].

Essentially, over the last few years, there has been a clear mandate to invest in HCV prevention and treatment, both nationally and abroad. Yet, aside from a few countries, such as Australia, France and the United Kingdom, most lag far behind from achieving the WHO elimination goals, including Canada [21, 22]. Several barriers are at play, including limited capacity of harm-reduction programs in controlling the spread of HCV, low uptake of HCV treatment, and more broadly, inadequate public health efforts addressing the competing priorities and socioeconomic circumstances affecting PWID, which inevitably constraint their capacity to engage in HCV care [23, 24]. In light of this rare opportunity to eliminate HCV as a public health threat, there is an urgency to better understand how to optimise access to well-evidenced prevention programs, improve uptake of HCV treatment and ensure that HCV elimination efforts do not overlook the broader health and social needs of affected communities [23, 24]. Overall, this thesis is concerned with addressing some of the barriers to achieving the targets around HCV elimination among PWID.

There is global consensus that HCV elimination will require, first and foremost, a strong foundation of evidence-based harm-reduction programs, and OAT is well-acknowledged as being key [5, 6]. OAT is the gold standard treatment for opioid use disorder and it typically includes methadone or buprenorphine/naloxone [25]. By providing structured access to these long-acting

opioids, OAT can reduce the frequency of illicit opioid use and exposure to unsafe injecting practices, and improve stability and day-to-day function [26-28]. In a 2017 systematic review, PWID receiving OAT were found to have on average a 50% lower risk of HCV infection relative to those who were not [29]. Despite being central to HCV prevention and elimination efforts, so far, the importance of OAT quality, and in particular the role of dosage, in influencing HCV infection risk has been overlooked. Yet, prescribing practices for OAT vary widely. Methadone and buprenorphine are often prescribed at lower dosages than those recommended by clinical guidelines, and at dosages patients feel are inadequate [30-32]. Although multiple studies have suggested that higher dosages of OAT are more effective in promoting treatment retention and in reducing withdrawal and illicit opioid use, no study has examined the link between the dose OAT and HCV infection. In Chapter 3 of this thesis, I examined the relationship between the adequacy of OAT dosage, using a combined indicator of dosage adequacy informed by clinical guidelines and patients' perceptions, and HCV infection risk among PWID.

Treatment for HCV infection has changed drastically over the past decade. Up until recently, standard of care included pegylated interferon and ribavirin, which was effective only in a subset of patients (~40-60%) and carried considerable side-effects [33]. In 2014, the development and introduction of effective and well-tolerated interferon-free DAA regimens transformed the management of HCV infection, providing an opportunity to stem rising liver disease burden [34-37]. However, access to HCV treatment among PWID has been very limited during the interferon-era [38-42] and this trend persisted even after DAAs were introduced in most settings [43]. Although the barriers to treatment uptake are multifactorial and complex [44-47], at their core has been an unsubstantiated concern among providers and policy-makers that the ongoing use of drugs and adoption of unsafe sharing practices would negate the benefits of treatment [48, 49]. Conversely, others have speculated that the opportunity to develop a therapeutic relationship with healthcare professionals and receive care during treatment could actually lead to decreases in drug use, particularly in the interferon-era, when therapy required close monitoring and care [50]. At a time when DAAs were forthcoming and discussions around whether or not PWID should be prioritized for HCV treatment were unfolding [51], in Chapter 4, I examined injection drug use

changes among PWID with recent HCV infection who were systematically referred for HCV clinical assessment and treatment and offered targeted health care services. As a follow-up to this aim, in a context where DAA therapies have already been introduced, in Chapter 5, I examined patterns of drug use and injection equipment sharing among people with recent injecting drug use or receiving OAT during and following DAA-based treatment.

Although HCV is considered a public health priority among PWID, studies evoking the perceptions of this marginalised group regarding their daily needs and concerns often describe HCV as a relative priority [52, 53]. For many PWID, HCV infection and associated liver-morbidity carry little weight relative to the more immediate worries that they encounter on a daily basis [52-54]. Overdose, vein damage, cellulitis, and other skin infections are some of the acute and pressing health threats PWID are confronted with [52, 53, 55-57]. More broadly, poverty, homelessness, violence, involvement in the street-based economy, the demands of funding and maintaining an illicit drug dependency, fear of arrest and incarceration and access to OAT and needle and syringe programs, all take precedence over HCV prevention or treatment [52, 53, 55-57].

In the midst of a global movement supporting HCV treatment-as-prevention, which prioritises PWID in order to achieve the most population-level benefits, advocates are calling for a people-centered approach that is responsive to the needs and concerns of affected communities [58-61]. The opioid crisis currently sweeping across North America [62, 63] re-emphasized the urgency of addressing the contextual forces that render individuals susceptible to injection-related harms. From a public health perspective, in order to reap the full benefits of HCV prevention and costly antiviral therapies, premature deaths from acquisition risks, now exacerbated by the opioid crisis, need to be addressed [3, 64, 65]. Moving beyond HCV as the primary focus of research, in Chapter 6, I examined the associations between three factors- OAT, housing and income, and patterns of injection among PWID. Recognizing that injection patterns are dynamic and sustained cessation is achieved by a fraction of individuals, I examine the extent to which these three factors can influence injection frequencies among PWID with diverse and enduring trajectories of injection drug use.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1 EPIDEMIOLOGY OF INJECTION DRUG USE AND ASSOCIATED HARMS

Injection drug use has now been documented in most countries and territories in the world [66]. According to a 2016 systematic review, it is estimated that there are 15.6 million PWID globally [66]. This estimate is consistent with a previous study [67]; yet it is likely conservative, given that injecting drug use is an illegal and stigmatised behaviour [66-68]. There is a notable difference in the age and gender profile of PWID across geographic regions, with a tendency for PWID in high-income countries to be older (>30 years of age) and to include a higher proportion of women relative to lower-income countries [66]. In most countries, the main types of drugs injected are opioids (~83%), followed by stimulants (~33%)[66].

In Canada, estimates suggest that there are between 90,000-110,000 PWID [69, 70]. Although there is variation, the typical socio-demographic profile of a Canadian who injects drugs is a man, aged 30-49, who has not completed high-school education [71]. Contrary to many other settings, Canada has a long-standing history and high prevalence of cocaine injection [72]. According to a nationwide epidemiological surveillance study among PWID, cocaine injection was reported by nearly two-thirds of participants (64.3%) in 2010-2012 [71]. Other commonly injected drugs identified in this survey were hydromorphone (48.3%), non-prescribed morphine (47.0%), oxycodone (37.7%) and heroin (26.7%) [71]. The higher proportion of PWID reporting injecting opioids other than heroin is reflective of the national opioid epidemic recorded over the last two decades, which has become a public health emergency [73, 74]. In Montréal, our group documented a tripling in the injection of prescription opioids between 2004 and 2009 among PWID followed in the HEPCO Cohort [75]. In Vancouver, a 10% increase in the immediate availability of prescription opioids on the streets was noted for each calendar year between 2010 and 2014 [76]. The type of drug injected is closely linked to the risk of HCV infection (further detailed in section 2.2.4) and other drug-related harms among PWID [71, 72].

For many PWID, drug use extends over long periods of time, up to 20-30 years following initiation of injection [77-79]. Given the more rapid and intense effects produced by injection drug use, this form of administration is associated with a more severe and complex clinical course compared to smoking, snorting or oral administration [80]. Relative to non-injecting routes, injection drug use carries a greater risk of police arrest, incarceration, involvement in sex work and homelessness, all of which are associated with increased adverse health outcomes [81-83]. After more than 30 years of research, numerous studies have shown that injection drug use is associated with a wide range of adverse health outcomes. Globally, more than half of PWID have been exposed to HCV, one in six are living with human immunodeficiency virus (HIV), and one in ten have active hepatitis B [66]. The public health burden associated with injection drug use is also reflected in the increased risk of overdose, suicide, homicide, psychiatric comorbidities and traumas, compared to the general population [1, 84, 85]. The mortality rate of PWID is 15 times greater than the general population [1].

2.2 HEPATITIS C

2.2.1 HEPATITIS C: VIROLOGY, PATHOGENESIS AND CLINICAL COURSE

HCV was discovered in 1989 and was originally known as the non-A non-B hepatitis virus [86]. It is an enveloped, positive-sense, single-stranded RNA virus of the Flavivirdae family. It is classified into seven major genotypes, and as many as 100 subtypes [87]. The global distribution of HCV genotypes is diverse, reflecting differences in epidemiology, modes of transmission and ethnic variability [88]. In Canada, genotype 1 is predominant, as in most of North America, accounting for more than 60% of all HCV infection cases [88].

HCV infection typically occurs in two stages: acute, which is defined as the first six months following HCV acquisition and, chronic, defined as infection persisting beyond this period. In most cases, acute HCV infection is asymptomatic, with the exception of 15–30% of infected-people developing mild and non-specific flu-like symptoms that are common to many acute viral infections, such as fever and abdominal pain [89]. Jaundice and other more specific symptoms are rare [89]. Of adults acutely infected with HCV, it is estimated that 15–40% have spontaneous

resolution of their infection, with the remaining developing chronic infection [89]. Whether acute HCV infection spontaneously clears or persists is affected by a complex interplay of factors at the levels of the host and the virus [89]. Previous studies have reported that host factors like female sex, younger age, co-infection with HIV and a favorable genetic polymorphism in the interleukin-28 gene region involved in viral control, as well as virus-specific factors such as HCV genotype 1, may play a role in determining the acute HCV infection response [89]. Because resolution of HCV infection in the acute phase, without progression to chronic disease, is rarely accompanied by long-term sequalae, patients who spontaneously clear their infection are considered infection-free [89].

In most individuals, HCV RNA and anti-HCV antibodies are detectable within 2 and 12 weeks of exposure to HCV, respectively [89]. Chronic infection is determined by the presence of HCV RNA in the blood at least six months post-infection; anti-HCV positivity does not differentiate people who have cleared infection from those with active viremia [89].

Similar to the acute stage, chronic HCV infection is very often asymptomatic; a person may be infected with HCV for as long as 30 years or more before developing clinical symptoms of disease [89]. Chronic hepatitis C is characterized by slowly progressive hepatic inflammation, which can lead to the development of cirrhosis in approximately 16% of infected patients over 20 years [89]. The risk of HCV-related cirrhosis rises exponentially with duration of infection, estimated at 41% with 30 years of infection [89]. A number of host factors have been identified that are likely to accelerate fibrosis progression, namely male sex, older age, immunosuppression and presence of comorbidities like chronic HBV co-infection, diabetes and obesity, and heavy alcohol intake [88]. Once cirrhosis is established, the course of disease is unpredictable. While it can remain indolent for many years in some patients, it can progress to hepatocellular carcinoma, hepatic decompensation and death in others [89]. Following an episode of decompensation, the risk of death in the following year is between 15% and 20% [89]. Aside for liver-related morbidity, chronic HCV infection also causes a range of extrahepatic manifestations, including type 2 diabetes, heart disease, cryoglobulinemia and lymphoma [90].

2.2.2 TRANSMISSION OF HCV

HCV is primarily transmitted through percutaneous exposure to infected blood or blood-derived bodily fluids [91]. Globally, the primary routes of transmission are blood transfusions, medical injections and procedures, and injection drug use [91]. In resource-constrained settings, medical practices, including the reuse of needles and syringes and poor quality screening of blood products in transfusion centres, account for a large proportion of new HCV infections [91]. Conversely, in developed countries, following implementation of blood donor screening in the early 1990s, injection drug use became the main transmission route [91]. In Canada, an estimated 85% of new HCV infection cases occur among PWID [2, 92]. Additional, yet marginal routes of HCV transmission are sexual (typically observed among HIV-positive men who have sex with men), mother-to-infant, tattooing, skin piercing and sharing of toothbrushes and razors [91].

2.2.3 EPIDEMIOLOGY OF HCV INFECTION

In 2015, the global prevalence of HCV infection was estimated to be 1% (95% CI 0.8–1.1), which equates to 71.1 (62.5–79.4) million people infected [93]. Over the same year, ~1.8 million new cases of infection were estimated, for an overall incidence rate of 23.7 per 100,000 [94]. Although high-quality data on the number of people living with HCV in Canada are absent, it is estimated, based on modeling studies, that approximately 250,000 Canadians are infected, for an overall prevalence similar to the global estimate (~0.8%) [2, 95, 96]. National incidence data for HCV infection is even more fragmented. Available estimates indicate that, each year, approximately 5500 people become newly infected with HCV [97-99].

The high public health burden associated with HCV is reflected in the significant morbidity and mortality worldwide. In 2016, an estimated 400,000 people died from hepatitis C globally, primarily due to life-threatening complications such as cirrhosis and hepatocellular carcinoma [20, 100]. This estimate represents a 22% increase since 2000[20] and is projected to continue to rise in the absence of significant treatment scale-up [101].

In Canada, HCV causes more years of life lost than any other infectious disease [2, 102] and the prevalence of advanced liver disease is increasing [103]. In a modeling study examining the burden of HCV infection nationally, it was estimated that compared with 2013, cases of compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver-related deaths are expected to increase 89%, 80%, 205% and 160%, respectively, by 2035 [103]. The only type of cancer with increasing mortality rates in both men and women is liver cancer, a trend primarily attributed to long-standing HCV infection [2]. HCV infection is the leading cause for liver transplantation [2]. Overall health care costs associated with HCV (excluding treatment) are expected to increase by 60% from 2013 until the projected peak in 2032, mainly due to cirrhosis and its complications [99]. The lifetime cost for an individual with HCV infection in 2013 was estimated to be $65,000 [99].

2.2.4 EPIDEMIOLOGY OF HCV INFECTION AMONG PWID

In a 2017 global systematic review, it was estimated that among the ~15.6 million people with recent injecting drug use (defined as having injected within the previous 12 months), 52.3% (representing 8.2 million) are HCV-antibody positive [66] and, according to a follow-up study, 39.2% (representing 6.1 million) are actively infected with HCV [104]. In Canada, it is estimated that 30.7% of PWID have viremic (i.e., active) HCV infection [104].

Contrary to estimates on HCV prevalence, no pooled global data exists on HCV incidence. A study conducted in Vancouver documented a decline in HCV incidence among PWID from 27.9/100 person-years [95% confidence interval (CI): 22.6, 33.6] in 1996–99 to 4.9/100 person-years [95% CI: 3.1, 7.4] in 2006–2012 [105]. Another study comparing temporal trends in HCV incidence among PWID across geographical regions noted a significant decline in settings like Melbourne and Amsterdam, but consistently high rates (≥20 per 100 person-years) in Montreal, San Francisco and Baltimore between 2000 and 2011 [106]. At current levels, injection drug use is projected to account for 43% of new HCV infection cases globally between 2018 and 2030 [107]. In North America, this proportion is estimated at 77% [107].

Sharing of contaminated injection equipment is the strongest determinant of HCV transmission among PWID [108]. While the re-use of needles and syringes is well recognized as a key route for viral transmission, ancillary injection paraphernalia have garnered support over the past two decades as additional sources [109]. It is estimated that HCV can survive outside the body at room temperature for up to three weeks [110, 111], and studies identified HCV viral particles in drug-mixing containers, filters and rinse water previously used by PWID [112]. In a systematic review examining associations between injection equipment sharing and risk of HCV infection among PWID, the estimated relative risks were 1.94 (95% CI: 1.53, 2.46) for syringe sharing, 2.42 (95% CI 1.89, 3.10) for drug preparation containers or "cookers", 2.61 (95% CI 1.91, 3.56) for drug preparation filter or "cotton", and 1.98 (95% CI 1.54, 2.56) for rinse water [113]. Considering also that the sharing of drug preparation equipment is typically more widespread than the sharing of syringes, it may account for a relatively larger proportion of new cases of transmission [108, 113]. In a surveillance study among PWID in Canada conducted in 2012-2012, 16% reported borrowing someone's used needles or syringes in the prior six months [71]. Conversely, 35% reported borrowing other injection equipment (e.g., water, filter, cooker, spoons, swabs) [71]. Overall, the high viral transmission rate per injection event, the high viral prevalence in the population (and thus, high risk of exposure) and the extended length of viral survival on inanimate surfaces are believed to contribute to the high transmission of HCV among PWID [111, 114].

Sharing behaviours are highly influenced by specific injection drug use patterns, which are dynamic over time [72, 115]. For example, relative to heroin, cocaine injection is associated with a two to three-fold greater risk of HCV infection [7, 115, 116]. This risk has been mainly attributed to the increased likelihood of exposure to contaminated blood among cocaine injectors as a result of their high frequency of injection during binge days (i.e., up to 30 injections per day) [117-120]. Similarly, injection of prescription opioids, which has increased dramatically in North America over the last two decades [73, 89, 121-124], has been linked to a relatively higher risk of HCV infection. Research from our group noted that compared to injection of other drugs, people injecting prescription opioids have a three-fold higher risk of acquiring HCV [75]. In the United States, an

almost four-fold increase in the injection of prescription opioids between 2004 and 2014 was accompanied by a doubling of the rate in acute HCV infection [125]. A greater frequency of injection combined with increased sharing behaviours have been put forward as potential reasons for the increased risk of infection in this group [126].

2.2.5 TREATMENT FOR HEPATITIS C

Unlike most other chronic viral infections, HCV infection can be cured. Because HCV replicates in the cytoplasm of hepatocytes without integrating the host genome, successful treatment results in long-lasting viral eradication [127]. Sustained virological response (SVR), most commonly measured as SVR12 or SVR24, is defined as having undetectable HCV RNA in the serum 12 or 24 weeks after completion of therapy, and is tantamount with virological cure [89, 128]. SVR is also associated with long-term health benefits. It leads to a decrease in the risk of hepatic decompensation, hepatocellular carcinoma and mortality (liver-related and all-cause), as well as cirrhosis regression [127-130]. Patients whose infection has been eradicated before having developed cirrhosis are estimated to have a life expectancy similar to that of uninfected people [131]. In patients with cirrhosis, viral eradication eliminates the risk of liver failure and significantly reduces the risk of hepatocellular carcinoma [131, 132].

Up until 2014, standard therapy for HCV infection involved weekly subcutaneous injections of pegylated interferon and oral ribavirin [35, 133-136]. Both medications are known to have indirect viral activity against HCV infection, yet their specific mechanisms of action remain poorly understood [137]. This combination treatment regimen had poor efficacy, with SVR estimates as low as 40% in patients infected with the genotype 1, which is the most common genotype profile [33, 138]. Across all genotype profiles, SVR was estimated at 40-60% [33, 138]. Additionally, treatment was associated with many side effects and a complex therapeutic management profile [35, 138]. Indeed, potential adverse events associated with therapy impacted most, if not all, organ systems, with symptoms ranging from mild to severe in intensity and frequency [138]. Pegylated interferon carries significant side-effects, many of which can be life-threatening, such as autoimmune reactions, ischemia, infections, depression, anxiety and suicidal thoughts [134, 139]. In addition to being teratogenic,

ribavirin can cause serious hemolytic anemias and worsening of cardiac disease [134]. Because of this complex side-effect profile, patients with certain pre-existing health conditions, such as mental illness or autoimmune disease, were considered ineligible to treatment [138]. Treatment success was further hampered by poor compliance and adherence, given the considerable side-effects [138]. In addition to poor efficacy and tolerability, this therapy regimen was lengthy (24 to more than 48 weeks) [138].

Remarkable medical advances have completely changed the landscape of HCV treatment in the last decade, as additional pharmaceutical options have become available with progressively improving efficacy and tolerability [34-37]. In 2011, the first generation of DAA regimens became available [37, 140, 141]. In contrast to previous treatment combinations, which had nonspecific antiviral effects, these novel therapeutic regimens directly impact the replicative machinery of the virus [34]. Initially, DAAs had several deficiencies, including high viral resistance, multiple drug-drug interactions and side-effects, and had to be administered in conjunction with pegylated-interferon [37, 140, 141]. However, these regiments were gradually replaced by subsequent generations of DAAs, with progressively improved efficacy, tolerability, duration of treatment and resistance profile. In 2014, the first interferon-free DAAs became available [141-143], and in 2016, the first pan-genotypic therapies were introduced [37]. Currently, DAA treatments have excellent efficacy (>95% SVR), few drug-drug interactions, are short in duration (8-12 weeks), administered orally and carry a low pill burden (once-daily administration) [144].

The effectiveness of HCV therapies among PWID has been demonstrated in several studies. According to a 2013 systematic review, PWID receiving treatment with interferon/ribavirin therapy had high levels of adherence (82%, 95% CI 74%-89%), low-treatment discontinuation (22%, 95% CI 16%-27%), and SVR rates similar to estimates observed in non-PWID populations (56%, 95% CI 50%-61%) [145]. More recently, a second systematic review focusing on DAA regimens noted that 88% of PWID achieved SVR following DAA-based HCV treatment [146].

Labelled as one of the most expensive oral medications in history, interferon-free DAA regimens came with a prohibitively high price tag, leading to discussions around prioritisation of treatment [147-149] and restrictions in reimbursement to people with advanced liver disease and without substance use [150-153]. In Canada, the initial list price for a 12-week course of sofosbuvir/velpatasvir – one of the most commonly used DAA combination- was reported at $60,000 shortly after licensing by Health Canada in 2016 [5].

2.2.6 HCV REINFECTION

People who have cleared their HCV infection, either spontaneously or following antiviral treatment, remain at risk of HCV reinfection. Because the benefits of HCV treatment are lost in the event of reinfection, there has been considerable interest in examining the rate of HCV reinfection following SVR. So far, studies conducted among PWID showed that the risk of HCV reinfection following treatment with either pegylated-interferon +/- ribavirin and DAA-based therapies are low (<3 per 100 person-years) [154-156]. However, the vast majority of these studies included a broad definition of "active PWID" (e.g., people who injected in the past year), possibly leading to an underestimation of the HCV reinfection risk among those with a truly high-risk profile of reinfection [157]. A more recent study, conducted among PWID who reported injecting in the past week (the majority of whom injected on a daily basis) noted a reinfection incidence of 21.5/100 person-years (95% CI 13.00-35.65) [158].

2.3 PREVENTION AND ELIMINATION OF HCV INFECTION

The development of a prophylactic HCV vaccine has been challenging, primarily due to the large diversity of the virus and its high mutation rate [159, 160]. For this reason, HCV prevention efforts rely primarily on delivering a package of harm-reduction programs that can reduce the risk of HCV acquisition among PWID [5, 6, 11, 161]. Harm-reduction programs encompass a range of health and social services, including needle and syringe programmes, OAT, drug consumption rooms, provision of basic necessities, such as stable housing and income, psychosocial support and education and counseling [162]. Among the various programs available, OAT and needle and syringe

programmes are considered the two cornerstone tools in HCV prevention, given long-standing evidence demonstrating their prevention benefit [7, 113, 163, 164].

Over the past few years, the advent of DAA therapies has added a new tool to the HCV prevention toolkit. The considerable efficacy (>95%), minimal toxicity, short treatment duration (12–24 weeks), simplified dosing (all oral, once-daily regimens) and monitoring schedules of DAA regimens are expected to increase HCV treatment uptake and responses among PWID, making HCV treatment-as-prevention a possibility [5, 6, 161]. Antiviral treatment harnesses preventive potential by removing infected individuals from the pool of transmitters, thereby averting future infections [165]. While evidence supporting the prevention utility of DAAs is yet to become available [12, 166], several mathematical modeling studies have indirectly supported this premise [14-16, 18, 147, 167-178].

Overall, the high cure rate and tolerability of these novel pharmaceutical options for the treatment of HCV infection, combined with a potentially broader community benefit of enhancing treatment uptake, have prompted the World Health Organization to call for the global elimination of HCV as a major public health threat by 2030 [20]. To this end, in 2016, the WHO has developed the first global health sector strategy on viral hepatitis to guide a coherent global public health response. Although the strategy addresses all five hepatitis viruses (hepatitis A, B, C, D, and E), it has a strong focus on HCV [20]. In brief, the strategy outlines a vision, goals and a series of impact (incidence and deaths) and coverage of service delivery (access to testing and treatment, blood safety, safe injection practices, and harm reduction services) targets, towards elimination of viral hepatitis as a major public health concern by 2030 [20]. Following calls from WHO, several countries [179-181], including Canada [2], have developed a national action plan for the elimination of HCV as a public health threat, outlining targets and suggested practices adapted to their settings.

The feasibility of HCV elimination as a public health threat is the focus of ongoing discussion [6, 161, 182-185]. Although the tools and means exist to prevent HCV acquisition and transmission, multiple

barriers and knowledge gaps remain in order to reach the ambitious milestones set by the WHO [6, 161, 182-185]. While harm-reduction programs have been successful in reducing the spread of HIV [186], their impact has been relatively lower for HCV [7, 113, 163], highlighting a need to examine how best to optimize their delivery. Furthermore, uptake of HCV treatment has historically been low among PWID [38-42], partly due to unsubstantiated concerns among providers and payers regarding the risk of reinfection [47, 151, 187]. This trend continues to persist in the vast majority of regions [9, 18, 41, 188, 189]. To achieve HCV elimination goals, a significant increase in HCV treatment uptake is necessary, particularly among PWID who account for the majority of HCV infection cases [165]. Other barriers include poor characterization of local HCV epidemiology to inform intervention planning and monitoring, poor coverage of harm-reduction programs and poor testing rates, resulting in a high number of HCV-infected persons being unaware of their infection [6, 23, 46].

2.3.1. OVERVIEW OF OAT

OAT is considered one of the key prevention strategies in HCV [7, 113, 163, 164]. It refers to the long-term treatment with an opioid agonist medication recognized for use in the treatment of opioid use disorder [25]. The most commonly prescribed forms of OAT are methadone and buprenorphine maintenance treatment. They are both designed to be offered as ongoing treatment, with indefinite duration, with the goals of reducing or eliminating illicit opioid use and, as a result, to decrease its associated negative outcomes, such as injection and sexual risk behaviors, criminal activity and mortality [142].

Methadone was the first widely used from of OAT and was the standard of care for opioid dependence until recent years. It is a long-acting synthetic opioid that acts as a full agonist at the mu (μ) opioid receptor. Initially developed to manage pain in the 1940s, methadone was introduced as maintenance treatment for heroin dependence following an increase in heroin use in the United States in the 1950-1960 [190, 191]. Since then, it has been studied extensively and prescribed widely as a first-line treatment option for opioid use disorder. When offered at a therapeutic dosage, methadone provides relief from opioid withdrawal and cravings, and blocks the euphoric effects of self-administered opioids [192]. Numerous studies have demonstrated that

methadone is safe and effective for the treatment of opioid use disorder and prevents drug-related harms, including crime and mortality [193-195]. As with methadone, buprenorphine was initially developed to manage pain and only later used for treating opioid use disorders. In Canada, it was approved by Health Canada as a combination medication with naloxone in 2007 and became increasingly popular in recent years [196]. Unlike methadone, which is a full agonist, buprenorphine is a partial agonist, thereby exerting weaker opioid effects at the μ opioid receptor site. This "ceiling effect" lowers the risk of respiratory depression, overdose and diversion, and contributes to the superior safety profile of buprenorphine relative to methadone [197]. Through co-formulation with naloxone, the safety profile is further amplified, as this opioid antagonist reduces the risk of diversion and non-medical use [198]. Similar to methadone, a number of studies have demonstrated the safety and efficacy of buprenorphine/naloxone in the management of opioid use disorders [28].

The efficacy of OAT is highly dependent on dosage. Two systematic reviews illustrated that methadone doses of at least 60mg/day are more effective at retaining individuals in treatment and reducing illicit opioid use compared to lower doses [26, 27]. In a 2003 systematic review performed for the Cochrane Collaboration, authors examined treatment outcomes in relation to four different dose ranges for methadone: low (1– 39 mg), medium (40– 59 mg), high (60– 109 mg), and very high (≥ 110 mg) [26]. Based on findings from 11 randomized controlled studies and 10 controlled prospective studies, they found that doses above 60mg/day were more effective at retaining individuals in treatment, reducing illicit opioid use and lowering withdrawal symptoms compared to lesser doses, although for those above 110mg/day, there was uncertainty regarding the added benefit [26]. These findings were supported by a second review conducted in 2010 [27]. Similarly, for buprenorphine, the results of a 2014 Cochrane Collaboration systematic review, based on 31 clinical trials, concluded that doses of at least 16mg/day produce more favorable treatment outcomes, notably reduced illicit opioid use and retention in treatment [28]. For this reason, national clinical guidelines on opioid management in Canada [25], the United States [199] and the United Kingdom [200], and also guidelines proposed by the WHO [201]

recommend offering doses of at least 60mg/day for methadone and 16mg/day for buprenorphine, all the while tailoring the dose to patients' needs and preferences.

More recently, studies have increasingly highlighted the importance of patients' subjective perceptions of OAT dosage in driving favorable OAT outcomes, above and beyond the actual dosage. In a retrospective register-based study of 60 OAT patients receiving either methadone or buprenorphine/naloxone in Helsinki, Finland, patients who rated their treatment as inadequate had higher symptoms of opioid craving and withdrawal, and more positive urine samples for co-used drugs, including benzodiazepines (40% vs. 8%), amphetamine (35% vs. 7%) and cannabis (22% vs 8%) relative to those who rated it as adequate [202]. The mean daily dosage for both methadone and buprenorphine were similar across the two groups [202]. In a multi-site randomized controlled trial in France comparing settings for methadone initiation (specialized centers vs primary care) among 145 patients, the authors examined predictors of non-adherence to treatment one year following treatment initiation [203]. After adjusting for potential confounders, including socio-demographic, drug use and social circumstances, it was noted that patients who perceived their methadone dose as inadequate (either too low or too high) were three times more likely to be non-adherent to treatment at the one-year visit relative to those who rated it as adequate [203]. Furthermore, in a qualitative study of 19 methadone-maintained patients in Bronx, New York, perceiving one's dose as adequate was positively associated with a willingness to continue treatment [30].

The level of prescribed OAT dose and patients' perceptions of the adequacy of dosage are both important in influencing treatment outcomes. Supporting this, a meta-analysis compared the relative importance of methadone dose (≥ 60 vs <60 mg/day, defined as high/low) and dosing strategy (flexible/fixed) in influencing treatment retention [204]. Of note, with flexible treatment approaches, the OAT dose is adjusted to individual need rather than following pre-determined fixed-dose regimens, in order to account for differences in severity of addiction, chronicity, potency of main opioid used, tolerance acquired, and idiosyncratic issues [204]. The authors of this study found that retention in treatment was greater when OAT was delivered at (i) high doses,

across both dosing strategies, and (ii) with a flexible-dosing strategy, across high/low categories of dose [204]. The authors concluded that OAT doses that are relatively high *and* adjusted to the needs of patients are likely to achieve the most optimal retention level [204].

2.3.2 OAT FOR HCV PREVENTION

There is considerable evidence indicating that OAT reduces illicit opioid use and sharing of injecting equipment [205]. Furthermore, a 2016 systematic review by the Cochrane Collaboration illustrated that PWID receiving OAT have, on average, a 50% lower risk of HCV infection compared to those who are not [206]. Consequently, national [2] and international guidelines [20, 179, 207] on HCV prevention recommend increasing access to OAT among PWID as a key prevention strategy. However, despite significant evidence highlighting the role of OAT dosage in influencing treatment outcomes, to date, little consideration has been given to its role in influencing HCV infection risk. Only one study has compared the risk of HCV infection in relation to prescribed OAT dose [208]. The authors documented a similar reduction in risk for PWID receiving low [hazard ratio (HR): 0.58] and high doses (HR: 0.68), relative to those not receiving OAT [208].

2.3.3 HCV TREATMENT-AS-PREVENTION

Epidemiological data report persistently high levels of HCV transmission among PWID even in setting with high harm-reduction coverage, suggesting that, without additional intervention, achieving substantial reductions in HCV transmission and prevalence among PWID is unlikely [209]. Additionally, modeling studies suggest that further harm-reduction scale-up in these settings may only achieve modest reductions in HCV prevalence and may require several decades before meaningful reductions (>50%) are attained [210]. These observations have led to increased calls on delivering antiviral treatment-as-prevention for HCV infection to enhance the prevention benefit achieved through harm-reduction programs. In addition to the value of delivering cure in HCV-infected people who receive treatment, antiviral therapy may carry substantial population-level benefit by reducing the pool of circulating virus in a community, thereby decreasing the likelihood of onward transmission [11, 165, 209]. A core premise of treatment-as-prevention is to target and

prioritise PWID, because they represent the population most likely to transmit the infection [11, 165, 209].

Treatment-as-prevention has first been studied and advocated for in the field of HIV, and there is some epidemiological evidence suggesting that treating HIV-infected people lowers their likelihood of infecting others [211, 212]. Theoretically, treatment-as-prevention is more achievable with HCV than with HIV, given that HCV treatment has the distinct advantage of being finite and curative [165].

Empirical evidence, whether through clinical trials or observational studies, supporting the value of HCV treatment-as-prevention is lacking, yet several studies are ongoing [12, 166]. Meanwhile, several dynamic mathematical modeling studies have investigated the potential impact of HCV treatment-as-prevention and provided some theoretical support. These studies mechanistically model HCV transmission such that reductions in HCV prevalence through scale-up of treatment are linked to an individual's risk of acquiring infection, and therefore incidence [209]. The dynamic element implies that susceptible PWID can acquire HCV at a rate proportional to the background viremic prevalence, which decreases as HCV treatment increases. Collectively, these studies have shown that modest levels of HCV treatment scale-up, whether with traditional interferon-containing treatments [15, 167-172], or with new DAAs [14, 16, 18, 147, 173-178], could reduce HCV chronic prevalence and incidence among PWID in most settings. For example, a modeling study conducted among PWID in Montreal estimated that a 15% yearly increase in the number of people initiating HCV treatment could reduce HCV prevalence and incidence by 34% and 32% over 10 years, respectively [176]. In Vancouver, scaling-up the annual HCV treatment rate among PWID from 5 to 76 per 1000 PWID, could halve HCV prevalence over a period of 15 years [14].

2.3.4 LOW ACCESS AND UPTAKE OF HCV TREATMENT AMONG PWID AND ASSOCIATED BARRIERS

Because PWID account for the majority of new HCV infections, particularly in high-income countries, treatment-as-prevention and HCV elimination efforts rely heavily on expanding access and uptake of HCV treatment in this group [147-149]. Yet, despite the individual and population-level benefits of offering treatment to PWID, studies documenting uptake of interferon-based HCV treatment in diverse settings estimated that it was very low [38-42]. For example, in a cohort of 1257 current and former PWID in Vancouver, only 6% were estimated to have initiated HCV treatment between 1998 and 2010 [39]. Similar trends have persisted in the DAA era, as highlighted by studies conducted in Canada [41, 188], the United States [9, 189] and Europe [18]. With the exception of a few countries, like Australia, where access to HCV treatment has been recently expanded significantly [213], in most parts of the world, currents trends remain insufficient to substantially reduce HCV prevalence and incidence rates, and to achieve HCV elimination targets [43, 174]. Available global estimates suggest that only 2% of the HCV-infected population has been treated so far [43].

The sub-optimal level of treatment uptake is the consequence of multiple barriers acting at the levels of the patient, provider and system [44-47]. Among PWID, reported barriers to treatment uptake include absence of noticeable symptoms, misconceptions around available treatments, fear of treatment-associated side-effects, feelings of stigma and prejudicial attitudes from providers, limited financial resources and competing priorities related to housing, acute medical conditions and daily drug use [9, 44-47, 59]. Among providers, limited training and experience in caring for patients with drug use disorders, concerns of HCV treatment-associated side effects, particularly with interferon-based regimens, and presumed poor patient compliance, exacerbation of injection drug use and high risk of re-infection following treatment have been noted [44, 46, 47, 59, 214]. More broadly, at the health system level, suboptimal HCV screening and assessment, and the absence of treatment settings adapted to the needs of PWID represent important barrier to treatment access [44, 47, 59]. The delivery of HCV care in tertiary settings, with

limited integration of addiction, psychiatric and social care, inflexible appointment policies and lengthy waiting times makes the navigation of treatment difficult for PWID [47].

As highlighted by Lazarus et al, "the current situation is likely a legacy of the medical community's initial outlook on hepatitis C treatment for PWID, which was to not treat current or even former injectors" [48]. Perceptions around treatment worthiness have consistently limited access to HCV care in this marginalised group [215, 216]. Although multiple studies showed that the efficacy and safety of HCV treatment is similar among PWID and non-PWID populations, several international and national treatment guidelines in the 1990s and early 2000s recommended against treating PWID for hepatitis C [217-221]. Simple, tolerable and effective DAAs have eliminated the major barriers posed by interferon-based therapies to expanding access to PWID, including poor tolerability and the need for close monitoring and care. Even so, in response to the initially high costs of DAA therapies, restrictions were set by payers, including national governments and others [150-153]. Indeed, guidelines in Canada [150], the United States [152, 153] and Europe [151] restricted DAA treatment access to people without current or prior history of drug use.

Clinical practice guidelines have been updated regularly in recent years, as new generation DAA regimens became available [187, 222-228]. While some of the initial restrictions have been lifted in many settings as a result of innovative financing arrangements, strong leadership and patient engagement [222], others are still in place [229]. Additionally, many physicians still remain hesitant to treat PWID [49, 230]. In a 2016 survey of practitioners delivering HCV care in the DAA era, only 15% were willing to treat people who were actively injecting drugs [49]. Among the reasons identified for withholding treatment, non-adherence to therapy and risk of HCV reinfection due to ongoing, relapse or escalation of drug use emerged as the most common [49]. In the DAA-era, concerns have been put forward that the simplified treatment regimens will cause PWID not to fear re-treatment and lead them to avoid engaging in safe injection practices [231].

Contrasting concerns around ongoing or increasing drug use and high risk behaviours following treatment, others have suggested that these behaviours could actually decrease [50]. During HCV

treatment, PWID benefit from ongoing therapeutic relationships and harm reduction education provided by physicians, nurses, counsellors and other allied health provides. There is some evidence that screening and counseling could lead to reductions in drug use and injection equipment sharing among PWID [156, 232]. In addition, PWID accessing HCV treatment typically have access to ancillary health care services and support, including primary care and addiction treatment, such as OAT, which could foster additional opportunities to discuss and address drug use and risk behaviors [233, 234].

While the presumed impact of HCV treatment on drug use behaviours continues to have considerable implications for practice, little empirical data exists to inform the debate. Only two studies have examined whether and how drug use and sharing practices change following treatment, and both have been conducted in the interferon-era [235, 236]. Among 124 people with a history of injecting in Australia, injection drug use remained stable and ancillary injection equipment sharing decreased during and six months post-treatment [235]. Among 93 PWID followed in an international multi-centre clinical trial, drug injecting and alcohol use decreased during and/or six months post-treatment, yet no changes were noted for sharing behaviours [236].

2.4 BEYOND HCV

The recent development of very effective antiviral therapies has fueled a global momentum to eliminate HCV as a public health threat by 2030 [20]. Because PWID account for the majority of new and existing infection cases, the HCV epidemic has become a public health priority in this population [58]. Meanwhile, increasingly prevailing narratives surrounding HCV treatment-as-prevention and HCV elimination among PWID have been critiqued for overly medicalising the public health response to the detriment of addressing broader health and social needs in this population [58-61]. Furthermore, the relatively limited success of HCV-oriented interventions in curbing the HCV epidemic, combined with the opioid crisis currently sweeping across North America, have led to a renewed interest in addressing the broader structural and contextual factors affecting the health and well-being of PWID outside of the HCV-infection arena [58-61]. From a public health perspective, in order to reap the full benefits of HCV prevention and costly

antiviral therapies, premature deaths from acquisition risks, now exacerbated by the opioid crisis, need to be addressed [3, 64, 65].

For PWID, the risk of HCV infection exists in a context of many other health and social concerns [52, 53]. Injection drug use is associated with a high risk of overdose, vein damage, abscesses, cellulitis, and other skin infections, and many of these harms have increased in recent years [52, 53, 55-57]. For many individuals, the distant threat of possible HCV-related liver disease often carries little weight relative to these more immediate concerns [52-54]. A qualitative research study conducted among PWID in Montreal pointed out that during periods of intense drug consumption and street-involvement, avoiding HCV acquisition is not perceived to be a priority [54]. Together, these findings emphasize the need for a patient-oriented approach to HCV prevention and elimination that includes a broader consideration of factors impacting on injection drug use behaviours and drug-user health.

Contextual factors have been shown to play an important role in shaping drug use behaviours and related harm [237]. The "risk environment" framework [60], which has been developed specifically for illicit drug users, depicts the physical, social and economic space within which drug users interact and function, and which influences their drug use behaviours, and more broadly, their health and well-being. A wide range of structural factors can impact injection drug use behaviours and associated harms and be potentially modifiable at the public health and policy-level [60, 61, 237]. Of these, housing, income and access to addiction treatment have been consistently identified as primary concerns among PWID [54, 139, 238].

2.4.1 INJECTION CESSATION

Because injection cessation ends the inherent physical consequences related to injection practices, it has traditionally been at the core of addiction treatment programs and philosophies, and the primary objective of public health approaches tackling injection-related harm [239]. As a primary target for intervention, injection cessation and its associated determinants have collectively been the focus of numerous investigations to date. Studies conducted in Canada [240-

[246], the United States [77, 247-251], Australia [233], Europe [252, 253] and Asia [254] have illustrated that short-term injection cessation episodes, typically defined as spanning a three-month up to a twelve-month period, are common among PWID. In a sample of 1004 PWID in Montreal followed up to a four-year period, nearly 20% reported an episode of injection cessation of at least seven months [246]. Similarly, of 1663 PWID in Vancouver followed for a median of three years, over one half had at least one six-month injection cessation event [242]. In Melbourne, Australia, of 467 PWID followed up to six years, nearly a fifth reported injection cessation that lasted at least one year [233].

The subjective motivations underlying injection cessation are highly diverse and personal among PWID. In a qualitative study of 20 former and 11 current heroin users in New York City, the most common personal motivations surrounding injection cessation identified fell under three general themes: (i) the desire for an improved quality of life, (ii) the desire to do right by family and others and (iii) fear of a particular outcome, such as HIV infection, job loss or death, sometimes conceptualized in terms of a "quit or else" ultimatum [255]. Other studies have identified reasons relating to social reactions (e.g., stigmatization by others) [256] and personal crises characterized by major shifts in attitudes towards drugs [257].

Despite the diversity of motivations prompting PWID to stop injecting, the key role played by health and social services in enabling or impeding attempts to cease injecting has been consistently demonstrated. In a qualitative study examining factors influencing periods of injection cessation among PWID in Vancouver, access to low-threshold and harm reduction-oriented addiction treatment was one of the key factors identified by participants [139]. Furthermore, having a regular place to live and access to other basic necessities such as stable employment, were perceived as key in enabling attempts to transition away from injecting [139]. Other studies examining determinants of injection cessation episodes among PWID have documented similar findings [77, 233, 240-254]. OAT, stable housing and employment are among the most consistent factors linked to injection cessation among PWID [77, 233, 240-254].

While the link between OAT, stable housing and employment circumstances and injection cessation episodes is well-established, prior research investigating this relationship has two main limitations. On one hand, short-term injection cessation episodes do not reflect long-term injection patterns [248, 249], which oftentimes extend over decades [77, 252]. Conversely, injection cessation is an overly-simplistic metric of a favorable behavior change [258].

2.4.2 LONG-TERM PATTERNS OF INJECTION FREQUENCY

Although injection cessation episodes are common, studies have collectively suggested that, for the majority of PWID, these short-term behavior changes are not sustained. In a sample of 365 PWID in San Francisco, California, who were followed quarterly for an average of two years, 29% reported ceasing injection drug use for at least three months [249]. However, two-thirds of these reported injection drug use at a subsequent follow-up visit [249]. Among 1327 PWID in Baltimore followed semi-annually up to 12 years, 71% indicated at least one episode of six-month injection cessation and of these, two-thirds reported injection drug use at a later follow-up visit [248]. The authors of this study estimated the median time to injection drug use following an episode of injection cessation to be one year [248].

Only two prospective studies, with multiple repeated measures of injection drug use patterns and long-term follow-up, have characterized trajectories of injection drug use over time [77, 252]. A study carried out in Baltimore, Maryland examined longitudinal patterns of injection drug use over 20 years in a community sample of 1,716 PWID. The authors identified five distinct trajectory profiles of drug injection: two “use” patterns (32% engaged in persistent injection, and 16% had episodes of cessation and relapse) and three injection cessation patterns (19% early cessation, 16% delayed cessation, and 18% late cessation) [77]. A second study conducted in a sample of 740 PWID in Amsterdam examined longitudinal patterns of injecting frequency over a nine-year period [252]. In three of the five groups identified, frequency of injecting was sustained over time: rare to no injecting (22.8%), variable injecting (18.5%) and constant daily or several times daily injecting (15.1%) [252]. The other two trajectories displayed slow (31.5%) and more rapidly (12%) decreasing trends, the latter ending in nearly no injecting after six years [252].

Collectively, these studies suggest that long-term injection patterns are heterogeneous among PWID and that sustained cessation is achieved by a fraction of individuals, oftentimes following long periods of injection. Hence, short-term injection cessation is an overly-simplistic indicator of a "successful behaviour change" because, for most PWID, it does not reflect long-term injection patterns.

Relatedly, considering complete injection cessation as the only outcome of public health interest discounts other changes in injection patterns with potential to reduce drug-related harm that may be more practical and achievable by some PWID [258]. Of all studies having examined changes in injection drug use [77, 233, 240-254], only two [247, 252] also considered changes in injection frequency in the absence of complete cessation. Yet, it is now well-acknowledged that defining abstinence as the only marker of success is tantamount to setting the bar for drug-use behaviour change at its highest point [259]. In contrast to traditional abstinence-based philosophies, harm reduction-oriented programs and policies value any incremental change as an achievement if it aligns with people's subjective goals and capacities, recognising that many are not willing or ready to engage in total abstinence [260, 261].

In sum, while the role of socioeconomic circumstances and addiction treatment in enabling short-term injection cessation episodes has been widely studied, the extent to which these factors can influence injection frequencies among PWID with diverse and enduring trajectories of injection drug use remains unexamined. Because these factors closely reflect underlying contextual and structural forces surrounding injection drug use [237], findings can guide the development of appropriate public health and social initiatives.

2.5 SUMMARY AND KEY GAPS

Hepatitis C, a progressive disease that over 20 to 40 years can lead to liver cancer and premature death, is a key public health concern among PWID [2, 20]. The recent development of very effective HCV therapies with cure rates greater than 95% [34-37] has fueled a national [2] and international

interest [20] in eliminating HCV as a public health threat. PWID are at the core of hepatitis C prevention and treatment efforts, given the high incidence and prevalence of HCV infection in this group [2, 20]. As efforts are unfolding towards HCV elimination goals, a number of barriers and key gaps remain to be addressed. First, OAT is considered a gold-standard prevention tool for HCV prevention and key to elimination efforts [2, 20, 179, 207] . Yet, little is known about the importance of OAT dosage in influencing the risk of HCV acquisition. Having a better understanding of this relationship could inform the optimisation of OAT delivery in HCV prevention. Second, HCV elimination efforts rely heavily on increasing uptake of HCV treatment among PWID [14, 165, 209]. Yet, current treatment initiation rates are sub-optimal [38-42], and one of the main barriers to access relates to concerns among providers and policy-makers that injection drug use and risk behaviors would increase following treatment, negating the benefits of costly therapy [47, 151, 187]. However, to date, only two studies have examined drug use behaviours following HCV treatment, both of which have been conducted in the interferon era [235, 236]. Finally, because the burden of HCV is borne disproportionately by a marginalised population who has multiple competing health and social concerns, there is increasing recognition that global elimination of HCV as a public health threat will require more than improved HCV prevention and treatment [58-61]. The high burden of injection-related harms and elevated mortality among PWID that are unrelated to HCV [1, 84, 85] highlight the importance of taking a broader view on drug user health. For PWID, housing, income and access to addiction treatment are three of the most important day-to-day concerns [139]. A better understanding of the extent to which these factors relates to injection patterns among PWID could help inform the development of public health and social initiatives with ramifications extending beyond HCV-related outcomes.

2.6 OBJECTIVES

Overall, this thesis is concerned with addressing some of the barriers to achieving the targets around HCV elimination among PWID.

The specific objectives are to:

1. Examine the joint association of prescribed dosage of OAT and patient-perceived dosage adequacy with risk of HCV infection among PWID in a community-based sample of PWID
   This objective is addressed in Chapter 3.

2. Explore the relationship between HCV treatment and patterns of drug use and injection equipment sharing among PWID
   This objective is addressed in Chapters 4 and 5.

3. Investigate the association between OAT, housing and income stability, and injection frequency among PWID with diverse longitudinal injection patterns.
   This objective is addressed in Chapter 6.

2.7 CONTEXT OF THIS THESIS

To address the objectives outlined in this thesis, I capitalised on data collected as part of four different studies, all of which have been conducted among PWID and have a central focus on HCV. A brief overview of each study is provided below.

HEPCO: Chapters 3 and 6

Study design and aims: The St.Luc Cohort is an ongoing, open prospective cohort study established in 1988 in Montréal to study determinants of HIV transmission. Over the years, the cohort's objectives underwent two major updates to capture emerging research questions. First, in 2004, the focus was expanded to include determinants of primary HCV infection, and the Hepatitis Cohort (HEPCO), an embedded cohort of HCV-antibody negative PWID, was constituted. Second, in 2011, the cohort's objectives were further expanded to include an emphasis on HCV reinfection and associated determinants. Aside for these primary aims, the cohort also investigates access to care for HCV infection, as a secondary objective.

Recruitment and eligibility criteria: Participants are recruited via different strategies, namely i) referrals from community-based programmes catering to the needs of PWID, such as rehabilitation centres, needle exchange programs, shelters, and food banks, ii) Addiction Medicine Clinic of the Centre Hospitalier de l'Université de Montréal (CHUM), and iii) word-of-mouth. To be eligible, participants must report having injected drugs within the previous six months and be 18 years of age or older. Initially, only HIV-negative participants were recruited. Later on, HCV-antibody negative PWID (2004-), and HCV-RNA negative (2011-) became eligible for enrolment. Chronically HCV-infected PWID (HCV antibody and RNA positive) are also followed at one year-intervals to address secondary aims. Following each of the two main updates to the cohort's objectives, participants already enrolled in the former cohort were invited to participate in the new HCV incidence studies.

Study procedures: Follow-up visits were scheduled every six months up until 2011, and every three months thereafter. At each visit, blood samples are drawn for HIV/HCV testing and behavioral data are collected by means of an interviewer-administered questionnaire. Questionnaires elicit detailed information on socio-demographic characteristics, the types of drugs consumed and their frequency, high-risk drug use patterns (e.g., sharing of injection equipment), access to healthcare services and markers of socioeconomic disadvantage, including homelessness, incarceration and involvement in street-based drug activities. All participants newly infected with HCV are provided with post-test counselling and are systematically referred for medical follow-up at the Addiction Medicine program of the CHUM, which offers multidisciplinary services for patients with drug-related problems, including hepatitis C and HIV treatment. Participants sign an informed consent form in compliance with institutional review board regulations of the Research Centre of the CHUM and receive a small stipend (CAD$15–$20) at each visit.

IMPACT: Chapter 4

Study design and aims: IMPACT was a prospective cohort study conducted between 2007 and 2015 in Montreal. The overall aim was to investigate the relationship between interferon-based antiviral treatment and drug use behaviours and quality of life among PWID with acute HCV infection and offered systematic access to HCV clinical assessment and targeted health care services.

Recruitment and eligibility criteria: Participants were recruited through the St. Luc/HEPCO cohort and local community- and hospital-based collaborating clinics, including the Addiction Medicine program of the CHUM. To be eligible for enrolment, participants were required to be at least 18 years of age, to have injected drugs in the previous six months, and to be infected with acute HCV, defined as having either i) an anti-HCV antibody or RNA positive test within six months following an anti-HCV antibody negative test, or ii) an acute symptomatic infection with evidence of hepatitis illness (i.e., jaundice or alanine aminotransferase (ALT) elevation ≥ 10 times the upper

limit).

Study procedures: Once enrolled, participants were actively linked to the CHUM Addiction Medicine clinic for HCV-infection follow-up, assessment for treatment suitability and HCV-related care by a multidisciplinary team of clinicians, nurses and social workers. Participants with contra-indications to treatment due to severe co-morbidity were offered targeted health care services. Pegylated interferon-alpha (12–24 weeks) was offered to all other participants who did not spontaneously resolve their infection. As the DAA therapies were gradually developed and approved in clinical care in Montreal in 2013, participants eligible for treatment were offered the possibility of delaying therapy with interferon in wait for the newer ones; DAA were not available before the end of the study. After enrolment, participants were followed-up and evaluated at six-month intervals for up to four study visits. At each visit, a short interviewer-administered questionnaire was used to collect information on socio-demographic characteristics, injection drug use, living situation, health-related quality of life and access to health care services, including opioid agonist treatment. Clinical data (treatment initiation, adherence, sustained viral response) were also retrieved through consultation of patients' charts. A stipend of CAD$30 was offered to all participants upon completion of the questionnaire, as compensation for their time. All participants signed an informed consent in compliance with institutional review board regulations of the Research Centre of the CHUM.

SIMPLIFY/D3FEAT: Chapter 5

Study design and aims: SIMPLIFY and D3FEAT were two international, multicentre, open-label, single-arm, phase IV trials, conducted between March and October 2016 (SIMPLIFY) and June 2016 and February 2017 (D3FEAT). Their overall aim was to evaluate the efficacy and safety of HCV DAA treatment and its impact on clinical and non-clinical outcomes in HCV-infected people with recent injecting drug use or currently receiving OAT.

Recruitment and eligibility criteria: Recruitment was conducted through a network of drug and alcohol, hospital and community clinics and private practices at 25 sites in Australia (n=7), Canada (n=6), France (n=2), New Zealand (n=2), Norway (n=1), Switzerland (n=4), the United Kingdom (n=1), and the United States (n=1). Participants had to be >18 years of age, have chronic HCV infection and be HCV treatment-naïve. In SIMPLIFY, participants must have injected drugs in the last 6 months. In D3FEAT, participants must have injected drugs in the last 6 months or be receiving OAT.

Study procedures: Study procedures are similar across the 2 studies. Participants completed a self-administered behavioural questionnaire on a tablet computer at screening (pre-treatment assessment), baseline (treatment commencement), every 4th week during treatment (weeks 4, 8, 12 (end of treatment)), weeks 24 (sustained virological response (SVR)12) and 36 (SVR24), and six-month intervals thereafter (weeks 60, 84 and 108) for a total of 10 visits. They collected information on demographics, drug and alcohol use, injecting equipment sharing and drug treatment. In addition to behavioural surveys, study visits included standard laboratory testing (e.g., liver function tests, full blood count) and an assessment of adverse events and, at pre-specified select intervals, physical examinations (screening, baseline, weeks 4 and 12), HCV RNA testing (screening, baseline, weeks 12 and 24), HCV genotyping and fibrosis stage (screening). During treatment, participants attended the clinic on a weekly basis to receive their medication supply. Study nurses and physicians provided counselling and access to ancillary services (e.g., injection equipment, OAT) as per standard of care in their country. All participants provided written informed consent to participate and received the equivalent of AUS$20 reimbursement for their time at each visit. The study protocol was approved by St Vincent's Hospital, Sydney Human Research Ethics Committee and local ethics committees at all study sites, and was conducted according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines.

CHAPTER 3: OPIOID AGONIST TREATMENT DOSAGE AND PATIENT-PERCEIVED DOSAGE ADEQUACY, AND RISK OF HEPATITIS C INFECTION AMONG PEOPLE WHO INJECT DRUGS

This chapter has been published:

Artenie AA, Minoyan N, Jacka B, Høj S, Jutras-Aswad D, Roy É, Gauvin L, Zang G, Bruneau J. Opioid agonist treatment dosage and patient-perceived dosage adequacy, and risk of hepatitis C infection among people who inject drugs. CMAJ **2019**; 191(17): E462-e8.

Contributions: Andreea Adelina Artenie conceptualized and designed the study in collaboration with Julie Bruneau. Andreea Adelina Artenie conducted the statistical analyses, with guidance from Geng Zang, and drafted the first version of the manuscript. Julie Bruneau, Didier Jutras-Aswad and Élise Roy were co–principal investigators of the HEPCO Cohort at the time of this study. All of the authors contributed to the interpretation of data and critical revisions of the manuscript for important intellectual content. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Study overview in the context of this thesis: By providing structured access to long-acting opioids, OAT, typically involving methadone or buprenorphine/naloxone, can reduce the frequency of illicit opioid use and exposure to unsafe injecting practices, and improve stability and day-to-day function [26-28]. For these reasons, OAT is considered key to achieving HCV prevention and elimination[5, 6]. Yet, so far, the importance of OAT quality, and in particular the role of dosage, in influencing HCV infection risk has been overlooked. Methadone and buprenorphine are often prescribed at lower dosages than those recommended by clinical guidelines, and at dosages patients feel are inadequate [30-32]. Although multiple studies have suggested that higher dosages

of OAT are more effective in promoting treatment retention and in reducing withdrawal and illicit opioid use, no study has examined the link between the dose OAT and HCV infection. In this chapter, I examined the relationship between the adequacy of OAT dosage, using a combined indicator of dosage adequacy informed by clinical guidelines and patients' perceptions, and HCV infection risk among PWID.

Opioid agonist treatment and risk of hepatitis C infection among people who inject drugs: The role of prescribed dose and patient-perceived dosage adequacy

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3.1 ABTRACT

Background: Opioid agonist treatment (OAT) is considered key in preventing hepatitis C virus (HCV) transmission among people who inject drugs (PWID). The role of OAT dosage, however, is unclear. We investigated the joint association of prescribed OAT dose and patient-perceived dosage adequacy with HCV infection risk among PWID.

Methods: We followed prospectively PWID at risk of HCV infection (RNA-; Ab+/-) in Montreal (2004-2017). At 6- or 3-month intervals, participants were tested for HCV Ab or RNA, and completed an interviewer-administered behavioral questionnaire, reporting: current OAT exposure (yes/no), prescribed dose (methadone ≥60mg/day or buprenorphine ≥16mg/day categorised as high and low otherwise) and perceived dosage adequacy (adequate/inadequate). We then assigned participants into one of five exposure categories: no OAT; or OAT high/adequate, high/inadequate, low/adequate, low /inadequate. To estimate associations between categories of OAT dosage and incident HCV infection, we conducted Cox regression analyses, adjusting for multiple confounding factors.

Results: Of 513 participants (median age: 35.0; 77.6% male), 168 acquired HCV over 1422.6 person-years of follow-up [incidence: 11.8/100 person-years (95% confidence intervals (CI): 10.1-13.7)]. We observed a gradient in the relative risks of HCV infection across categories of OAT dosage. Compared to PWID not receiving OAT, adjusted hazard ratios were 0.43 (95%CI: 0.23-0.84), 0.61 (95%CI: 0.25-1.50), 1.22 (95%CI: 0.74–2.00) and 1.94 (95%CI 1.11–3.39) for those receiving dosages rated high/adequate, high/inadequate, low/adequate and low/inadequate, respectively.

Conclusion: HCV infection risk varies considerably according to OAT dose and patient-perceived adequacy, with associations indicating both protective and harmful effects relative to no OAT exposure.

3.2 INTRODUCTION

In North America, ongoing transmission of hepatitis C virus (HCV) is fueled by the opioid epidemic. From 2004 to 2014, a two-fold increase in the annual incidence of acute HCV infection was documented in the United States, mirroring increases in treatment admissions characterized by opioids injecting throughout the same period [125]. In Montreal, Canada, our group documented that injection of prescription opioids tripled over 2004-2009 among people who inject drugs (PWID) followed in the HEPCO Cohort, and this practice was linked to a nearly two-fold greater risk of HCV infection relative to injecting other drugs [75].

Pharmacotherapy with opioid agonist treatment (OAT), the recommended first-line treatment for opioid use disorder [25], can prevent HCV infection, with an estimated average risk reduction of 50% [164]. The role of OAT dosage in moderating this relationship is unclear, however [164]. Higher doses (≥60mg/day for methadone and ≥12-16mg/day for buprenorphine), which are typically recommended by clinical practice guidelines for the management of opioid use disorders [25, 199-201], are more effective in promoting treatment retention and reducing withdrawal and illicit opioid use [26-28, 193]. Increasing evidence also highlights the importance of patients' subjective perceptions of OAT dosage in influencing treatment outcomes, irrespective of prescribed dose. Adequate dosage perceptions have been linked to reduced opioid craving and poly-drug use [202], greater treatment adherence [203] and willingness to continue treatment [30]. Yet, many patients receive doses lower than those considered clinically optimal and/or doses that they perceive inadequate [30-32].

In the context of an ongoing global movement to eliminate HCV as a public health threat by 2030 [20], and in light of evidence that OAT scale-up will be central to achieving this goal [14], this study seeks to improve our understanding of how to optimise OAT provision for the prevention of HCV transmission. We aimed to investigate the joint association of prescribed OAT dose and patient-perceived dosage adequacy with HCV infection risk among PWID.

3.3 METHODS

Study design and sample

We used observational data collected in HEPCO, a prospective cohort established in Montreal in 2004 to assess determinants of HCV infection among PWID. Our recruitment and follow-up criteria have been previously published [115, 232]. HEPCO recruits participants through street-level strategies and community-program referrals. To be eligible, participants must report having injected drugs within the previous 6 months and be aged ≥18. Initially, only HCV-seronegative participants, at risk of primary HCV infection, were recruited. Since 2011, recruitment expanded to include HCV-seropositive, RNA-negative PWID, who had cleared their infection and became at risk of reinfection. Eligibility for the present study was restricted to HEPCO participants who reported using opioids and/or being on OAT at least at one study visit, and who had a minimum of two total visits.

Cohort visits were scheduled at 6-month intervals up to 2011 and at 3-month intervals thereafter, consistent with the need for more frequent testing intervals to assess HCV reinfection [262]. Visits consisted of answering an interviewer-administered questionnaire and HCV antibody or RNA testing. Participants were asked to return for their test results two weeks after each visit for posttest counseling and service referrals. Those who did not report any injection drug use throughout a cumulative period of 24 months were no longer followed. Participants signed an informed consent in compliance with institutional review board regulations of the Centre Hospitalier de l'Université de Montréal and received a small stipend (CAD$15-20) at each visit.

Measures

Study outcome: The outcome of interest was time to incident HCV infection. Primary infection was defined by the presence of HCV antibodies at a follow-up visit among previously HCV-antibody negative participants. Blood specimens yielding positive results for HCV antibodies using enzyme immunoassay (Abbott Laboratories) were confirmed by reverse-transcription

polymerase chain reaction (Roche Diagnostic Systems). HCV reinfection was defined as a positive HCV RNA test at a follow-up visit among previously HCV RNA-negative participants. RNA testing was performed using the Qualitative COBAS AMPLICOR Test 2.0 up until 2013, and the *COBAS Ampliprep*/*COBAS Taqman Quantitative* Test v2.0 (Roche) or the RealTime *HCV* assay (Abbott) thereafter.

Study exposure: At each visit, participants reported current OAT enrolment (yes/no), prescribed dose (mg/day), and perceived dosage adequacy (adequate/too low/too high). In line with OAT guidelines for the management of opioid use disorders [25, 199-201] and similar to a previous study [208], we categorised prescribed OAT dose as high if methadone ≥60mg/day or buprenorphine (combined with naloxone) ≥16mg/day, and low otherwise. We further stratified perceived dosage adequacy as adequate or inadequate, the latter category being applied to participants who reported their dose as too high or too low. We then assigned each participant to one of 5 exposure categories: no OAT; or OAT high/adequate, high/inadequate, low/adequate, low /inadequate. In a sub-analysis, we replaced high/low categories informed by *a priori*-specified thresholds, with high/moderate/low categories based on tertiles observed in our sample. This categorisation was done to examine the presence of a linear trend between prescribed OAT dose and HCV infection and does not reflect clinically-indicated thresholds. In Quebec, OAT is subsidized by the provincial public drug benefit program.

Covariates: We identified potential confounding variables based on previous studies examining the relationship between OAT and HCV infection [29]. These included: age (years), gender (male/female), college education (yes/no), injecting duration (years), past-month cocaine injection (yes/no), past-month unstable housing, past 3- or 6-month incarceration (depending on follow-up period), and previous HCV infection. As previously [234], unstable housing was defined as living on the street, in shelters or in apartment-hotels rented on a monthly basis. Since OAT access and HCV infection risk might have changed over time, we also considered follow-up period (2004-2011 vs. 2011-2017) as potentially confounding. Opioid injection and injection frequency

are postulated to be on the causal pathway between OAT and HCV infection risk and were therefore not considered confounding.

Statistical analyses

For all participants, follow-up started at the first visit at which opioid use and/or OAT exposure was reported (henceforth, considered baseline) and ended at the time of HCV infection or alternatively, at the last visit. We estimated the date of HCV infection using the midpoint between the last negative and first positive HCV test.

We first plotted Nelson–Aalen estimators of the cumulative hazard of HCV infection stratified by OAT dosage. Suitable for a graphical representation of the effects of time-varying exposures, the plot illustrates the estimated number of times one could theoretically acquire HCV over a given time period [263, 264]. At each time point, the relative risk of HCV infection across any two exposure categories can be estimated. Second, we employed time-varying Cox regression models to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) of associations between OAT dosage and HCV infection risk. A multivariable model was fit, adjusting for injecting duration and gender as *a priori* confounders, plus any factors identified as potentially confounding, based on a 5% change-in-estimate criterion [265]. With the exception of gender, education and previous HCV infection, we updated all variables at each visit to reflect the most recent information recorded. The linearity assumption for Cox regression was evaluated by plotting Martingale residuals for continuous variables [266]. Both age and injecting duration appeared to be linearly related to HCV infection risk and were therefore analyzed in continuous form. Because of correlation between age and injecting duration (Pearson correlation coefficient, r: 0.70), only the latter was included in the multivariable model. Missing data were infrequent (<0.5% for any one variable) and were imputed by the median and modal values for continuous and categorical variables, respectively. Since it was relatively uncommon for participants to perceive their OAT dose as too high if inadequate (19.7%), we performed sub-analyses excluding

these observations to aid interpretation. Statistical analyses were performed using SAS®, version 9.3 software.

3.4 RESULTS

Between November 2004 and August 2017, we recruited 780 PWID, of whom, 604 (77.4%) reported having used opioids and/or being on OAT at least at one visit. Of these, 513 (84.9%) completed a minimum of two visits and made up our study sample. We found no statistically significant differences between participants who did (n= 513) and did not (n=91) have a minimum of two visits for most variables, including OAT dosage, except for age and prior HCV infection: participants with at least two visits were older (median age: 35.0 vs 29.0, p<0.01) and more likely to have been HCV-infected previously (30.8% vs 19.8%, p=0.03).

The baseline characteristics of participants, overall and stratified by categories of OAT dosage, are presented in Table 1. The majority were male (77.6%), with median age and injecting duration of 35.0 and 9.5 years, respectively. Among participants enrolled in OAT (n=159), 61 (38.4%), 25 (15.7%), 49 (30.8%) and 24 (15.1%) reported their OAT dosage as high/adequate, high/inadequate, low/adequate and low/inadequate, respectively.

The median number of study visits per participant was 6 (interquartile range: 3-10). Over a total observation period of 1422.6 person-years of follow-up, 168 participants (32.7%) acquired HCV, for an incidence rate of 11.8 per 100 person-years (95% CI: 10.1-13.7).

Table 2 presents crude and adjusted HR for associations between OAT dosage and HCV infection risk relative to no OAT exposure. We observed a gradient in the relative risk of HCV infection across the four categories of OAT dosage. In multivariable analyses, PWID reporting their OAT dosage to be high/adequate had the lowest risk of HCV infection (aHR: 0.43; 95%CI: 0.23–0.84). In PWID who rated OAT as high/inadequate and low/adequate, the risk of HCV infection was lower (aHR: 0.61; 95%CI: 0.25-1.50) and slightly higher (aHR: 1.22; 95%CI: 0.74-2.00), respectively, relative to PWID not receiving OAT, yet these estimates were imprecise and

statistically non-significant. For PWID reporting their OAT dosage to be low/inadequate, risk of HCV infection was nearly two-fold greater (aHR: 1.94; 95%CI: 1.11-3.39) relative to those not receiving OAT.

Results were comparable in sub-analyses excluding observations at which OAT dosage was perceived to be too high (data not shown). In sub-analyses replacing high/low categories of prescribed OAT dose with high/moderate/low categories based on tertiles, we noted a linear trend between dose and HCV infection risk (Table 3). Nelson-Aalen curves showed a gradient in the cumulative hazard of HCV infection across categories of OAT dosage, mirroring results from Cox regression analyses. (Figure 1).

3.5 DISCUSSION

Our study showed the degree to which prescribed dose and patient-perceived dosage adequacy influence the association between OAT exposure and HCV infection risk among PWID. We found that, compared to no OAT, exposure to a high OAT dose (methadone ≥60mg or buprenorphine ≥16mg) is associated, on average, with a 60% lower risk of infection if dosage is perceived adequate. In contrast, relative to no OAT, exposure to a low OAT dose is associated with a two-fold greater risk of HCV infection if dosage is perceived inadequate. Exposure to high/inadequate and low/adequate doses did not influence HCV risk to a statistically significant degree relative to no OAT exposure. However, taken together, estimates were consistent with a graded effect of prescribed OAT dose and patient-perceived dosage adequacy on HCV infection risk. Importantly, our findings are indicative of the potential for both protective and harmful effects of OAT dosage depending on these factors.

The only other study to have compared HCV infection risk in relation to prescribed OAT dose documented a similar reduction in risk for PWID receiving low (HR: 0.58) and high doses (HR: 0.68), relative to those not receiving OAT, yet neither association was statistically significant [208]. In contrast, the role of patients' perceptions of OAT dosage adequacy in HCV prevention among PWID has not been previously explored to our knowledge. However, growing evidence is

supporting their role in driving favorable treatment outcomes [30, 202, 203], and patients' views on the adequacy of OAT dosage are increasingly recognized as a valuable complement to providers' perspectives in defining targets for optimal treatment [267].

Although our study suggests that exposure to a high dose of OAT that is also subjectively perceived as adequate is most likely to confer an HCV prevention benefit, it remains to be established how to balance clinically-recommended doses with patients' preferences. If a low dose is perceived adequate by patients, and an increase is not desired, the potentially limited HCV prevention benefit conferred through OAT treatment should be discussed. Our finding of a nearly two-fold greater risk of HCV infection among PWID receiving a low and subjectively inadequate OAT dose, compared to those not enrolled in OAT, is particularly worrisome. For most participants in our study, inadequately perceived OAT dosages were reportedly too low, which could lead to increased illicit drug use and risk behaviours [26], potentially explaining this finding. While further research is needed to explore reasons leading to low and/or inadequate OAT dosing, prior studies have flagged social stigma surrounding OAT [30] and a predominance of abstinence-oriented ideologies among prescribers and treatment settings [32]. Altogether, our study supports the need to ensure that OAT programs provide care following best-practice guidelines and that clinicians work with patients to identify a suitable dose that is most likely to be clinically effective while meeting their individual needs. Our study also highlights the need to ensure access to alternative agonist pharmacotherapies and harm reduction services, offering a diversified set of complementary HCV prevention strategies to meet the varied needs of PWID.

Limitations

First, residual confounding of the estimated associations cannot be ruled out, despite our efforts to adjust for known confounders. For example, the reduced HCV infection risk observed among PWID whose OAT dosage was high/adequate could be partly attributed to having greater motivated to reduce risk behaviours relative to other participants. Second, selection bias as a result of losses to follow-up may have affected our estimates. Our follow-up rates are fairly high

for a PWID population, however, and participants lost to follow-up were similar to those retained with respect to most baseline characteristics, diminishing the likelihood of this risk. Third, because it was based on self-report, misclassification of OAT dosage is possible. However, in one study of PWID in Amsterdam, authors validated self-reported methadone dosage and found excellent correlation between self-report and prescription registry data [268]. Finally, our focus on the joint effect of two measures of OAT dosage on HCV infection risk may have limited our power to detect statistically significant associations, particularly for the high/inadequate category, which had few events.

3.6 CONCLUSION

In sum, HCV infection risk varies substantially according to a combined indicator of OAT dosage informed by prescribed dose and patients' perceptions. Our results suggest that, to benefit from a lower risk of HCV infection while on OAT, PWID must be prescribed a high dose that is also perceived adequate. In light of ongoing global calls to broaden OAT access to foster HCV elimination, our study suggests that simply expanding access may not be enough and that OAT dosage should be central to any HCV prevention strategy.

Table 1: Baseline characteristics of people who inject drugs enrolled in the HEPCO Cohort, by prescribed opioid agonist treatment (OAT) dose, categorised according to clinical guideline recommendations*, and patient-perceived dosage adequacy

Variable	Not enrolled in OAT (n = 354)	OAT dosage High OAT dose and perceived adequate (n = 61)	High OAT dose and perceived inadequate (n = 25)	Low OAT dose and perceived adequate (n = 49)	Low OAT dose and perceived inadequate (n = 24)	p value
Mean age, years (SD)	35.8 (10.8)	39.5 (10.7)	38.4 (9.6)	34.9 (9.7)	32.3 (7.9)	0.02
Median age, years (IQR)	33.9 (26.9 - 44.3)	40.7 (31.1 - 47.3)	37.5 (32.2 - 43.0)	33.3 (27.4 - 42.3)	31.3 (26.7 - 35.6)	0.03
Male gender	284 (80.2%)	43 (70.5%)	16 (64.0%)	36 (73.5%)	19 (79.2%)	0.25
College education or higher	74 (20.9%)	22 (36.1%)	10 (40.0%)	13 (26.5%)	11 (45.8%)	<0.01
Mean duration of injection, years (SD)	11.0 (10.2)	18.2 (9.4)	16.5 (11.5)	13.4 (9.9)	11.6 (8.8)	<0.01
Median duration of injection, years (IQR)	7.8 (2.8 - 16.2)	18.0 (10.1 - 26.1)	15.0 (4.7 - 25.0)	12.3 (4.6 - 20.3)	9.7 (4.0 - 16.1)	<0.01
Opioids injection, past mo	260 (73.4%)	33 (54.1%)	22 (88.0%)	37 (75.5%)	22 (91.7%)	<0.01
Cocaine injection, past mo	191 (54.0%)	28 (45.9%)	8 (32.0%)	25 (51.0%)	11 (45.8%)	<0.01
High frequency of injection (≥30 injections), past mo	208 (58.8%)	20 (32.8%)	13(52.0%)	22 (44.9%)	19 (79.2%)	<0.01
Unstable housing, past mo	147 (41.5%)	16 (26.2%)	4 (16.0%)	8 (16.3%)	7 (29.2%)	<0.01
Incarceration, past 3 or 6 mo‡	76 (21.5%)	12 (19.7%)	5 (20.0%)	9 (18.4%)	7 (29.2%)	0.87
Previous HCV infection	76 (21.5%)	34 (55.7%)	14 (56.0%)	25 (51.0%)	9 (37.5%)	<0.01
2004-2011 follow-up wave (vs. 2011-2017)	199 (56.2%)	21 (34.4%)	12 (48.0%)	27 (55.1%)	10 (41.7%)	0.02

Note: HCV= hepatitis C virus, IQR= interquartile range, SD= standard deviation

Data are presented as no. (percentage) unless otherwise indicated.

*****Prescribed dose was categorised as high if methadone ≥60mg/day or buprenorphine ≥16mg/day, and low otherwise.

†*p*-value derived from ANOVA and Kruskal-Wallis test for age and duration of injection, and χ^2 test for all other variables.

‡Depending on follow-up wave.

Table 2: Hazard ratios for associations between incident hepatitis C virus (HCV) infection and opioid agonist treatment (OAT) prescribed dose, categorised according to clinical guideline recommendations* and patient-perceived dosage adequacy

Variable	No. of observations	No. of p-y of follow-up	No. of incident cases	Rate per 100 p-y	unadjusted HR (95% CI)	adjusted HR¶ (95% CI)
OAT dosage						
Not enrolled in OAT	1831	782.78	118	15.07	1.00 (ref.)	1.00 (ref.)
High OAT dose and perceived adequate	663	274.07	10	3.65	0.28 (0.15 - 0.54)	0.43 (0.23 - 0.84)
High OAT dose and perceived inadequate	214	86.28	5	5.80	0.43 (0.17 - 1.05)	0.61 (0.25 - 1.50)
Low OAT dose and perceived adequate	510	207.15	20	9.65	0.79 (0.49 - 1.28)	1.22 (0.74 - 2.00)
Low OAT dose and perceived inadequate	211	72.32	15	20.74	1.46 (0.85 - 2.50)	1.94 (1.11 - 3.39)
Age, years†‡					0.83 (0.76 - 0.90)	
≤31,6	856	430.95	86	19.96		
>31,6 - ≤40,4	859	375.57	39	10.38		
>40,4 - ≤48,2	856	326.55	26	7.96		
>48,2	858	289.53	17	5.87		
Gender						
Female	664	281.18	36	12.80	1.00 (ref.)	1.00 (ref.)
Male	2765	1141.41	132	11.56	1.00 (0.69 - 1.45)	0.74 (0.50 - 1.10)
College education or higher						
No	2472	1062.6	140	13.18	1.00 (ref.)	
Yes	957	359.99	28	7.78	0.55 (0.37 - 0.82)	
Duration of injection, years†					0.79 (0.72 - 0.87)	0.85 (0.77 - 0.94)
≤7,2	857	399.79	91	22.76		
>7,2 - ≤15,3	859	403.14	41	10.17		
>15,3 - ≤25,0	856	331.85	22	6.63		
>25,0	857	287.82	14	4.86		
Cocaine injection, past mo						
No	2088	886.91	52	5.86	1.00 (ref.)	1.00 (ref.)
Yes	1341	535.69	116	21.65	3.17 (2.28 - 4.40)	2.85 (2.04 - 3.99)
Unstable housing, past mo						
No	2579	1075.58	88	8.18	1.00 (ref.)	1.00 (ref.)
Yes	850	347.01	80	23.05	2.34 (1.72 - 3.17)	2.14(1.54 - 2.96)
Incarceration past 3 or 6 mo §						
No	3068	1245.82	121	9.71	1.00 (ref.)	1.00 (ref.)
Yes	361	176.78	47	26.59	2.32 (1.65 - 3.27)	1.80 (1.26 - 2.56)
Previous HCV infection						
No	2148	972.59	138	14.19	1.00 (ref.)	1.00 (ref.)
Yes	1281	450	30	6.67	0.43 (0.29 - 0.64)	0.73 (0.46 - 1.15)
Follow-up wave						
2004-2011	912	551.26	96	17.41	1.00 (ref.)	
2011-2017	2517	871.34	72	8.26	0.64 (0.47 - 0.87)	

Note: CI= confidence interval, HR= hazard ratio, p-y= person-years

*****Prescribed dose was categorised as high if methadone ≥60mg/day or buprenorphine ≥16mg/day, and low otherwise.

†Age and duration of injection were analysed in continuous form in Cox regression models. HR represent the effect of a 5-year increase.

‡Because of correlation with injecting duration (Pearson correlation coefficient, r: 0.70), this variable was not entered in the multivariable Cox regression model.

§ Depending on follow-up wave.

¶ The final multivariable model adjusted for duration of injection (years), gender (male/female), cocaine injection (yes/no), unstable housing (yes/no), incarceration (yes/no) and previous HCV infection (yes/no).

Table 3: Hazard ratios for associations between incident hepatitis C virus (HCV) infection and opioid agonist treatment (OAT) prescribed dose, categorised according to tertiles* and patient-perceived dosage adequacy

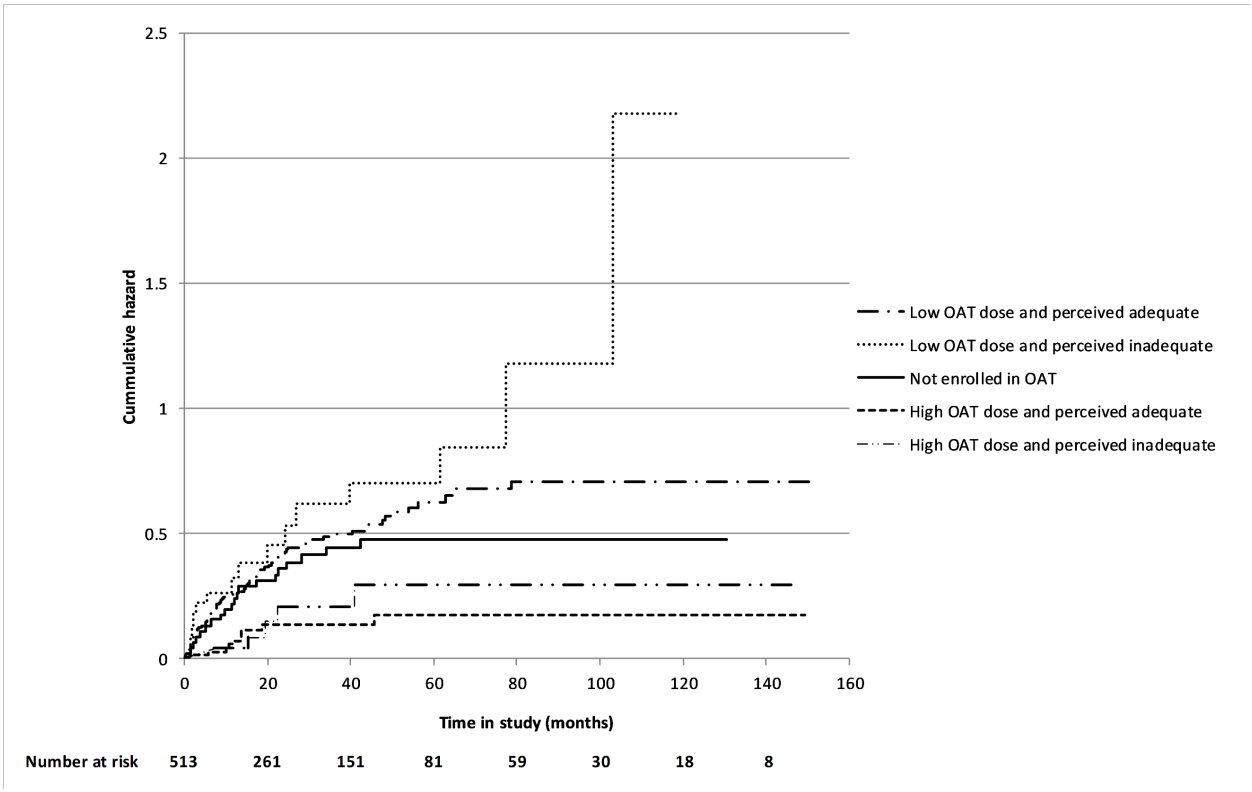
Variable	No. of observations	No. of p-y of follow-up	No. of incident cases	Rate per 100 p-y	unadjusted HR (95% CI)	adjusted HR¶ (95% CI)
OAT dosage						
Not enrolled in OAT	1831	782.78	118	15.07	1.00 (ref.)	1.00 (ref.)
High OAT dose and perceived adequate	390	167.10	4	2.39	0.18 (0.07 - 0.50)	0.27 (0.10 - 0.74)
High OAT dose and perceived inadequate	113	49.90	2	4.01	0.32 (0.08 - 1.28)	0.37 (0.09 - 1.49)
Moderate OAT dose and perceived adequate	402	156.06	12	7.69	0.59 (0.32 - 1.07)	0.93 (0.50 - 1.72)
Moderate OAT dose and perceived inadequate	139	49.28	6	12.18	0.83 (0.37 - 1.89)	1.40 (0.61 - 3.24)
Low OAT dose and perceived adequate	381	158.05	14	8.86	0.75 (0.43 - 1.31)	1.21 (0.68 - 2.14)
Low OAT dose and perceived inadequate	173	59.41	12	20.20	1.42 (0.78 - 2.58)	1.95 (1.06 - 3.59)

Note: CI= confidence interval, HR= hazard ratio, p-y= person-years

*****Prescribed dose was categorised as high if methadone >80mg/day or if buprenorphine >14mg/day, moderate if methadone >45 and ≤ 80 mg/day or if buprenorphine >8 and ≤ 14 mg/day, and low if methadone >0 and ≤ 45mg/day or if buprenorphine ≤8 mg/day.

†Adjusted for gender (male/female), duration of injection (years), past-month cocaine injection (yes/no), past-month unstable housing (yes/no), past 3- or 6-month incarceration (yes/no), and previous HCV infection (yes/no)

Figure 1: Nelson–Aalen estimates of the cumulative hazard of hepatitis C virus infection according to prescribed dosage of opioid agonist treatment and patient-perceived dosage adequacy.



CHAPTER 4: SHORT-TERM INJECTION DRUG USE CHANGES FOLLOWING HEPATITIS C VIRUS (HCV) ASSESSMENT AND TREATMENT AMONG PERSONS WHO INJECT DRUGS WITH ACUTE HCV INFECTION

This chapter has been published:

Artenie AA, Zang G, Daniel M, Fortier E, Jutras-Aswad D, Puzhko S, Bruneau J. Short-term injection drug use changes following hepatitis C virus (HCV) assessment and treatment among persons who inject drugs with acute HCV infection. Int J Drug Policy **2017**; 47: 239-43. doi: 10.1016/j.drugpo.2017.05.033

Contributions: Andreea Adelina Artenie and Julie Bruneau conceptualized and designed the study. Andreea Adelina Artenie conducted the statistical analyses, with guidance from Geng Zang, and drafted the first version of the manuscript. Julie Bruneau and Didier Jutras-Aswad were co–principal investigators of the IMPACT study at the time of this study. All of the authors contributed to the interpretation of data and critical revisions of the manuscript for important intellectual content. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Study overview in the context of this thesis: Epidemiological data report persistently high levels of HCV transmission among PWID even in setting with high harm-reduction coverage, suggesting that, without additional intervention, achieving substantial reductions in HCV transmission and prevalence among PWID is unlikely [209]. In addition to delivering cure in infected patients, HCV treatment may carry population-level benefits, by reducing the pool of circulating and subsequent likelihood of viral transmission [10, 11]. Yet, unsubstantiated concerns among providers and policy-makers around ongoing and/or escalating risk behaviours following HCV treatment represent one of the main barriers to increasing treatment initiation among PWID [48, 49]. So far, few studies have examined patterns of drug use and sharing behaviours following HCV treatment among PWID [235, 236]. At a time when interferon-based therapies were still the standard of care for HCV infection, and highly efficacious and well-tolerated DAA regimens were forthcoming [51], in

this chapter, I examined injection drug use changes among PWID with recent HCV infection who were systematically referred for HCV clinical assessment and treatment and offered targeted health care services.

Short-term injection drug use changes following hepatitis C virus (HCV) assessment and treatment among persons who inject drugs with acute HCV infection

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4.1 ABSTRACT

Background: It is unclear whether treatment and care for hepatitis C virus (HCV) infection can help people who inject drugs (PWID) modify their injection drug use behaviours. This study examined changes in injection drug use among PWID with acute HCV systematically referred for HCV clinical assessment and treatment and offered targeted health care services, over the course of one year.

Methods: The study sample included PWID with documented acute HCV infection recruited and followed-up semi-annually at least twice in IMPACT (2007-2015), a longitudinal community-based prospective study in Montréal, Canada. Following enrolment, participants with contra-indications to treatment due to severe co-morbidity were offered targeted health care services. Pegylated interferon-alpha (12-24weeks) was offered to all other participants who did not spontaneously resolve their infection. At each study visit, data were collected on socio-demographic factors and drug use patterns. Logistic regression was used to assess changes in injection drug use at one-year follow-up.

Results: Of the 87 eligible participants (mean age: 35.6; 78.2% male), 21.8% received treatment [(RT), Sustained virological response: 84.2%], 25.3% spontaneously resolved their infection (SR), 14.9% had contra-indication(s) (CIT) and 37.9% chose not to engage in HCV care post-diagnosis (NE). In multivariable analyses adjusting for age, gender and injection drug use at baseline, the RT [Adjusted odds ratio (AOR): 0.18; 95% Confidence interval (CI): 0.04, 0.76)], SR (AOR: 0.34; 95% CI: 0.08, 1.40), and CIT (AOR: 0.24; 95% CI: 0.05, 1.22) groups were less likely to report injection drug use at follow-up relative to the NE group.

Conclusion: PWID who received treatment, spontaneously resolved their infection or presented with treatment contra-indication(s) reported reduced injection drug use at one-year follow-up relative to those who did not engage in therapy. Findings suggest that the benefits of HCV assessment and treatment may extent to helping PWID modify their injection drug use patterns.

4.2 INTRODUCTION

Among people who inject drugs (PWID), the median global hepatitis C virus (HCV) prevalence is estimated at 67% and is as high as 90% in certain settings [269]. In the United States, the number of HCV-related deaths between 2003-2013 has surpassed 60 other nationally notifiable infectious conditions combined [270]. It is widely acknowledged that timely engagement in HCV care, involving HCV testing and counselling, and assessment and treatment for those infected is key in reducing HCV-related morbidity and mortality [271, 272].

More recently, research has attempted to investigate whether the benefits of HCV care may extend beyond liver-related outcomes [273-275]. Among PWID, there is some evidence to suggest that HCV treatment could have positive impacts on drug use behaviours. PWID engaged in treatment have access to regular monitoring and care, creating opportunities to receive counselling and discuss behaviour change [276-278]. Concurrent access to ancillary health care services and support, including primary care and addiction treatment may also play a role in influencing behaviour changes [279-281]. To date, only one study has specifically examined injection drug use changes in relation to HCV treatment exposure [275]. In this study of 124 PWID with acute or early chronic HCV followed for a median of 1.8 years in Australia, no association was found between treatment for HCV infection and past-month injection drug use [275].

For decades, interferon-based therapy has been the standard of care for HCV. In light of the availability of new highly efficacious and well-tolerated therapies for HCV, recently shown to be associated with high cure rates among PWID [282], achieving an understanding of the impact of treatment on drug use behaviours in this population is particularly important in order to inform the ongoing debate on which patient groups to prioritize for treatment and related cost-benefit analyses [283].

IMPACT was a longitudinal prospective cohort study in Montreal designed to investigate the effect of antiviral treatment on behaviour change in a community-based sample of current PWID with acute HCV, who were systematically referred for HCV clinical assessment and offered

targeted health care services. The primary objective of this study was to compare eligible IMPACT participants who received treatment to those who chose not to engage in HCV care post-diagnosis with respect to their drug use changes over the course of a year. A subset of participating PWID were not eligible for treatment, either because they had spontaneously cleared the infection, or had contra-indications to therapy. As a secondary objective, we examined one-year injection drug use changes among these two groups and compared them with those who did not engage in HCV care.

4.3 METHODS

Study design and participants

Enrolment in IMPACT took place between November 2007 and March 2015 and participants were recruited from two main sources: i) the Saint Luc Cohort, a community-based ongoing prospective cohort study examining determinants of HCV and human immunodeficiency virus (HIV) transmission among current PWID (n=94, 80.3%) and ii) local community- and hospital-based collaborating clinics, including the addiction medicine clinic at the Centre Hospitalier de l'Université de Montréal (CHUM) (n=23, 19.7%).

To be eligible for enrolment in IMPACT, participants were required to be at least 18 years of age, to have injected drugs in the previous six months, and to be infected with acute HCV, defined as having either i) an anti-HCV antibody or RNA positive test within six months following an anti-HCV antibody negative test, or ii) an acute symptomatic infection with evidence of hepatitis illness (i.e., jaundice or alanine aminotransferase (ALT) elevation ≥ 10 times the upper limit). Exclusion criteria included pregnancy and HIV-seropositivity.

Eligible individuals were systematically referred to the CHUM addiction medicine clinic for HCV-infection follow-up, assessment for treatment suitability and HCV-related care by a multidisciplinary team of clinicians, nurses and social workers. Psychiatric comorbidities or ongoing illicit drug use did not exclude patients from proceeding to treatment. Participants

willing to be treated but who presented with contra-indications to HCV therapy due to severe mental health co-morbidity assessed by an addiction psychiatrist, or who were too socially unstable (e.g., multiple recent overdoses combined with unstable housing conditions) were offered targeted health care services. Those who did not resolve spontaneously within 20 weeks of estimated infection were offered pegylated interferon for 12-24 weeks, depending on early response, genotype and initial viral load. As the DAA therapies were gradually developed and approved in clinical care in Montreal in 2013, participants eligible for treatment were offered the possibility of delaying therapy with interferon in wait for the newer ones. Treatment cost was covered under the provincial healthcare insurance plan.

Participants were enrolled into the study a median of six days after receiving their HCV test result (interquartile range: 1 – 20, range: 0 – 126), and were subsequently followed up and evaluated at six month intervals for up to four study visits (i.e., to two years follow up) by the research team, located two blocks from the CHUM Addiction Medicine clinic. A short interviewer-administered questionnaire was used to collect information on socio-demographic characteristics, injection drug use and related behaviours. A stipend of CAD $30.00 was offered to all participants upon completion of the questionnaire, as compensation for their time. All participants signed an informed consent in compliance with institutional review board regulations of the CHUM. Participation to the study was independent from the HCV care provided. As part of the consent form, participants provided consent to access their medical chart for information on HCV care.

Measures

The outcome of interest was past-month injection drug use assessed dichotomously at the third study visit corresponding to 12-month follow-up. Given that participants initiated therapy at different time points following enrolment [median: 1.6 months (interquartile range: 0.7 – 3.8)], visit three was chosen as the endpoint for this study to ensure that all had the opportunity to complete treatment.

The primary exposure variable was HCV care, consisting of four categories: received treatment, spontaneously cleared the infection, presented with a contra-indication to treatment, and chose not to engage in HCV care. The latter group included those who refused to engage in the HCV assessment process and, as of 2013, those who delayed treatment as newer and more effective regimens for chronic HCV infection were going to be made available.

Covariates accounted for in statistical analyses included variables previously identified as important correlates of reduction or cessation of injection drug use [246, 275], namely: age, gender, education, injection drug use in the month prior to baseline assessment, duration of injection drug use, recent homelessness, defined as having slept on the streets or in shelters within the past month, and receipt of opioid agonist therapy (OAT) at the time of the baseline interview. Duration of drug use was expressed as a dichotomous variable with the cut point being the median duration of injection drug use (eight years).

Statistical analyses

Descriptive statistics, including means, standard deviations (SD) and frequency distributions, were used to summarize participants' characteristics at baseline assessment. Main analyses included univariate and multivariable logistic regression models to estimate crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) for the associations between HCV treatment and injection drug use at follow-up. The multivariable model adjusted for age, gender, and covariates identified as influential, potentially confounding factors based on the 10% change-in-estimate criterion [284]. Specifically, variables that altered any of the unadjusted effect estimates by at least 10% were deemed to have a confounding effect and were retained in the final multivariable model.

To examine if our results were influenced by the changing landscape of HCV treatment over the course of the study period, as the new DAA therapies were gradually introduced in clinical care

in 2013, we conducted a sensitivity analysis, restricting our study sample to participants who were recruited up until February 2013, when the majority of eligible patients were treated (n=18/19). For all analyses, *p*-values were two-sided, with $P<0.05$ used as a criterion for statistical significance. Statistical analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC).

4.4 RESULTS

The present study included all participants who had completed three study visits. Of 117 enrolled, one was excluded, as he had developed chronic HCV infection by the time that the clinical assessment was made, 16 (13.7%) had yet to return for their second or third follow-up visits and 13 (11.1%) were lost to follow-up, five of whom are known to have died. Eighty-seven participants formed the sample for this study. There were no statistically significant differences between the baseline characteristics of participants included in the study (n= 87) and those who were not (n= 30) (supplementary table).

Table 1 presents participants' descriptive characteristics at baseline assessment. Their mean age was 35.6 (SD: 10.2) and most (n=68, 78.2%) were male. Approximately half had completed high school (n=51, 58.6%), reported recent homelessness (n=37, 42.5%), and were injecting for eight years or longer (n=44, 50.6%). A majority (n=76, 87.4%) reported past-month injection drug use. Cocaine was the most frequently injected drug in our sample (n=71, 81.6%), followed by prescription opioids (n=61, 70.1%) and heroin (n=46, 50.9%). Slightly more than a third of participating PWID reported current OAT (n=33, 37.9%).

Overall, 19 participants (21.8%) received HCV treatment, 22 (25.3%) spontaneously cleared their infection, 13 (14.9%) had a contra-indication to treatment and 33 (37.9%) chose not to engage in HCV care. Among treated participants, 16 completed all prescribed injections, two interrupted treatment early (at three and six weeks) and one discontinued at the request of the treating physician when he became infected with HIV and required treatment in the chronic phase. Sixteen participants (84.2%) who received treatment achieved sustained virological response, defined as the absence of detectable HCV RNA 24 weeks following the last injection.

Table 1 further describes the characteristics of participants at baseline assessment according to HCV treatment and categories of non-treatment. Overall, those who received treatment appeared to have higher levels of education and to be more likely to receive OAT relative to participants in the other three groups. They were also less likely to be homeless and to report past-month injection drug use. Participants for whom treatment was contra-indicated appeared to be older compared to the other PWID.

Results from the univariate and multivariable logistic regression analyses, addressing aims one and two, are presented in Table 2. Regarding aim one, we found that participants who received treatment were significantly less likely to report injection drug use at one-year follow-up compared to those who chose not to engage in HCV care post-diagnosis (adjusted OR: 0.18; 95% CI: 0.04 - 0.76). Regarding aim two, we found that the odds of reporting injection drug use at follow-up were considerably lower among participants with a contra-indication to therapy (adjusted OR: 0.24; 95% CI: 0.05 - 1.22) and those who spontaneously resolved their infection (adjusted OR: 0.34; 95% CI: 0.08 - 1.40) relative to those who opted not to engage in HCV care, yet results were imprecise, illustrated by the large 95% CI surrounding the estimated effect sizes.

In the sensitivity analysis, restricting the study sample to participants recruited up until February 2013, 59 participants were included, classified as following: 18 received treatment, 14 spontaneously resolved their infection, 9 had a contra-indication to therapy and 18 chose not to engage in therapy. The odds of reporting injection drug use at one-year follow-up remained lower in all three groups, namely those who received treatment (adjusted OR: 0.24; 95% CI: 0.05 – 1.29), spontaneously cleared their infection (adjusted OR: 0.40; 95%CI: 0.07 – 2.36) and had a contra-indication to therapy (adjusted OR: 0.40; 95% CI 0.07 – 2.36), compared to those who chose not to engage in HCV care, though the 95% CI were wider compared to the original analyses, as expected.

4.5 DISCUSSION

The primary aim of this study was to compare short-term changes in injection drug use among active PWID with acute HCV infection who received antiviral treatment relative to those who chose not to do so. Our results indicate that treatment receipt was associated with a lower likelihood of reporting injection drug use at follow-up, a few months after the end of the treatment course for most, relative to those who chose not to engage in HCV care. These novel findings support a growing evidence suggesting that the benefits of HCV care are broader in scope [273] and extend to improving PWID's quality of life. Altogether, these results could serve to further support expanding treatment access to this patient population.

A number of factors may explain our finding. Close monitoring and counselling during treatment coupled with the prospect of being cured may have encouraged PWID to make positive lifestyles changes and to alter their drug use patterns [276-278]. Access to an individualized treatment plan in a multidisciplinary health care setting offering primary, addiction and psychiatric care, may have also contributed to their capacity to modify behaviour [279-281]. Furthermore, our study indicates that treated participants may have been representative of a group of PWID who were more likely to make changes in response to acquiring HCV compared to those who chose not to engage in HCV care, as a greater proportion were already engaged in addiction treatment at study entry and appeared to have greater overall social stability.

The only other study examining the relation between HCV treatment and drug use changes among PWID reported no association between the two [275]. The authors of this investigation did not distinguish among the reasons for non-treatment, potentially explaining the non-significant findings. Untreated participants represent a heterogeneous group with respect to need for treatment, treatment access or medical follow-up. Behavioural changes are likely to differ among PWID who choose not to engage in HCV care relative to those who present with contra-indications to treatment but are engaged in care, and those who spontaneously clear their infection.

Our secondary aim was to compare one-year injection drug use changes among participating PWID ineligible for treatment, either because they had spontaneously cleared the infection, or had contra-indications to therapy, and those who chose not to engage in HCV care. Results indicated a substantial inverse association in both groups compared, though these results were imprecise, likely due to the small sample size. For PWID among whom treatment was delayed because of contra-indications to interferon therapy, findings could reflect a response to increased medical intervention, as these individuals were offered access to tailored multidisciplinary care. Similarly, it is possible that access to close monitoring during the acute phase to detect potential HCV clearance may have played a role among those who spontaneously cleared their infection. Supporting this presumption, a greater proportion of PWID in these three groups reported past six-month regular medical care at one-year follow-up [84% (treated) 76.9% (spontaneous resolution) and 68.2% (contra-indication)] compared to those who did not to engage in HCV care (42.4%). We did not note a significant increase in the proportion of participants initiating OAT over the course of the study period, suggesting that other health interventions are likely to have played a role. Of note, a majority of participating PWID are primarily cocaine users, and therefore, not eligible for OAT. Further research is needed to investigate which aspects of HCV care are likely to help support changes in drug use patterns among PWID.

The most important strength of our study is that it is the only one to have been conducted in a sample of active PWID recruited from the community, many of whom were not engaged in care at study outset, thereby illustrating real-world responses following access to HCV assessment and treatment among PWID.

There are some limitations in this study. First, participant self-selection with regard to engagement in HCV assessment and treatment is likely to have influenced our findings. To address this, we accounted for a number of possible confounding variables in our analyses. In addition, it is worth noting that participants were all recently infected with HCV and were

systematically offered access to HCV care, diminishing the likelihood that other confounders such as variable duration of infection and provider-related factors, interfered with our findings. Second, losses to follow-up may have affected our results, though the baseline characteristics of those lost to follow-up and those retained in the study did not appear to be different. Third, although the main independent variable, HCV treatment, was collected through clinical data, the outcome, injection drug use, was assessed through self-report, and is therefore prone to social desirability bias. Fourth, the relatively modest sample size of the study affected our ability to obtain more precise results. Fifth, our study was conducted during a period of time when HCV treatment was interferon-based. The landscape of treatment has changed since, with DAA being the standard of care in most settings now. Therefore, it is unclear if our findings are generalizable to current HCV treatment regimens. Findings could be applicable to the extent that treatment with DAA is offered in conjunction with counseling and preventive health messages and as part of a multidisciplinary care program, as in our study. Furthermore, while the individuals included in our study may not be representative of the patient population considered for treatment in the current DAA era, the fact that our study noted positive changes in injection drug use in a sample of PWID with ongoing risk behaviours is a strength and relevant to the "treatment as prevention" model of care. Finally, given that our study focused only on changes in injection drug use measured at two time points using a binary variable and considering the large 95% CI surrounding the effect estimates, we cannot rule out the possibility that our findings reflect natural fluctuations in injection drug use behaviours over time.

4.6 CONCLUSION

In sum, our results suggest that receipt of HCV treatment is associated with a lower likelihood of reporting injection drug use relative to no engagement in HCV care, at least in the short term. Moreover, findings also suggest that HCV treatment may be only one of several interventions around HCV care that are likely to positively impact injection drug use behaviours. Altogether, these findings further emphasize the importance of offering readily access to HCV assessment and treatment to HCV-infected PWID. Alternatively, PWID for whom treatment is not indicated,

or readily available, would likely benefit from timely engagement in care addressing their substance use, mental health and/or related conditions.

Table 1: Descriptive characteristics of participants at baseline assessment (n=87)

Characteristic	Total N=87 n (%)	RT (N=19) n (%)	SR (N=22) n (%)	CIT (N=13) n (%)	NE (N=33) n (%)
Age [Mean (SD)]	35.6 (10.2)	34.9 (9.3)	36.6 (9.5)	39.7 (12.4)	33.7 (10.2)
Male gender	68 (78.2%)	15 (79.0%)	16 (72.7%)	10 (76.9%)	27 (81.8%)
Completed high school education	51 (58.6%)	14 (73.7%)	12 (54.6%)	7 (53.9%)	18 (54.6%)
Recent homelessness	37 (42.5%)	6 (31.6%)	10 (45.5%)	6 (46.2%)	15 (45.5%)
Injection drug use in past month	76 (87.4%)	14 (73.7%)	19 (86.4%)	13 (100%)	30 (90.9%)
Current OAT	33 (37.9%)	10 (52.6%)	9 (40.9%)	5 (38.5%)	9 (27.3%)
Injected for 8 years or more	44 (50.6%)	9 (47.4%)	13 (59.1%)	7 (53.9%)	15 (45.5%)

Note: RT= received treatment; SR= spontaneously cleared the infection; CIT= had a contra-indication to treatment; NE= chose not to engage in HCV care; OAT= opioid agonist treatment; SD= standard deviation

Table 2: Univariate and multivariable associations of hepatitis C virus (HCV) treatment and other characteristics assessed at baseline with injection drug use at one-year follow-up (n= 87)

Characteristic	Unadjusted OR (95% CI)	*p*-value	Adjusted OR* (95% CI)	*p*-value
HCV treatment				
RT versus NE	0.15 (0.04 - 0.61)	0.01	0.18 (0.04 - 0.76)	0.02
SR versus NE	0.30 (0.08 - 1.18)	0.08	0.34 (0.08 - 1.40)	0.14
CIT versus NE	0.22 (0.05 - 1.02)	0.05	0.24 (0.05 - 1.22)	0.09
Age (5-year increase)	0.95 (0.91 - 0.99)	0.03	0.95 (0.90 - 0.97)	0.04
Male versus female gender	0.86 (0.27 - 2.70)	0.79	1.10 (0.30 - 4.05)	0.89
Completed high-school education	0.92 (0.36 - 2.38)	0.87		
Injection drug use in past month	3.6 (0.99 - 13.15)	0.05	3.98 (0.91 - 17.34)	0.07
Recent homelessness	1.16 (0.45 - 2.98)	0.76		
Current OAT	0.70 (0.27 - 1.82)	0.46		
Injected for 8 years or more	0.92 (0.36 - 2.34)	0.87		

Note: OR= odds ratio; CI= confidence interval; RT= received treatment; SR= spontaneously cleared the infection; CIT= had a contra-indication to treatment; NE= chose not to engage in HCV care; OAT= opioid agonist treatment

*The final multivariable model adjusted for age (years), gender (male/female) and past-month injection drug use at baseline (yes/no)

Supplementary Table 1: Descriptive characteristics of included (n= 87) and excluded (n= 30) participants measured at baseline assessment

Characteristic	Included n=87 n (%)	Excluded n=30 n (%)	*p*-value*
Age [Mean (SD)]	35.6 (10.2)	34.5 (11.4)	0.61
Male gender	68 (78.2%)	24 (80.0%)	0.83
Completed high school education	51 (58.6%)	17 (56.7%)	0.85
Recent homelessness	37 (42.5%)	9 (30.0%)	0.23
Injection drug use in past month	76 (87.4%)	27 (90.0%)	0.7
Current OAT	33 (37.9%)	7 (23.3%)	0.15
Injected for 8 years or more	44 (50.6%)	13 (43.3%)	0.49

Note: OAT= opioid agonist treatment; SD= standard deviation

* *p*-value is based on the pooled t-test for the continuous variable age, and the χ^2 test for all categorical variables

CHAPTER 5: PATTERNS OF DRUG, ALCOHOL USE AND INJECTION EQUIPMENT SHARING AMONG PEOPLE WITH RECENT INJECTING DRUG USE OR RECEIVING OPIOID AGONIST TREATMENT DURING AND FOLLOWING HEPATITIS C VIRUS TREATMENT WITH DIRECT-ACTING ANTIVIRAL THERAPIES: AN INTERNATIONAL STUDY

This chapter has been published:

Artenie AA, Cunningham EB, Dore GJ, Conway B, Dalgard O, Powis J, Bruggmann P, Hellard M, Cooper C, Read P, Feld JJ, Hajarizadeh B, Amin J, Lacombe K, Stedman C, Litwin AH, Marks P, Matthews GV, Quiene S, Erratt A, Bruneau J, Grebely J. Patterns of drug, alcohol use and injection equipment sharing among people with recent injecting drug use or receiving opioid agonist treatment during and following hepatitis C virus treatment with direct-acting antiviral therapies: An international study. Clin Infect Dis **2019**. Doi: 10.1093/cid/ciz633. [Epub ahead of print], by permission of Oxford University Press.

Contributions: Andreea Adelina Artenie conceptualized and designed the study in collaboration with Julie Bruneau and Jason Grebely. Andreea Adelina Artenie conducted the statistical analyses and drafted the first version of the manuscript. Julie Bruneau and Jason Grebely were co–principal investigators of the SIMPLIFY and D3FEAT trials at the time of this study. All of the authors contributed to data collection, interpretation of results and critical revisions of the manuscript for important intellectual content. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Study overview in the context of this thesis: Remarkable medical advances have completely changed the landscape of HCV treatment in the last decade, as additional pharmaceutical options have become available with progressively improving efficacy and tolerability. Short-course, all-oral DAA regimens are curative in >95% of treated persons and carry few or no side effects [5, 9]. The introduction of DAA treatment marks a shift away from the demanding therapeutic

engagements of injectable interferon-based treatments to the relatively simple management of well-tolerated, all-oral regiments [285]. While previous studies, conducted in the interferon-era, showed some decreases in drug use and/or injection equipment sharing following treatment [235, 236, 286], concerns have arisen that the simplified treatment provision with DAAs may diminish opportunities to have a positive impact on non-clinical outcomes such as risk behaviours [285], or possibly even lead to increases [49]. As a follow-up to the previous study (Chapter 4), in a context where DAA therapies have already been introduced, in this chapter, I examined patterns of drug use and injection equipment sharing among people with recent injecting drug use or receiving OAT during and following DAA-based treatment.

Patterns of drug, alcohol use and injection equipment sharing among people with recent injecting drug use or receiving opioid agonist treatment during and following hepatitis C virus treatment with direct-acting antiviral therapies: An international study

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5.1 ABSTRACT

Background: In many settings, recent or prior injection drug use remain barriers to accessing direct-acting antiviral treatment (DAA) for hepatitis C virus (HCV) infection. We examined longitudinal patterns of drug and alcohol use and injection equipment sharing among people with recent injecting drug use or receiving opioid agonist treatment (OAT) during and following DAA-based treatment.

Methods: SIMPLIFY and D3FEAT are phase IV clinical trials evaluating the efficacy of DAA among people with past six-month injecting drug use or receiving OAT through a network of 25 international sites. Enrolled in 2016-2017, participants received sofosbuvir/velpatasvir (SIMPLIFY) or paritepravir/ritonavir/dasabuvir/ombitasvir±ribavirin (D3FEAT) for 12 weeks. Additionally, they completed a behavioural questionnaire before, during and after treatment, up to two years following treatment initiation. The impact of time in HCV treatment and follow-up on longitudinally measured behavioural outcomes was estimated using generalized estimating equations analyses.

Results: At screening, of 190 participants (mean age: 47; 74% male), 62% reported any past-month injecting (47% opioids, 39% stimulants), 16% past-month injection equipment sharing and 61% current OAT. Median alcohol use was 2 (AUDIT-C test, range 1-12). During follow-up, opioid injecting (OR: 0.95, 95%CI: 0.92-0.99) and sharing (0.87; 95%CI: 0.80-0.94) decreased, whereas no significant changes were observed for stimulant injecting (OR: 0.98, 95%CI: 0.94-1.02) or alcohol use (OR: 0.99; 95%CI: 0.95-1.04). No increasing patterns were noted for any outcome considered.

Conclusion: Injecting drug use and risk behaviours remained stable or decreased during and following DAA-based HCV treatment. Findings further support expanding HCV treatment to all, irrespective of injection drug use.

5.2 INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease, cirrhosis, and liver cancer, affecting >71 million people globally [287, 288]. The burden of HCV infection is disproportionately high among people who inject drugs (PWID) currently or formerly, such as those receiving opioid agonist treatment (OAT) for the management of opioid dependence [66, 68, 289]. The development of direct-acting antiviral (DAA) therapies, which are considerably more efficacious and tolerable than previous interferon-based combinations, makes HCV infection a curable disease in nearly all patients with access to treatment. Several studies, including some conducted by our group, have demonstrated high efficacy of DAA therapy among PWID, irrespective of whether or not they receive OAT or report recent injection [146]. However, uptake of treatment is low [290-292].

The high cost of DAA therapies led to restricted reimbursement in many settings [150, 151, 153]. Despite clinical guidelines recommending DAA treatment for nearly all patients with HCV [225, 293], recent drug and/or alcohol use persists as a restriction to accessing therapy [150, 151, 153]. Even in settings where such restrictions do not exist, many physicians are hesitant to treat people who are actively injecting drugs or receiving OAT given concerns regarding continuing or increasing injecting risk behaviours with a consequent risk of HCV reinfection [49].

To date, no study has examined whether and how patterns of drug use and injection risk behaviours change following DAA treatment. Three studies, conducted in the pre-DAA era, reported stable or decreasing drug-related behaviours during and in the immediate period post-treatment with pegylated interferon alpha (+/- ribarivin) [235, 236, 286]. Among 124 people with a history of injecting in Australia, injection drug use remained stable and ancillary injection equipment sharing decreased during and six months post-treatment [235]. Among 87 PWID in Montreal, Canada, PWID who engaged in HCV treatment were less likely to report injecting drug use at one-year follow-up compared to those who chose not to engage in care [286]. Finally, among 93 PWID followed in an international multicentre clinical trial, drug injecting and alcohol use decreased during and/or six-months post-treatment, yet no changes were noted for sharing

behaviours [236]. In addition to being limited by a short follow-up post-treatment, these investigations only reported average changes in drug use behaviours within the population and over time. Exploring whether and how trends evolve differently for some patients can help clinicians tailor therapeutic actions to optimize health outcomes. Therefore, the aim of this study was to examine longitudinal patterns of drug and alcohol use and injection equipment sharing among people with recent injecting drug use or receiving OAT during and following DAA-based treatment for chronic HCV infection.

5.3 METHODS

Study design and sample

This study is a pooled analysis of two international, multicentre, open-label, single-arm, phase IV trials, evaluating the efficacy and safety of HCV DAA treatment and its impact on clinical and non-clinical outcomes in HCV-infected people with recent injecting drug use or currently receiving OAT: SIMPLIFY and D3FEAT (ClinicalTrials.gov: NCT02336139 and NCT02498015 respectively). Study procedures are similar across the two studies and have been previously published along with efficacy and safety findings [294, 295]. Briefly, participants received sofosbuvir/velpatasvir once daily (SIMPLIFY) or paritepravir/ritonavir/dasabuvir/ ombitasvir±ribavirin twice daily (D3FEAT) for 12 weeks. Recruitment was conducted through a network of drug and alcohol, hospital and community clinics and private practices at 25 sites in Australia (n=7), Canada (n=6), France (n=2), New Zealand (n=2), Norway (n=1), Switzerland (n=4), the United Kingdom (n=1), and the United States (n=1). Recruitment occurred between March and October 2016 in SIMPLIFY and June 2016 and February 2017 in D3FEAT. Participants had to be >18 years of age, have chronic HCV infection and be HCV treatment-naïve. In SIMPLIFY, participants must have injected drugs in the last 6 months. In D3FEAT, participants must have injected drugs in the last 6 months or be receiving OAT. A total of 190 participants were recruited (SIMPLIFY: N=103; D3FEAT: N= 87).

Procedures

Participants completed a self-administered behavioural questionnaire on a tablet computer at screening (pre-treatment assessment), baseline (treatment commencement), every 4th week during treatment (weeks 4, 8, 12 (end of treatment)), weeks 24 (sustained virological response (SVR)12) and 36 (SVR24), and six-month intervals thereafter (weeks 60, 84 and 108) for a total of 10 visits. Questionnaires were developed through focus-testing with PWID and have been used by our group previously in the ACTIVATE study [296]. They collected information on demographics, drug and alcohol use, injecting equipment sharing and drug treatment. In addition to behavioural surveys, study visits included standard laboratory testing (e.g., liver function tests, full blood count) and an assessment of adverse events and, at pre-specified select intervals, physical examinations (screening, baseline, weeks 4 and 12), HCV RNA testing (screening, baseline, weeks 12 and 24), HCV genotyping and fibrosis stage (screening). During treatment, participants attended the clinic on a weekly basis to receive their medication supply. Study nurses and physicians provided counselling and access to ancillary services (e.g., injection equipment, OAT) as per standard of care in their country. All participants provided written informed consent to participate and received the equivalent of AUS$20 reimbursement for their time at each visit. The study protocol was approved by St Vincent's Hospital, Sydney Human Research Ethics Committee and local ethics committees at all study sites, and was conducted according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines.

Measures

Five behavioural outcomes were evaluated in relation to HCV treatment: i) injection drug use (any), ii) opioid and iii) stimulant injection, iv) injection equipment sharing and v) alcohol use. Opioids included heroin or prescription opioids, and stimulants included cocaine or amphetamine. Injection equipment sharing was defined as receptive sharing of needles, syringes, spoons or mixing containers, drug solution, water or filters. Alcohol use was assessed using the

Alcohol Use Disorders Identification Test–Consumption (AUDIT-C, score range: 1-12) [297]. Scores of three or more (women) and four or more (men) indicate hazardous consumption or active alcohol use disorders [297]. Receipt of OAT was also evaluated in relation to HCV treatment, and defined as treatment with methadone, buprenorphine or buprenorphine-naloxone. Non-injected opioids and stimulants were examined as secondary outcomes, given their limited connection to HCV infection and liver-related outcomes. Except for alcohol, all variables were assessed on a binary scale (yes/no), with respect to the previous month (drugs) or currently (OAT). Alcohol use was evaluated in count form.

Statistical analyses

Descriptive statistics were used to summarize participants' characteristics at screening. Main analyses involved estimating average changes in behaviours over time using a generalized estimating equation (GEE) extension of logistic regression. GEE models were specified using a binomial family function and a logit link, and an identity family function and a Poisson link for binary and count variables, respectively. Models estimated the effect of time since screening on each outcome using the odds ratio (OR) and 95% confidence interval (CI). The time effect was assessed in incremental study visits, irrespective of varying time lapses between visits. To control for behavioural changes attributed to changing OAT patterns over time, models were adjusted for this factor as a time-varying covariate. Fixed covariates (e.g., age, gender) had no influence on parameter estimates and were therefore not included in the models.

Since assessment of average behavioural patterns could mask heterogeneity among individuals over time, in secondary analyses, group-based trajectory modelling was used to visually inspect the presence of distinct longitudinal patterns. This method is used to identify relatively homogeneous clusters of trajectories of stability or change over time in the presence of repeated observations [298, 299]. For each behavioural outcome, the number of groups and their shape were informed by previous studies examining drug use trajectories [77, 252] and several statistical criteria [298, 299]. We considered models with up to four and five groups for binary and count outcomes,

respectively. For each outcome, the final number of groups was determined by selecting the model that maximized the Bayesian information criteria, as long as Bayes factor was <0.1 and membership in each trajectory group was more than 5%. To describe the shape of trajectories, quadratic and cubic polynomials were considered sufficiently flexible for binary and count variables, respectively. We then obtained more parsimonious models by excluding polynomial terms that did not attain statistical significance at the 5% level.

At the time of this analysis (November 2018), follow-up was still ongoing, and analyses were conducted on available data. To minimize the potential for selection bias due to losses to follow-up, while accounting for participants who had yet to come back for a study visit, we developed a conservative definition of study retention *a priori*, and re-fitted the GEE models among individuals who met this criterion. Study retainment was defined as having completed all five visits of screening and during treatment, and an additional any two afterwards. Overall, 151 (79.5%) met our pre-defined criteria for study retention. Missing values due to participant non-response were infrequent (<4% for any one variable) and were left as is. Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and the traj macro [25].

5.4 RESULTS

Characteristics of study participants

Table 1 presents the characteristics of the 190 participants at screening. Overall, nearly three-quarters of participants were male (74%) with mean age of 47 (standard deviation: 9). Most had injected drugs in the past month (62%) and were receiving OAT (61%). Major drug classes injected were opioids (47%) and stimulants (39%). Sixteen percent reported sharing injection equipment in the past month. The median alcohol use score, evaluated by the AUDIT-C test, was two [interquartile range (IQR): 0-4]. Although similar in age and gender distribution, compared to participants recruited in D3FEAT, those enrolled in SIMPLIFY were more likely to report recent unstable housing (22% vs 12%), drug use (e.g., injection drug use: 75% vs 47%) and injection

equipment sharing (22% vs 8%) and were less likely to be receiving OAT (52% vs 72%), consistent with study inclusion criteria.

Average behavioural changes during and following HCV treatment

During follow-up, participants had a median of eight visits (IQR: 7-9) and contributed to a total of 1471 observations. Figure 1 presents the overall proportion of participants reporting each behavioural outcome and their median alcohol use at each visit. Table 2 presents the results of GEE analyses. As Ors remained unchanged after adjusting for OAT, only adjusted estimates are presented. A modest decrease was noted for any injection drug use: each additional study visit was associated, on average, with a 4% decrease in odds of past-month injecting. When examining classes of injected drugs separately, only opioid injecting decreased over time whereas stimulant injecting did not. For sharing of injection equipment, a more pronounced decrease was noted: each additional study visit was associated, on average, with a 13% decrease in odds of past-month sharing. Alcohol use, receipt of OAT and non-injecting stimulant use did not appear to change during follow-up. A modest and non-statistically significant decrease was observed for non-injecting opioid use.

Trajectories of behavioural outcomes during and following HCV treatment

Figure 2 presents results of group-based trajectory analyses for four behavioural outcomes: opioid and stimulant injecting, injection equipment sharing and alcohol use. Supplementary Table 1 presents the model selection process. For opioids, three distinct injection probability trajectories were identified: no (40%), sustained (33%) and decreasing (27%) injection. Among participants presenting with a decrease in opioid injecting, the decline was gradual and persistent throughout treatment and during the 2-year follow-up period. For stimulant injecting, three different trajectories were identified: no (60%), sustained (22%) and inconsistent (18%) injection. For injection equipment sharing, a two-trajectory group was identified, one of no sharing (89%) and one of decreasing sharing (11%). As with opioids, the decline in sharing probability was

gradual and persistent across the follow-up period. For alcohol, four distinct trajectories were identified, all of which remained stable during and following HCV treatment: no (31%), low (20%), moderate (33%) and high (16%) use. Trajectories for OAT receipt and non-injecting opioid and stimulant use remained stable throughout follow-up (Supplementary Figure 1).

Retention in follow-up

With the exception of being slightly older (mean age: 47 vs 44, p= 0.09), participants classified as retained in follow-up (n= 151) were similar to those who were not (n= 39) with respect to all other characteristics (Supplementary Table 2). In GEE analyses restricted to participants retained in follow-up, Ors remained largely unchanged (Supplementary Table 3).

5.5 DISCUSSION

This pooled analysis of two international multicentre studies evaluated longitudinal patterns of drug use behaviours during and following DAA-based HCV treatment among people with recent injecting drug use or receiving OAT, who often face difficulties accessing treatment [49, 150, 151, 153]. Our study has two main findings. First, drug and alcohol use remained stable during follow-up or decreased slightly. Second, sharing of injection equipment underwent a gradual decrease over time. These findings are encouraging, given that sharing behaviours are the main driver of HCV reinfection among PWID [88]. Importantly, behavioural patterns were not transient but appeared to be persistent during the two-year follow-up. Taken together, our findings do not support concerns of increasing injection drug use or risk behaviours following DAA-based HCV treatment, and further endorse the removal of barriers to access for all infected PWID, irrespective of ongoing injection drug use.

The introduction of DAA treatment marks a shift away from the demanding therapeutic engagements of injectable interferon-based treatments to the relatively simple management of well-tolerated, all-oral regiments [285]. While previous studies, conducted in the interferon-era, showed some decreases in drug use and/or injection equipment sharing following treatment [235,

[236, 286], concerns have arisen that the simplified treatment provision with DAAs may diminish opportunities to have a positive impact on non-clinical outcomes such as risk behaviours [285], or possibly even lead to increases [49]. Our study does not support this. Rather, it seems that for the majority of DAA-treated patients, engagement in treatment is unlikely to modify their drug use patterns. For some, however, it may be a cue prompting motivation to decrease HCV risk behaviours and injection drug use. This finding underscores the importance of providing counselling and access to ancillary services alongside HCV treatment to ensure that patients have access to all the tools necessary to support them in making broader drug use changes.

Aside from a potential impact of treatment, it is also possible that the stable or decreasing drug use patterns observed reflect a moment in time when individuals were ready to make broader health changes, which in turn motivated HCV treatment-seeking. Supporting this premise is the stable OAT pattern observed throughout follow-up in those reporting OAT at screening, which contrasts with more common patterns of cycling-in and out of addiction treatment [300]. In a study examining determinants of DAA treatment initiation among PWID, participants identified similar circumstances as "the right time for treatment" [301]. For more vulnerable and marginalised populations, HCV treatment is situated within a context of competing every day concerns [302]. It is therefore important that personal attitudes be considered in decisions around HCV treatment readiness and that any window of opportunity for engagement in care is fully seized upon.

While most participants reported low or moderate levels of alcohol use, approximately 16% reported heavy use, according to AUDIT-C criteria [297], and this pattern remained consistent throughout follow-up. Among people with chronic hepatitis C, heavy alcohol use has been linked to excess mortality [64]. While additional research is needed to document its impact on liver-related outcomes among people who achieved viral eradication, there is some evidence suggesting that liver complications post-SVR are lowest in people who do not drink alcohol [303]. Clinical practice guidelines on the management of HCV recommend that all patients undertaking treatment be offered counselling and support to avoid harmful alcohol consumption [225, 293, 304].

Our study has several limitations. First, given the absence of a comparison group of PWID not receiving DAA treatment, we cannot attribute behavioural changes to HCV treatment or any one intervention. Second, behavioural outcomes were based on self-reported data, which are prone to socially-desirable responding and recall error. Although behaviours may be under-estimated, self-reported information on drug use has been shown to be reliable and valid, particularly if assessed through computer-assisted surveys [305, 306]. Third, even though follow-up was fairly high for a drug-using population, and no differences in drug use patterns were found among participants who were and were not retained, our data may have been influenced by losses to follow-up. Long-term changes should be interpreted with caution given the smaller number of participants followed-up in later years.

Lastly, findings may not be generalizable to the broader population of current and former PWID. Our study sample was fairly well engaged in health services and a relatively modest proportion (16%) reported sharing behaviours compared to the prevalence typically reported among community-recruited PWID [115, 307]. Despite a broad geographic distribution of study participants, all were recruited in high-income settings, where there is typically greater capacity for HCV and addiction care delivery relative to low- and middle-income countries. Finally, participants had weekly contacts with healthcare professionals while on treatment, and it is unclear whether findings would be similar in the context of a simplified monitoring strategy, for which there is growing interest [308]. However, even if simplified HCV treatment options become available, many PWID may continue to benefit from regular monitoring and support while on treatment [309].

5.6 CONCLUSION

Altogether, our study indicates that drug and alcohol use remain stable or decrease slightly and injection equipment sharing decreases during and following DAA-based HCV treatment among people with recent injecting or receiving OAT. These findings further support expanding HCV treatment to all infected PWID, irrespective of ongoing injection drug use. More broadly, our study suggests that even in the era of simplified DAA therapies, there are ways to enhance the delivery of treatment to afford opportunities for harm reduction. Additional research is needed

to elucidate which interventions during HCV treatment can promote reductions in injection equipment sharing. While the majority of people undergoing HCV DAA treatment will achieve cure, reductions in sharing behaviours and risk of HCV reinfection post-treatment will likely not be achieved unless treatment services include HCV counselling and are integrated with addiction treatment and harm-reduction services.

Table 1: Descriptive characteristics at study entry for people with recent injection drug use or receiving opioid agonist treatment (OAT) recruited and followed in SIMPLIFY and D3FEAT (N= 190)

Variable	Total (N= 190)	SIMPLIFY (N= 103)	D3FEAT (N= 87)
Age, years [Mean (SD)]	47 (9)	47 (9)	47 (10)
Male gender	141 (74%)	74 (72%)	67 (78%)
Completed high school education	92 (49%)	50 (49%)	42 (49%)
Unstable housing, past 6 months	33 (18%)	23 (22%)	10 (12%)
Any injection drug use, past month	117 (62%)	77 (75%)	40 (47%)
Opioid injection, past month	88 (47%)	58 (56%)	30 (35%)
Stimulant injection, past month	58 (39%)	39 (39%)	19 (23%)
Non-injecting opioid use, past month	42 (23%)	26 (26%)	16 (19%)
Non-injecting stimulant use, past month	48 (26%)	28 (28%)	20 (24%)
Sharing of injection equipment, past month	28 (16%)	22 (22%)	6 (8%)
Currently receives OAT	114 (61%)	53 (52%)	61 (72%)
Alcohol use score [a] [Median (IQR)]	2 (0 – 4)	2 (0 – 4)	1 (0 – 4)
≥ Advanced fibrosis [b]	32 (18%)	18 (19%)	14 (16%)

Note: SD= standard deviation; IQR= interquartile range

Except for age and gender, data were unavailable for two participants recruited in D3FEAT. Missing values are reflected in the frequency distributions for each variable.

[a] Measured using the AUDIT-C test

[b] Advanced fibrosis was defined as having a METAVIR score of F3 or higher

Table 2: Changes in behavioural outcomes during and following direct-acting antiviral treatment for hepatitis C virus infection among people with recent injection drug use or receiving opioid agonist treatment (OAT) recruited and followed in SIMPLIFY and D3FEAT, by incremental study visits (N= 190)

Variable	Adjusted OR (95% CI) [a,b]	*p*-value
Injection drug use, past month	0.96 (0.92 - 0.99)	0.02
Opioid injection, past month	0.95 (0.92 - 0.99)	0.01
Stimulant injection, past month	0.98 (0.94 - 1.02)	0.33
Sharing injection equipment, past month	0.87 (0.80 - 0.94)	<.01
Alcohol use, past month	0.99 (0.95 - 1.04)	0.75
Current OAT	0.99 (0.97 - 1.02)	0.45
Non-injecting opioid use, past month	0.96 (0.91 - 1.01)	0.16
Non-injecting stimulant use, past month	1.00 (0.97 - 1.03)	0.94

Note: OR= odds ratio; CI= confidence interval;

[a] Adjusted for OAT at each visit

[b] The estimated OR indicates the average behaviour change across two consecutive visits, irrespective of time lapses between visits.

Figure 1: Proportion reporting injecting drug use and sharing of injection equipment (A), median alcohol use (B) and proportion receiving opioid agonist treatment (OAT) and non-injecting drugs (C) at each visit, during and following direct-acting antiviral treatment for hepatitis C virus infection among people with recent injection drug use or receiving OAT recruited and followed in SIMPLIFY and D3FEAT (N= 190). Drug use outcomes and OAT refer to the past month and current period, respectively. Baseline visit refers to the date of treatment initiation. Follow-up periods 1, 2 and 3 correspond to weeks 60, 84 and 108 since treatment initiation, respectively. At screening, the sample size is 188 rather than 190 because behavioural data were unavailable for two participants recruited in D3FEAT. Abbreviations: SCR, screening BL, baseline; W, week; ETR, end of treatment; SVR, sustained virological response, FU, follow-up.

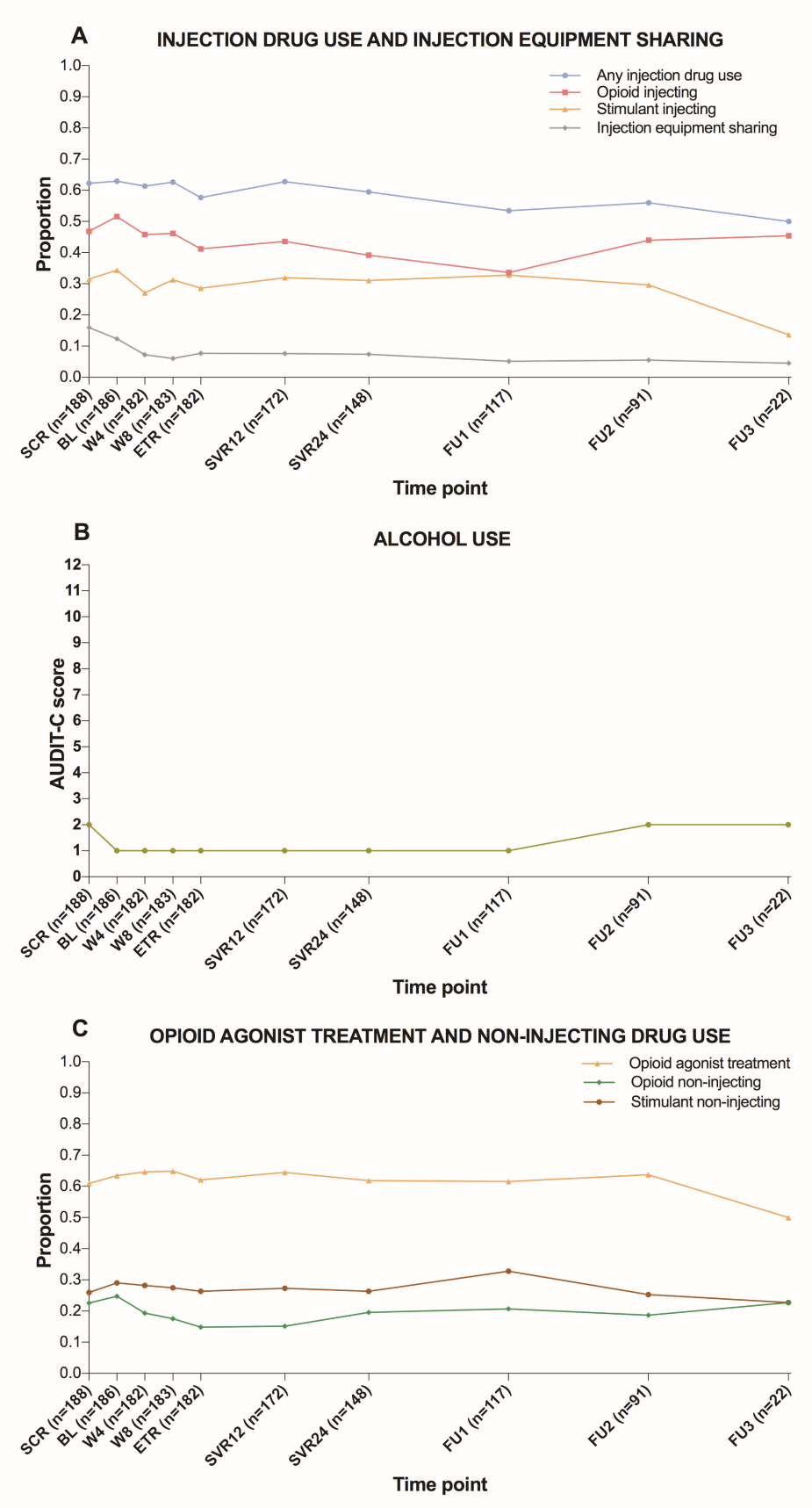
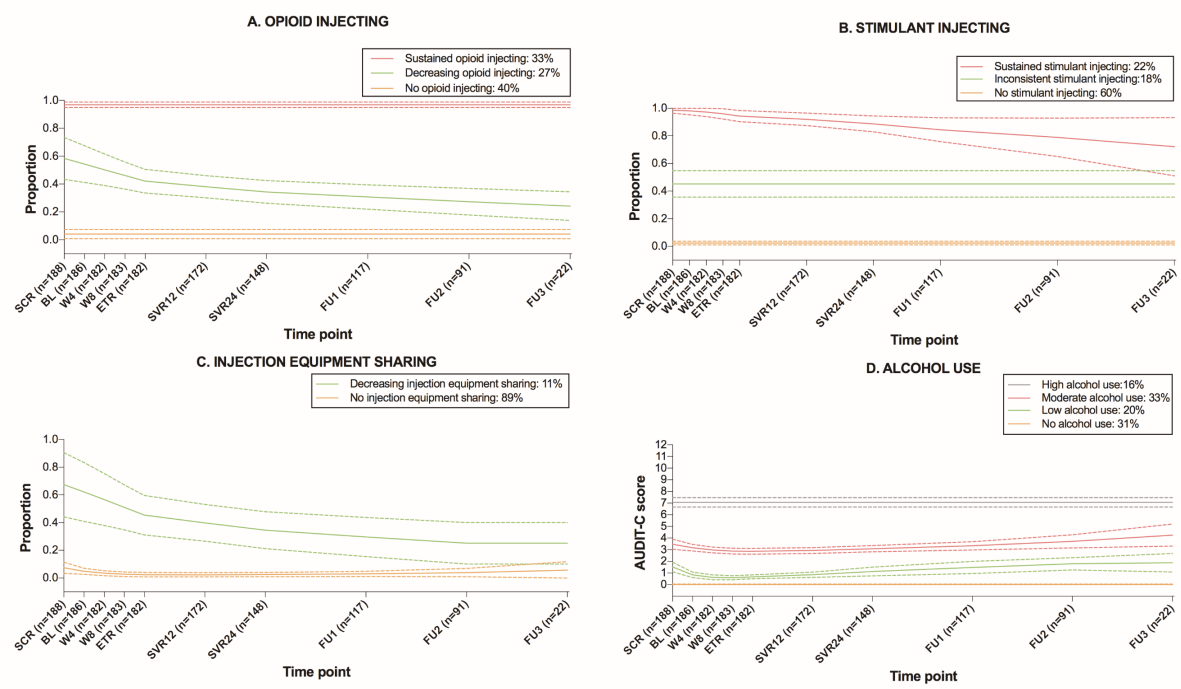

A
INJECTION DRUG USE AND INJECTION EQUIPMENT SHARING
Any injection drug use
Opioid injecting
Stimulant injecting
Injection equipment sharing
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
SCR (n=188)
BL (n=186)
W4 (n=182)
W8 (n=183)
ETR (n=182)
SVR12 (n=172)
SVR24 (n=148)
FU1 (n=117)
FU2 (n=91)
FU3 (n=22)
Time point
B
ALCOHOL USE
AUDIT-C score
12
11
10
9
8
7
6
5
4
3
2
1
0
SCR (n=188)
BL (n=186)
W4 (n=182)
W8 (n=183)
ETR (n=182)
SVR12 (n=172)
SVR24 (n=148)
FU1 (n=117)
FU2 (n=91)
FU3 (n=22)
Time point
C
OPIOID AGONIST TREATMENT AND NON-INJECTING DRUG USE
Opioid agonist treatment
Opioid non-injecting
Stimulant non-injecting
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
SCR (n=188)
BL (n=186)
W4 (n=182)
W8 (n=183)
ETR (n=182)
SVR12 (n=172)
SVR24 (n=148)
FU1 (n=117)
FU2 (n=91)
FU3 (n=22)
Time point

Figure 2: Trajectories of behavioural outcomes during and following direct-acting antiviral treatment for hepatitis C virus infection among people with recent injection drug use or receiving opioid agonist treatment recruited and followed in SIMPLIFY and D3FEAT (N= 190). Solid lines represent the estimated probability of each behavioural outcome for each group and dashed lines represent 95% confidence intervals. Behaviours refer to the past month period. Baseline visit refers to the date of treatment initiation. Follow-up periods 1, 2 and 3 correspond to weeks 60, 84 and 108 since treatment initiation, respectively. At screening, the sample size is 188 rather than 190 because behavioural data were unavailable for two participants recruited in D3FEAT. Example of interpretation: for stimulant injecting, 22% of participants injected stimulants at nearly all visits, 18% oscillated between injecting and non-injecting patterns and 60% never injected. Abbreviations: SCR, screening BL, baseline; W, week; ETR, end of treatment; SVR, sustained virological response, FU, follow-up



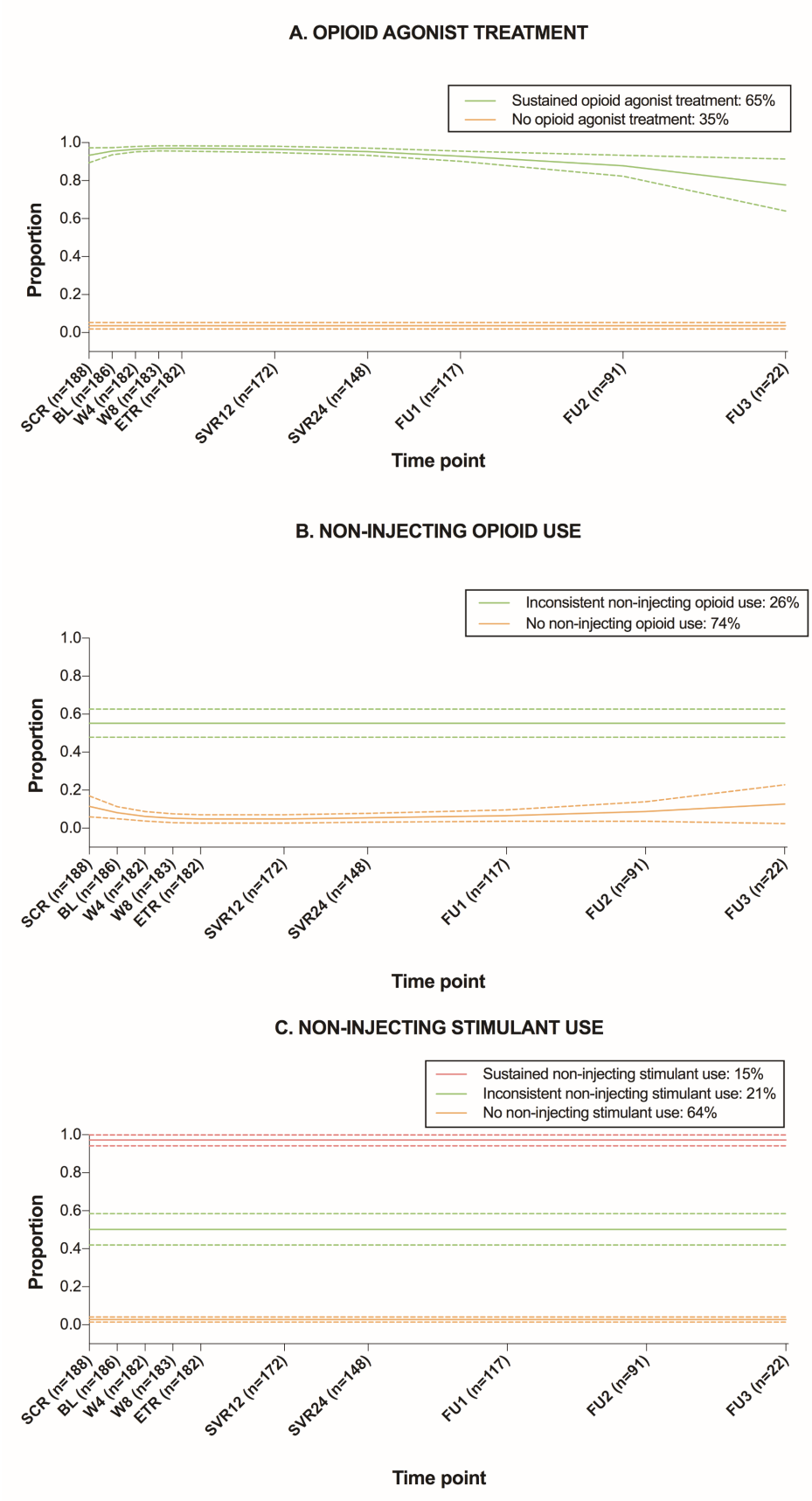
Supplementary Table 1: Model selection criteria in group-based trajectory analyses

Variable	Model	No. of groups	Polynomial order	BIC	Ref	Bayes factor
Opioid injection	A	1	2	-1016.62	NA	NA
	B	2	2 2	-686.35	A	3.68E-144
	C	3	2 2 2	-654.41	B	1.34E-14
	D	4	2 2 2 2	-654.64	C	1.26
	E	3	0 1 0	-639.9	C	3.97E-07
Stimulant injection	A	1	2	-915.77	NA	NA
	B	2	2 2	-592.35	A	3.47E-141
	C	3	2 2 2	-570.14	B	2.26E-10
	D	4	2 2 2 2	-577.68	C	1.88E+03
	E	3	0 0 1	-553.27	C	2.50E-11
Sharing injection equipment	A	1	2	-431.62	NA	NA
	B	2	2 2	-385.31	A	7.72E-21
	C	3	2 2 2	-392.82	B	1.83E+03
	D	2	2 1	-381.68	B	2.65E-02
Alcohol use	A	1	3	-3961.75	NA	NA
	B	2	3 3	-2695.25	A	0
	C	3	3 3 3	-2413.17	B	3.12E-123
	D	4	3 3 3 3	-2353.37	C	1.07E-26
	E	5	3 3 3 3 3	-2313.6	D	5.35E-18
	F	5	0 3 2 2 0	-2288.76	E	1.63E-11
	G	4	0 3 2 0	-2330.88	D	1.71E-10

For each behavior, the last row presents the final model

NA: non-applicable

Supplementary Figure 1: Trajectories of receipt of opioid agonist treatment (OAT; A), and non-injecting opioids (B) and stimulant use (C) use during and following direct-acting antiviral treatment for hepatitis C virus infection among people with recent injection drug use or receiving OAT recruited and followed in SIMPLIFY and D3FEAT (N= 190). Solid lines represent the estimated probability of each behavioral outcome for each group and dashed lines represent 95% confidence intervals. OAT and drug use outcomes refer to the current and past month period, respectively. Baseline visit refers to date of treatment initiation. Follow-up periods 1, 2 and 3 correspond to weeks 60, 84 and 108 since treatment initiation, respectively. At screening, the sample size is 188 rather than 190 because behavioural data were unavailable for two participants recruited in D3FEAT. Abbreviations: SCR, screening BL, baseline; W, week; ETR, end of treatment; SVR, sustained virological response, FU, follow-up.


A. OPIOID AGONIST TREATMENT
Sustained opioid agonist treatment: 65%
No opioid agonist treatment: 35%
Proportion
1.0
0.8
0.6
0.4
0.2
0.0
SCR (n=188)
BL (n=186)
W4 (n=182)
W8 (n=183)
ETR (n=182)
SVR12 (n=172)
SVR24 (n=148)
FU1 (n=117)
FU2 (n=91)
FU3 (n=22)
Time point
B. NON-INJECTING OPIOID USE
Inconsistent non-injecting opioid use: 26%
No non-injecting opioid use: 74%
Proportion
Time point
C. NON-INJECTING STIMULANT USE
Sustained non-injecting stimulant use: 15%
Inconsistent non-injecting stimulant use: 21%
No non-injecting stimulant use: 64%
Proportion
Time point

Supplementary Table 2: Descriptive characteristics at study entry for people with recent injection drug use or receiving opioid agonist treatment (OAT) recruited in SIMPLIFY and D3FEAT (N= 190), stratified by whether or not they were retained in follow-up

Variable	Retained N=151	Not retained N=39	p-value
Age, years [Mean (SD)]	47 (9)	44 (10)	0.09
Male gender	112 (74%)	29 (74%)	0.98
Completed high school education	75 (50%)	17 (46%)	0.68
Unstable housing, past 6 months	24 (16%)	9 (23%)	0.29
Any injection drug use, past month	95 (63%)	22 (56%)	0.46
Opioid injection, past month	70 (46%)	18 (46%)	0.98
Stimulant injection, past month	46 (31%)	12 (32%)	0.95
Non-injected opioid use, past month	35 (23%)	8 (21%)	0.76
Non-injected stimulant use, past month	43 (29%)	6 (16%)	0.10
Sharing of injection equipment, past month	21 (15%)	7 (18%)	0.68
Currently receives OAT	89 (59%)	27 (69%)	0.26
Alcohol use [a] [Median (IQR)]	1 (0 - 4)	2 (0 - 5)	0.69

Note: SD= Standard deviation; IQR= interquartile range

[a] AUDIT-C score

Supplementary Table 3: Changes in behavioral outcomes during and following direct-acting antiviral treatment for hepatitis C virus infection among people with recent injection drug use or receiving opioid agonist treatment (OAT) recruited in SIMPLIFY and D3FEAT, and retained in follow-up (N= 151)

Variable	Adjusted OR (95% CI) [a]
Injection drug use, past month	0.96 (0.92 - 0.99)
Opioid injection, past month	0.95 (0.92 - 0.99)
Stimulant injection, past month	0.98 (0.94 - 1.03)
Sharing injection equipment, past month	0.88 (0.81 - 0.96)
Alcohol use	1.00 (0.95 - 1.05)
Current OAT	0.99 (0.97 - 1.02)
Non-injecting opioid use, past month	0.97 (0.92 - 1.02)
Non-injecting stimulant use, past month	0.99 (0.96 - 1.02)

Note: OR= odds ratio; CI= confidence interval

[a] Adjusted for OAT at each visit

CHAPTER 6: SOCIOECONOMIC STABILITY AND OPIOID AGONIST TREATMENT ARE ASSOCIATED WITH LOWER INJECTION FREQUENCY AMONG PEOPLE WITH DISTINCT TRAJECTORIES OF INJECTION DRUG USE

This chapter is currently under review for publication:

Artenie AA, Fortier E, Høj S, Minoyan N, Gauvin L, Sylvestre M.-P., Jutras-Aswad D, Bruneau J. Socioeconomic stability and opioid agonist treatment are associated with lower injection frequency among people with distinct trajectories of injection drug use. Addiction [Submitted November 14, 2019]

Contributions: Andreea Adelina Artenie conceptualized and designed the study in collaboration with Julie Bruneau. Andreea Adelina Artenie conducted the statistical analyses and drafted the first version of the manuscript. Julie Bruneau and Didier Jutras-Aswad were co–principal investigators of the HEPCO Cohort at the time of this study. All of the authors contributed to the interpretation of results and critical revisions of the manuscript for important intellectual content. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Study overview in the context of this thesis: The global movement currently advocating for HCV treatment-as-prevention, which prioritises PWID in order to achieve the most population-level benefits, has been critiqued for overly medicalising the public health response to HCV infection, to the detriment of addressing broader health and social needs in this population [58-61]. In order to reap the full benefits of HCV prevention and costly antiviral therapies, premature deaths from acquisition risks, now exacerbated by the opioid crisis, need to be addressed [3, 64, 65]. For many PWID, poverty, homelessness, violence, involvement in the street-based economy, the demands of funding and maintaining an illicit drug dependency, and access to OAT and needle and syringe programs, all take precedence over HCV prevention or treatment [52, 53, 55-57]. Moving beyond HCV

as the primary focus of research, in Chapter 6, I examined the associations between three modifiable factors- OAT, housing and income, and patterns of injection among PWID. Recognizing that injection patterns are dynamic and sustained cessation is achieved by a fraction of individuals, I examine the extent to which these three factors can influence injection frequencies among PWID with diverse and enduring trajectories of injection drug use.

Socioeconomic stability and opioid agonist treatment are associated with lower injection frequency among people with distinct trajectories of injection drug use

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6.1 ABSTRACT

Background: We characterized trajectories of injection drug use in a community-based sample of people who inject drugs (PWID) over 7.5 years, and examined the extent to which three modifiable factors- housing, income and opioid agonist treatment relate to injection frequencies across distinct trajectories.

Methods: We used 2011-2019 data from a prospective cohort of PWID in Montreal with repeated follow-up at three- or one-year intervals, when participants reported recent injection patterns, socioeconomic circumstances and addiction treatment. We defined injection frequency as the number of injection days (0-30), reported for each of the past three months. We used group-based trajectory modeling to estimate trajectories of injection and the trajectory group-specific average shift upward/downward associated with exposure to each time-varying modifiable factor.

Results: Based on 19,527 injection frequency observations accrued by 529 PWID (18.3% female, median age: 41), we identified five trajectories: sustained injection (24% infrequent; 20% fluctuating; 14% frequent), gradual decline (12%), and cessation (29%). Stable housing, stable income sources and opioid agonist treatment were each independently associated with a lower injection frequency in nearly all trajectory groups (range: 2-14 fewer injection days/month).

Conclusion: Despite the observed diversity in trajectories of injection, socioeconomic stability and opioid agonist treatment were consistently associated with a lower injection frequency.

6.2 INTRODUCTION

Of the estimated 15.6 million people who inject drugs (PWID) globally, 18% are living with human immunodeficiency virus (HIV) and 52% have been infected with hepatitis C virus (HCV) [310]. The public health burden associated with injection drug use is also reflected in the increased risk of overdose, suicide and overall mortality among PWID compared to the general population [1].

Given the considerable reductions in injection-related harm during periods of injection cessation, episodes of cessation and associated determinants have been the focus of several investigations to date [240, 242-245, 248-250, 311]. Although individual experiences and circumstances surrounding cessation are diverse [255, 312], factors reflecting socioeconomic stability such as housing and income, and opioid agonist treatment (OAT) have been consistently identified as key in enabling these episodes [240, 242-245, 248-250, 311]. All prior studies, however, have examined injection cessation as a discrete endpoint, generally in reference to a one-month to 12-month period, despite the widely-recognized view of drug dependence as a chronic, relapsing condition [313].

For many PWID, short-term behavioral changes are not sustained [248, 249] and do not reflect long-term injection patterns, which oftentimes extend over decades [77]. Only two prospective studies, with multiple repeated measures of injection drug use patterns and long-term follow-up, have characterized trajectories of injection drug use over time [77, 252]. In Baltimore, Maryland, five distinct trajectory profiles of drug injection were noted in a sample of PWID followed for 20 years: two “use” patterns (32% engaged in persistent injection, and 16% fluctuated between episodes of cessation and relapse) and three injection cessation patterns (19% early cessation, 16% delayed cessation, and 18% late cessation) [77]. Five broad trajectory patterns were also documented among PWID in Amsterdam [252]. In three of the five groups identified, injection was sustained over time (23% infrequent, 19% variable and 15% daily), whereas in the other two, it declined (32% gradually and 12% rapidly) [252].

Collectively, these studies suggest that long-term injection patterns are heterogeneous among PWID and that sustained cessation is achieved by a fraction of individuals, oftentimes following

long periods of injection. For PWID unable or unwilling to completely stop, reducing the frequency of injection may be an achievable target, and is a favorable interim alternative because of the diminished risk of injection-related harms [314, 315]. However, the extent to which socioeconomic circumstances and addiction treatment can influence injection frequencies among PWID with diverse and enduring trajectories of injection drug use remains unexamined. Because these factors closely reflect underlying contextual and structural forces surrounding injection drug use [237], findings can guide the development of appropriate public health and social initiatives. Our objectives were therefore (i) to characterize long-term trajectories of injection drug use among active PWID living in a large urban North-American city and (ii) to examine how housing, income and OAT relate to injection frequency in the context of these diverse longitudinal injection patterns.

6.3 METHODS

Study design and population

We used observational data collected in HEPCO, an ongoing community-based prospective cohort of PWID living in Montreal, initiated in November 2004. The primary aims of HEPCO are to investigate factors associated with incident HCV infection and the natural history of HCV infection following seroconversion. Secondary aims are to examine access to care for HCV infection and estimate HIV incidence rates. Our recruitment and follow-up criteria have been previously published [41, 75]. Briefly, HEPCO recruits participants through addiction treatment agencies, community-program referrals and street-level strategies such as word-of-mouth. To be eligible, participants must report having injected drugs within the previous six months and be 18 years of age or older. At each visit, participants answer an interviewer-administered behavioral questionnaire and are tested for HCV antibody or RNA. Follow-up visits are scheduled according to the participants' HCV infection status, in line with the cohort's aims. HCV-RNA negative participants and those who seroconvert during follow-up are followed every three months in order to address the primary aims of the study. Chronically HCV-infected PWID (HCV antibody and RNA positive) are followed at one year-intervals to address secondary aims. All participants

newly infected with HCV or HIV during follow-up are provided with post-test counselling and are systematically referred for medical follow-up at the Addiction Medicine program of the Centre Hospitalier de l'Université de Montréal, which offers multidisciplinary services for patients with drug-related problems, including hepatitis C and HIV treatment. Participants sign an informed consent form in compliance with institutional review board regulations of the Research Centre of the CHUM and receive a small stipend (Can$15–$20) at each visit.

This study was restricted to data collected as of March 2011, at which time the HEPCO protocol and questionnaire were updated to collect detailed information on injection frequency, until March 2019. During this period, 743 PWID were followed, of whom 468 (63%) were enrolled prior to March 2011 and 275 (37%) were newly recruited. Consistent with a previous study examining trajectories of injection drug use among active PWID [77], participants were included if they reported injection during a minimum of two visits, and had at least three follow-up visits (the minimum number of assessments needed to inform group-based trajectory modelling [316]).

Study variables

The HEPCO questionnaire elicited detailed information on sociodemographic characteristics, drug use patterns and addiction treatment. We defined the outcome variable for trajectory analyses as the number of injection days (0-30) in each of the past three months, reported at each study visit. We considered three modifiable factors in relation to frequency of injection across trajectories– housing conditions, sources of income and OAT – in line with previous studies highlighting their role in promoting short-term injection cessation among PWID [240, 242-245, 248-250, 311]. As previously [115], we defined "stable housing" as living in an apartment or a house long-term as opposed to living in apartments or hotels rented on a monthly basis, in shelters, or on the street. Because most participants reported receiving income through social assistance (80%), we defined "exclusively stable income sources" as obtaining income exclusively through government benefits (welfare, unemployment benefits) and/or full-time or part-time employment, compared to income including street-based or illegal activities (e.g., panhandling, informal recycling, sex

work, drug dealing). We defined "OAT" as maintenance treatment with methadone or buprenorphine/naloxone. As with injection frequency, housing was assessed separately for each of the past three months. Because income and OAT were assessed in reference to the past three months globally, the values recorded at each visit were assigned to each of the past three months.

Sociodemographic variables measured at the first questionnaire from each participant as of March 2011 (henceforth, referred to as baseline), used to characterize trajectory groups, included age and duration of injection (years), self-reported gender (male/female), and education (having completed high school, yes/no). We also compared trajectory groups according to baseline assessments of the types of drugs used in the past three months: cocaine, opioids, alcohol and cannabis. Injection of other substances, such as amphetamine, was uncommon (i.e., <10%). Because most participants use alcohol, we also included a measure of binge drinking, as a measure of excessive alcohol use [317]. This variable was defined as having consumed ≥5 or ≥4 drinks in one occasion in the past month, for men and women, respectively [317].

Statistical analyses

We used group-based trajectory modelling to identify groups of individuals with similar patterns of injection frequency over the course of the study follow-up. Based on a finite mixture modeling strategy, this method identifies relatively homogeneous clusters of trajectories of stability or change over time in the presence of repeated observations [316]. Trajectories were estimated via maximum likelihood using the PROC TRAJ macro, embedded in SAS v. 9.4 (SAS Institute, Inc., Cary, North Carolina) [318].

We defined follow-up time as the number of months since baseline. Participants were censored at their last study visit or, alternatively, after 7.5 years of follow-up, when there were fewer than

50 remaining participants. We included this latter criterion to minimize the impact of small number of observations at later follow-up visits on the precision of trajectories.

We estimated a series of models, considering different trajectory group numbers and shapes, guided by prior research on trajectories of injection drug use [77, 252]. Starting with a quartic specification for trajectory shape, we first considered models with up to five trajectories [77, 252], and selected the model that maximized the Bayesian information criteria (BIC) [316]. For each trajectory, we then obtained more parsimonious models by excluding polynomial terms that did not attain statistical significance at the 5% level, in a step-wise manner. As part of the model estimation, each participant was assigned a posterior probability of belonging to each trajectory group and then classified into the single group for which he/she had the highest probability. The final model was assessed for goodness of fit based on average posterior probabilities for each of the groups, odds of correct classification, and comparison of model-estimated and posteriorly-assigned group probabilities. Adequate fit is indicated by average posterior probabilities ≥0.7, odds of correct classification ≥5, and close agreement between model-estimated and posteriorly-assigned group probabilities [319].

Previous studies have indicated that housing and income stability and OAT are themselves likely to fluctuate over time [300, 320, 321]. To examine associations between these time-varying factors and injection frequency while taking into account long-term injection trajectories, we included them in the base model. In this context, for each factor, we estimated trajectory group-specific coefficients and 95% confidence intervals (CI) to indicate the average shift upward/downward in the trajectory associated with exposure to each factor relative to no exposure. The estimated coefficients can be interpreted as: given membership in a trajectory group, how much higher (if coefficient is positive) or lower (if coefficient is negative) is the injection drug use trajectory for a unit increase in the covariate.

6.4 RESULTS

Description of study sample

Of 743 participants followed in HEPCO between March 2011 and 2019, 578 had at least three study visits, and of these, 529 had at least two visits where recent injection was reported. Relative to participants who had at least three study visits, those who did not (n= 165) were younger, had a slightly higher median injection frequency at baseline, and were less likely to report stable housing and exclusively stable income sources (Suppl. Table 1). Of the 578 participants with at least three follow-up assessments, participants who did not report injection at a minimum of two study visits (n= 49) were older, had a lower median past-month injection frequency and were less likely to report stable housing relative to those who did (n= 529; Suppl. Table 2).

The 529 participants included in this study contributed 6,509 visits during a 7.5-year follow-up period [98 (1.5%) visits were excluded because fewer than 50 participants per visit remained in follow-up after 7.5 years]. The median number of visits and follow-up time (years) per participant was 11 (interquartile range [IQR]: 6-17) and 4.9 (IQR: 3.1 - 6.6), respectively. Because injection frequency was recorded for each of the past three months at each visit, a total of 19,527 observations of injection frequency were recorded, equivalent to a median of 33 observations per participant. Table 1 summarizes the distribution of key factors at baseline and across selected visits (yearly intervals) during follow-up. A minority of participants were female (18.3%), with median age and duration of injection at baseline of 41 and 14 years, respectively.

Trajectories of injection frequency

The five-group solution provided the best fit (Suppl. Table 3). Both the average posterior probabilities and the OCC indicated adequate fit, as did a close resemblance between estimated and assigned group probabilities (Table 2). Figure 1 displays trajectories of injection frequency and 95% CI over the 7.5-year follow-up. We identified three groups in which frequency of injection was persistent over time: “infrequent injection, sustained” (24%), characterized by an average of 8-10 days of injection in a month, “fluctuating injection, sustained” (20%),

characterized by oscillations between 10 and 20 days of injection in a month, and "frequent injection, sustained" (14%), characterized by injection nearly every day of the month. We also noted two groups in which frequency of injection displayed a downward trend over time: "infrequent injection, cessation" (29%), characterized by a low frequency of injection initially (~5 days/month) decreasing to no injection over the first 3 years, and "frequent injection, declining" (12%), characterized by a high frequency of injection initially (~20 days/month) slowly decreasing to very low levels (~3 days/month). The median number of visits and total follow-up time across trajectory groups were similar (Suppl. Table 4)

Table 3 displays the baseline characteristics of participants assigned to each trajectory group. Participants assigned to the "fluctuating injection, sustained" and "frequent injection, sustained" groups were younger and had a shorter duration of injection compared to those in the other groups. PWID in the "frequent injection, sustained" group were the most likely to be female and to inject both cocaine and opioids, and least likely to report alcohol binging. In addition to being relatively older, PWID in the "infrequent injection, cessation", "infrequent injection, sustained" and "frequent injection, declining" groups were more likely to use non-injected cocaine. Participants in the "infrequent injection, cessation" group were the most likely to inject cocaine and not opioids, to drink alcohol, and to have had at least one binge episode. Education and cannabis use displayed little variation across trajectory groups.

Associations between modifiable factors and trajectory-group specific injection frequency

Considered individually, the three modifiable factors assessed – stable housing, exclusively stable income sources, and OAT – were associated with a lower injection frequency in each of the five trajectory groups (Table 4). In the multivariable model, nearly all associations remained statistically significant. The magnitude of the coefficient varied depending on the factor and trajectory group, spanning a range of 2 to14 fewer injection days. The sole exception was OAT, which was no longer associated with injection frequency in the "fluctuating injection, sustained" group.

6.5 DISCUSSION

Similar to previous studies [77, 252], among PWID followed in HEPCO throughout a 7.5-year period, the long-term patterning of injection frequency (days injected/month) could be broadly summarized into five distinct profiles. We noted three groups characterized by sustained injection at different frequencies (24% infrequent; 20% fluctuating; 14% frequent), one depicted by a gradual decline (12%), and another ending in sustained cessation (29%). These long-term injection patterns were closely related to the stage of injection career and drug preferences of participants. Compared to younger PWID with a shorter injection history, participants who were older and had a longer history of injection were more likely to decrease their injection frequency over time, achieve sustained cessation, or engage in a lower injection frequency throughout. In addition to being younger, PWID with a persistent trajectory of frequent injection seemed to have a relatively heavier drug use profile, with nearly two-thirds reporting injection of both, cocaine and opioids, and nearly half indicating non-injected cocaine use. Conversely, PWID who achieved injection cessation or had a steady pattern of infrequent injection were more likely to use cocaine by injection and by other routes of administration, possibly suggesting a voluntary harm reduction decision to avoid parenteral exposure to bloodborne pathogens [322]. However, PWID who achieved cessation were also more likely to report alcohol binges, associated with other health-related harms [323]. Taken together, these trajectory-group characteristics call for multidimensional and adaptative interventions to address the diversified needs of PWID.

Despite the observed diversity in individual trajectories of injection drug use, we found that factors relating to everyday living conditions—stable housing and stable income sources, and OAT were almost universally associated with a lower frequency of injection. While previous studies have shown that these factors are associated with short-term episodes of injection cessation [240, 242-245, 248-250, 311], our findings suggest that they are associated with a lower injection frequency among all PWID, irrespective of their underlying injection trajectory and whether or not they are on a path to cessation.

The importance of socioeconomic circumstances as powerful modulators of decision-making around drug-related behaviors has previously been documented among PWID. In a qualitative study examining determinants of injection cessation, having a regular place to live and access to other basic necessities such as stable employment, were the key factors identified among participants attempting to transition away from injection drug use [139]. Unstable housing and involvement in the street-based economy may intensify injection frequency through greater access to drugs, integration of environments where use is an accepted and encouraged practice, and as a result of the stress entailed by these circumstances [324-327]. It is also possible that these contexts are the result of a gradual depletion of one's economic resources given the increased financial demands of more intense drug use [324-327]. Although our study cannot establish temporality of estimated associations, a combination of both scenarios likely occurs in reality [324, 325].

As the recommended first-line treatment for opioid use disorder [25], an overwhelming level of evidence supports OAT in reducing symptoms of withdrawal and craving, thereby promoting injection cessation and reducing injection frequency [193, 194]. OAT programs also present opportunities for behavioral counselling and linkage to other harm-reduction services, which could also contribute to behavioral changes among PWID. It is unclear why the association between OAT and injection frequency was no longer evident among participants with a persistent and fluctuating trajectory after adjusting for stable housing and income. As a group with unstable injection patterns, it is possible that they engaged in OAT only when their socioeconomic circumstances were stable.

By and large, all three modifiable factors considered displayed an independent association with injection frequency, suggesting that improvements in any one of these domains may be accompanied by measurable behavior changes. To help PWID achieve and maintain socioeconomic stability and treatment engagement, adequate public health and social initiatives are needed. For most PWID, social assistance is insufficient to maintain a secure living and drug use, and many individuals have difficulty finding legitimate paid work due to lack of stable

housing, limited employable skills and low levels of education [327]. This emphasizes a need to develop and expand skill-building and employment opportunities and affordable, supportive housing programs that are flexible to the needs and realities of PWID. Housing First interventions, which provide access to permanent housing and supportive services, have been shown to be effective in improving residential stability and drug use among homeless individuals with active illicit drug use [328]. Initiatives to train women who inject drugs in specific economic livelihoods, such as tailoring, have been found to be acceptable and effective in lowering their involvement in sex trade [329, 330]. Similarly, OAT programs that are low-threshold, flexible and focused on maintenance and harm reduction rather than abstinence-oriented are more attractive to PWID and more likely to improve long-term retention in care [331]. To be sustainable, it is largely acknowledged that these initiatives must be complemented by broader policies addressing the structural forces contributing to the health and social disparities among PWID, such as criminalization and stigma [60].

The repeated follow-up of a community-based sample of PWID, combined with detailed assessment of injection patterns, contextual factors and addiction treatment create a unique opportunity to study long-term trajectories of injection and the extent to which modifiable factors relate to injection frequency across distinct trajectories in a manner that reflects their change over time. However, a number of limitations should be noted. First, as with most studies involving difficult-to-track populations [249, 332], some participants were lost to follow-up, potentially affecting the estimated prevalence of trajectory groups or their shape. Because injection frequency did not differ substantially at baseline between participants who had at least three study visits and those who did not, and the median follow-up time was similar across trajectory groups, we believe that losses to follow-up did not have a major impact on our findings. Second, reliance on self-reported data may have been influenced by socially-desirable reporting or recall errors. That said, interviewers were trained to display a non-judgmental attitude in order to minimize the risk of socially-desirable responding, and the recent reference frame of interview questions (i.e., past-month or past three months) minimizes the risk of recall errors. In addition, most studies suggest that self-reported drug-use behaviors of PWID populations are

valid [305]. Fourth, we were not able to establish the temporality of associations between modifiable factors and injection frequency. Additionally, residual confounding cannot be ruled out. Finally, given that our study sample does not constitute a random sample of the broader population of PWID in Montreal, the extent to which findings are generalizable to this population is unclear. Nevertheless, efforts were undertaken to recruit participants from a variety of sources to optimize representativity, and our sample displays characteristics similar to those of other PWID populations in Montreal [333].

6.6 CONCLUSION

In sum, our study suggests that, despite the diversity in injection drug use trajectories among PWID, stable housing, stable income sources and OAT are almost universally related to a lower injection frequency. The consistency of these associations suggests that there are ways to support all PWID in making small behavioral changes that could reduce their risks of injection-related harms, irrespective of whether or not they are in a position to stop injection. While all three factors are amenable to change, to achieve this, efforts are needed to invest in appropriate social and public health initiatives.

Table 1: Summary statistics [a] at select study visits among people who inject drugs followed in HEPCO, Montreal, 2011 – 2019

Covariate	Baseline (Year 0), N= 529	Year 1, N= 343	Year 2, N= 282	Year 3, N=263	Year 4, N= 221	Year 5, N=176	Year 6, N= 121	Year 7, N= 79
Female gender	97 (18.3%)							
Age, Mean (SD)	39.9 (10.4)	41.1 (10.1)	42.4 (10.3)	42.7 (10.5)	45.0 (10.4)	46.3 (10.3)	47.5 (9.9)	51.0 (8.6)
Age, Median (IQR)	40.6 (31.6 - 48.2)	41.6 (32.9 - 49.2)	42.9 (34.0 - 50.6)	43.2 (34.2 - 51.0)	45.0 (36.4 - 53.2)	47.1 (37.3 - 54.6)	48.5 (39.8 - 55.4)	53.7 (45.2 - 58.3)
Duration of injection, Mean (SD)	15.5 (10.6)	16.3 (10.4)	17.9 (10.6)	18.1 (10.7)	20.2 (11.0)	21.1 (10.6)	22.5 (10.8)	26.2 (11.0)
Duration of injection, Median (IQR)	14.4 (6.1 - 22.8)	15.2 (7.2 - 23.4)	16.6 (9.2 - 25.2)	16.9 (9.0 - 25.4)	18.6 (10.8 - 29.3)	19.5 (12.3 - 30.3)	21.2 (12.8 - 32.5)	27.0 (16.3 - 35.6)
Injection frequency [b], past month, Mean (SD)	12.2 (12.0)	10.5 (11.6)	9.6 (12.0)	10.1 (12.1)	9.2 (11.6)	7.9 (11.2)	8.6 (11.3)	8.6 (11.0)
Injection frequency [b], past month, Median (IQR)	7 (1 - 26)	4 (0 - 20)	3 (0 - 20)	3 (0 - 20)	2 (0 - 18)	1 (0 - 12)	2 (0 - 15)	3 (0 - 15)
Stable housing [c]	366 (69.2%)	230 (67.1%)	200 (70.9%)	175 (66.5%)	154 (69.7%)	127 (72.2%)	85 (70.3%)	64 (81.1%)
Exclusively stable income sources [d]	298 (56.3%)	199 (58.0%)	178 (63.1%)	155 (58.9%)	133 (60.2%)	113 (64.2%)	83 (68.0%)	60 (76.0%)
Opioid agonist treatment [d]	180 (34.0%)	141 (41.1%)	120 (42.6%)	121 (46.0%)	93 (42.1%)	67 (38.1%)	54 (44.6%)	32 (40.5%)

Note: IQR= interquartile range; SD= standard deviation

[a] Data are presented as No. (%) unless otherwise indicated

[b] Injection frequency was defined as the number of injecting days (0 – 30) in the past month

[c] Within the past month

[d] Within the past month

Table 2: Goodness of fit statistics based on a five-group solution among 529 people who inject drugs followed in HEPCO, Montreal, 2011 – 2019

Trajectory group	Average posterior probabilities [a]					Model-estimated group prevalence (%)	Posteriorly - assigned group prevalence (%)	Odds of correct classification
	Infrequent injection, cessation	Infrequent injection, sustained	Fluctuating injection, sustained	Frequent injection, decline	Frequent injection, sustained			
Infrequent injection, cessation	0.95	0.05	0.00	0.00	0.00	28.90	29.49	46.74
Infrequent injection, sustained	0.04	0.93	0.03	0.01	0.00	25.00	24.20	39.86
Fluctuating injection, sustained	0.00	0.04	0.92	0.02	0.01	19.90	20.23	46.29
Frequent injection, decline	0.00	0.01	0.04	0.92	0.02	11.80	11.91	85.96
Frequent injection, sustained	0.00	0.00	0.00	0.02	0.98	14.40	14.18	291.28

[a] The probabilities on the diagonal are the average posterior probabilities of group membership among persons assigned to the group, while the off-diagonals show the average posterior probability of group membership among persons not assigned to the group. Probabilities do not sum to one because of rounding.

Table 3: Baseline characteristics [a] associated with trajectory group membership among people who inject drugs followed in HEPCO, Montreal, 2011 – 2019

Variable	Infrequent injection, cessation (N= 156)	Infrequent injection, sustained (N= 128)	Fluctuating injection, sustained (N= 107)	Frequent injection, decline (N= 63)	Frequent injection, sustained (N= 75)
Age, Median (IQR)	42.6 (35.6 - 50.8)	42.8 (34.2 - 48.7)	36.3 (29.8 - 45.0)	39.2 (27.8 - 48.2)	35.4 (28.9 - 45.8)
Female gender	21 (13.5%)	18 (14.1%)	23 (21.5%)	13 (20.6%)	22 (29.3%)
Duration of injection, Median (IQR)	14.5 (5.9 - 22.3)	16.8 (8.1 - 25.8)	11.8 (5.9 - 20.0)	16.0 (3.4 - 25.3)	10.9 (4.0 - 20.7)
Completed high-school education	85 (54.5%)	75 (58.6%)	72 (67.3%)	36 (57.1%)	44 (58.7%)
Cocaine and/or opioids injection [b]					
Cocaine and opioids injection	24 (15.4%)	37 (28.9%)	42 (39.3%)	22 (34.9%)	45(60.0%)
Cocaine and no opioids injection	92 (59.0%)	66 (51.6%)	24 (22.4%)	21 (33.3%)	4 (5.3%)
Opioids and no cocaine injection	40 (25.6%)	25 (19.5%)	41 (38.3%)	20 (31.8%)	26(34.7%)
Non-injection cocaine use [b]	110 (70.5%)	87 (68.0%)	54 (50.5%)	39 (61.9%)	36 (48.0%)
Non-injected opioids use [b]	27 (17.3%)	20 (15.6%)	13 (12.2%)	4 (6.4%)	9 (12.0%)
Alcohol use [b]	120 (76.9%)	90 (70.3%)	78 (72.9%)	35 (55.6%)	35(46.7%)
≥1 binge alcohol episode [c]	79 (50.6%)	49 (38.3%)	37 (34.6%)	16 (25.4%)	15 (20.0%)
Cannabis use [b]	99 (63.5%)	88 (68.8%)	74 (69.2%)	42 (66.7%)	43 (57.3%)

Note: IQR= interquartile range

[a] Data are presented as No. (%) unless otherwise indicated

[b] Within the past three months

[c] Within the past month

Table 4: Associations between socioeconomic stability and opioid agonist treatment and injection frequency according to long-term trajectories of injection among people who inject drugs followed in HEPCO, Montreal, 2011 – 2019

Trajectory group/Factor	Univariable		Multivariable	
	Shift up/down in the trajectory*	95 % CI	Shift up/down in the trajectory*†	95 % CI
Infrequent injection, cessation				
Stable housing	-4.89	-5.97, -4.33	-3.96	-5.02, -2.90
Exclusively stable income sources	-3.92	-5.18, -2.66	-3.03	-4.15, -1.92
Opioid agonist treatment	-4.85	-6.27, -3.43	-2.81	-4.24, -1.38
Infrequent injection, sustained				
Stable housing	-4.63	-5.76, -3.50	-2.79	-3.81, -1.77
Exclusively stable income sources	-8.06	-8.98, -7.13	-6.19	-7.19, -5.19
Opioid agonist treatment	-3.94	-5.23, -2.66	-1.91	-2.95, -0.87
Fluctuating injection, sustained				
Stable housing	-8.32	-9.55, -7.09	-5.39	-6.88, -3.90
Exclusively stable income sources	-10.16	-11.12, -9.21	-8.61	-9.61, -7.62
Opioid agonist treatment	-7.16	-8.41, -5.92	0.04	-1.48, 1.55
Frequent injection, decline				
Stable housing	-9.63	-11.36, -7.89	-11.24	-12.91, -9.56
Exclusively stable income sources	-8.28	-10.08, -6.48	-12.59	-14.10, -11.08
Opioid agonist treatment	-9.00	-11.00, -7.00	-14.05	-15.52, -12.58
Frequent injection, sustained				
Stable housing	-11.60	-13.09, -10.12	-6.42	-7.99, -4.86
Exclusively stable income sources	-9.52	-10.85, -8.20	-3.72	-5.13, -2.31
Opioid agonist treatment	-6.77	-8.20, -5.34	-4.20	-5.61, -2.79

NOTE: CI= confidence interval

* β represent the average shift upward/downward in the trajectory associated with exposure to each factor. Example of interpretation: among PWID in the "infrequent injection, cessation" group, those living in stable housing have, on average, 3.96 fewer injecting days in a month relative to those living in unstable housing ([†]after adjustment for income and OAT)

Figure 1: Trajectories of injection frequency with 95% confidence intervals among 529 people who inject drugs followed in in HEPCO, Montreal, 2011 – 2019

Supplementary Table 1: Baseline characteristics [a] of participants who had a minimum of three study visits and those who did not, followed in HEPCO, Montreal, 2011 – 2019

Variable	Had ≥ 3 study visits (N=578)	Had < 3 study visits (N= 165)	*P* value [b]
Injecting frequency, Median (IQR)	8 (2 - 23)	10 (3 - 26)	0.08
Age, Median (IQR)	41.2 (32.2 - 48.3)	36.1 (29.8 - 47.2)	0.01
Duration of injection, Median (IQR)	14.3 (6.2 - 22.9)	13.4 (6.7 - 21.7)	0.68
Female gender	102 (17.7%)	29 (17.6%)	0.98
Lived in stable housing [c]	383 (66.3%)	96 (58.2%)	0.06
Exclusively stable income sources [d]	331 (57.3%)	82 (49.7%)	0.08
Opioid agonist treatment [d]	191 (33.0%)	47 (28.5%)	0.27

Note: IQR= interquartile range

[a] Data are presented as No. (%) unless otherwise indicated

[b] *P* values were calculated using the Mann-Whitney U test (for continuous variables) and Pearson's $\chi 2$ test statistic (for binary variables).

[c] Within the past month

[d] Within the past three months

Supplementary Table 2: Baseline characteristics [a] of participants who had a minimum of injection episodes and those who did not, followed in HEPCO, Montreal, 2011 – 2019

Variable	Had ≥2 two injection episodes (N= 529)	Had < 2 injection episodes (N=49)	*P* value [b]
Age, Median (IQR)	40.6 (31.6 - 48.2)	45.3 (41.7 - 52.2)	<0.01
Female gender	97 (18.3%)	5 (10.2%)	0.15
Injecting frequency, Median (IQR)	10 (2 - 25)	1 (0 - 6)	<0.01
Duration of injection, Median (IQR)	14.4 (6.1 - 22.8)	13.2 (6.5 - 26.0)	0.74
Lived in stable housing [c]	359 (67.9%)	24 (49.0%)	<0.01
Exclusively stable income sources [d]	298 (56.3%)	33 (67.4%)	0.14
Opioid agonist treatment [d]	180 (34.0%)	11 (22.5%)	0.10

Note: IQR= interquartile range

[a] Data are presented as No. (%) unless otherwise indicated

[b] *P* values were calculated using the Mann-Whitney U test (for continuous variables) and Pearson's $\chi 2$ test statistic (for binary variables).

[c] Within the past month

[d] Within the past three months

Supplementary Table 3: Model selection for group-based trajectory analyses

Model	No. of groups	Polynomial order	BIC	Ref.
A	1	4	-50860.94	-
B	2	4 4	-46594.28	A
C	3	4 4 4	-45119.84	B
D	4	4 4 4 4	-44627.62	C
E	5	4 4 4 4 4	-44290.42	D
G [a]	5	2 2 4 4 3	-44271.86	E

[a] Final model

Supplementary Table 4: Follow-up visits across trajectory groups among people who inject drugs followed in HEPCO, 2011-2019

Trajectory Group	Mean (SD)	Median (IQR)
Infrequent injection, cessation (N=156)	12.3 (7.5)	10 (6 - 17)
Infrequent injection, sustained (N= 128)	13.5 (8.2)	13 (6 - 18.5)
Fluctuating injection, sustained (N= 107)	11.5 (7.5)	9 (5 - 17)
Frequent injection, decline (N= 63)	11.4 (7.4)	10 (6 - 14)
Frequent injection, sustained (N= 75)	13.4 (8.6)	11 (6 - 19)

Note: SD, standard deviation; IRQ, interquartile range

7.0 DISCUSSION

In high-income countries, the burden of HCV infection is carried primarily by PWID [53, 66, 93, 289]. The extraordinary clinical performance of DAAs [34-37] has provided the impetus for the control and elimination of hepatitis C as a public health threat [2, 20]. It is well-acknowledged that HCV elimination efforts require, in addition to expanded HCV treatment access, a strong foundation of harm-reduction programs, particularly OAT and needle/syringe exchange programs, to reduce risk behaviours and HCV transmission [2, 20]. Although there is a clear global mandate to curb the HCV epidemic and a number of tools are available to do so, several key gaps and barriers remain. First, because HCV continues to spread even in settings where coverage of harm-reduction programs is relatively high [7, 113, 163], there is a need to examine how best to optimise the delivery of these interventions. In Chapter 3, I explored whether the dosage of OAT plays a role in influencing the risk of HCV infection, which could help optimise the provision of OAT for HCV prevention. Second, unsubstantiated concerns among providers and policy-makers around ongoing and/or escalating risk behaviours following HCV treatment represent one of the main barriers to increasing treatment uptake among PWID [47, 151, 187]. Because few studies have examined patterns of drug use and sharing behaviours during and following HCV treatment among PWID [235, 236], in Chapters 4 and 5, I examined this question in relation to interferon-based and DAA treatment, respectively. Finally, the high co-morbidity and mortality burden among PWID [1, 84, 85] compels us to look beyond HCV and consider strategies that have potential to reduce injection-related harms, more broadly [58-61]. In Chapter 6, I examined associations between socioeconomic circumstances and OAT and injection frequency among PWID with diverse and enduring trajectories of injection. In the following sections, I summarise the findings of each of the four studies included in this thesis and highlight the key limitations of each. I also discuss their public health implications and future research directions.

7.1 SUMMARY OF FINDINGS, KEY LIMITATIONS AND PUBLIC HEALTH IMPLICATIONS

OAT dosage adequacy and HCV infection risk

Building on well-established evidence surrounding the value of OAT in reducing the risk of HCV infection [164] and the role of adequate OAT dosage in enhancing treatment outcomes [26-28, 202, 203], in Chapter 3, I explored the relationship between OAT dosage and HCV infection risk. Capitalizing on longitudinal data collected as part of HEPCO, which is a long-standing prospective cohort study of PWID in Montreal (2004-2017), I found that the risk of HCV infection varies substantially according to the level of prescribed OAT dose and patient-perceived dosage adequacy. The lowest risk of HCV infection was observed among people prescribed higher doses that they also perceived to be adequate. Conversely, people prescribed low doses that they also perceived to be inadequate had a nearly two-fold greater risk of HCV infection relative to patients not receiving treatment. Overall, estimates were consistent with a graded effect of prescribed OAT dosage and patient-perceived dosage adequacy on risk of HCV infection. Importantly, findings were indicative of the potential for both protective and harmful effects of OAT dosage, depending on these factors.

These findings should be considered and interpreted in the context of potential biases affecting the internal validity of estimates. As described in Chapter 3, confounding, selection and information bias are all likely to have affected our estimates. Residual confounding is a particular concern, despite our careful attempt to minimize it through adjusting for multiple potential confounders. For example, the reduced risk of HCV infection observed among PWID whose dosage of OAT was high and perceived to be adequate could be partly attributed to having a greater motivation to adopt healthy behaviours relative to those not on OAT (e.g., to engage in healthcare services and to reduce HCV risk behaviours). Conversely, among PWID whose dosage of OAT was low and inadequate, a greater disease severity could lead to increased risk-taking behaviours and a lower motivation or capacity to initiate OAT. Selection bias due to losses to follow-up is also possible if participants who stopped being followed-up were systematically different in terms of OAT dosage adequacy and risk of HCV infection relative to those who

remained in the study. While it is encouraging that participants who had and did not have at least two study visits did not appear to be different in terms of OAT dosage adequacy and other characteristics at baseline, the risk of selection bias cannot be ruled out. For example, if over the course of the follow-up, participants prescribed a low OAT dose that they perceived to be inadequate were more likely to drop out of the study and to acquire HCV relative to those not receiving OAT, then the true HR comparing these two groups may have been under-estimated. Finally, if certain variables that were identified as potentially confounding were also intermediates on the causal path from OAT to HCV infection, such as incarceration [194], conditioning on such factors could artificially dilute the effect estimates. Some methods to reduce this kind of bias have been developed, such as marginal structural models estimated through inverse probability of treatment weighting, [334]. However, this approach has been developed in the context of large cohort studies [335] and is difficult to apply to relatively smaller studies, like ours, especially when i) fewer participants are retained at later follow-up visits, and ii) the exposure variable has multiple levels.

The difficulty in defining what constitutes an adequate OAT dose should also be acknowledged, given that the range of effective doses in the population is broad [336]. Furthermore, patients' preferences and expectations with regards to OAT can vary as well, with some participants seeking complete abstinence, and others looking to stabilize their use patterns while continuing to inject drugs [30]. This difficulty has been highlighted in a commentary written in response to our paper [337]. Although categorizing a continuous variable can lead to loss of information and possible biased estimates, as the relation between the independent and the dependent variable is assumed to be constant within intervals, we opted to categorize prescribed OAT dose for several reasons. First, since our exposure is a combined variable of OAT receipt (yes/no), prescribed dose and perceived dosage adequacy, it was not possible to examine the combined association of prescribed dose, in continuous form, with perceived dosage adequacy, without excluding all participants who are not exposed to OAT. Second, we combined data for two medications (methadone and buprenorphine), each with different dose regimens. Third, we did not expect to see a linear relationship between prescribed dose and HCV infection risk over the entire dose

range. For example, a systematic review concluded that methadone doses above a certain threshold (100-120mg) may not confer an additional prevention benefit [26]. As we highlighted in our response to the commentary[338], the thresholds we used in our study were based on the best available evidence around optimal effective doses at the population level [25, 199-201]. In addition, we explored potential heterogeneity across binary (i.e., high/low) categories of OAT dosage, informed by a priori-specified thresholds, with high/moderate/low categories based on tertiles observed in our sample, as a sub-analysis, which provided further support to our main findings. In recent years, instruments like the Opiate Dosage Adequacy Scale have been developed to help clinicians tailor the OAT dosage to patients' needs, which could be considered in the context of future studies on this topic [339].

Although a number of limitations may have affected our estimates, our results are in line with prior studies that showed a close relationship between the level of prescribed dose, patients' subjective perceptions of the adequacy of their dose and outcomes such as retention in treatment, management of withdrawal symptoms and reductions in illicit opioid use [26-28, 202, 203]. This strong evidence base strengthens the confidence we place in our findings. The greater risk of HCV infection in PWID receiving low and inadequate doses relative to those not enrolled in treatment was the one finding that was unanticipated. Possibly, more frequent treatment discontinuation or brief interruptions in this group could lead to greater withdrawal symptoms and increased risk-taking than ever before [340], although further research is needed to understand the underlying mechanism. Altogether, our study supports the need to ensure that OAT programs provide care following best-practice guidelines and that clinicians work with patients to identify a suitable dose that is most likely to be clinically effective while meeting their individual needs. For PWID among whom a higher dose is not indicated or not desired, access to alternative agonist pharmacotherapies, such as heroin-assisted treatment [25], and harm reduction services may be considered. Offering a diversified set of complementary HCV prevention strategies could help meet the varied needs and preferences of PWID [25].

Our findings are particularly timely considering evidence around the pressing need to scale-up OAT in order to achieve the HCV elimination goals [2, 20]. The WHO recommends that countries provide OAT to more than 40 people per 100 PWID in order to considerably reduce HCV transmission [341], yet a recent systematic review illustrated that most countries are below this threshold [104]. Because the risk of HCV infection does not appear to be systematically reduced for everyone receiving OAT, our study suggests that simply scaling-up OAT access may not be sufficient to achieving these goals, and that the dosage of treatment should be considered as part of our prevention efforts and public health guidelines on HCV elimination.

More broadly, with its novel focus on patients' subjective perceptions regarding the level of adequacy of their dose, our study emphasizes the importance of providing patient-centered care in a vulnerable population who has often experienced stigma and discrimination [342]. This point has been highlighted by a second commentary written in response to our paper[343]. Over the last two decades, there has been a significant rise in opioid use and injection in Canada and the United States [62, 63]. This increase has been paralleled by increasing rates of numerous adverse health outcomes, including HCV and HIV infection and overdose [62, 75, 125, 344]. In this context, our findings provide initial, observational evidence that the active involvement of patients in their care is associated with improved health outcomes, and could pave the way towards integrating the needs and preferences of this marginalized group as a key part of treatment decisions.

Drug use patterns in relation to HCV treatment

Antiviral treatment for HCV infection could play an important role in enhancing the prevention benefit conferred through OAT and other harm-reduction programs [14]. Because uptake of HCV treatment is low among PWID, understanding the influence of treatment receipt on drug use behaviours may have an effect on treatment accessibility for this population. Chapters 4 and 5 of this thesis contribute to the discussions around the potential impact of HCV treatment on drug use and risk behaviours among PWID.

The first study was conducted at a time when interferon therapy was the standard of care for HCV infection and DAA regimens were forthcoming. Drawing on data collected as part of the IMPACT study (2007-2015), I examined short-term changes in injection drug use among PWID in Montreal who were recently infected with HCV and who (i) received treatment, or who were not eligible for treatment because they (ii) had spontaneously cleared the infection or (iii) had contra-indications to therapy, relative to those who chose not to engage in HCV care post-diagnosis. The main finding of this study is that all three groups reported considerably lower odds (66 - 82% lower) of injection drug use at one-year follow-up relative to those who elected not to engage in therapy. PWID who received treatment displayed the greatest reduction in injection drug use, followed by those who had contra-indications to treatment and those who spontaneously cleared the infection.

This study has a number of strengths. Given that all recently-infected PWID were systematically offered access to HCV care, the potential for confounding introduced by factors related to provider characteristics (e.g., willingness to offer treatment depending on addiction severity) was minimised, as everyone was assessed for treatment eligibility and those with contra-indications were included as a separate group. Confounding introduced by patient characteristics (e.g., willingness to engage in HCV care and make drug-related changes depending on severity of HCV-infection symptoms) was also reduced for similar reasons. Additionally, the distinction made between participants based on the reasons for not engaging in HCV care after study enrolment is a novelty relative to prior research [235, 236], and a strength because it permits a more nuanced assessment of drug use changes in relation to different components of HCV care. Two other studies have examined injection drug use patterns in relation to interferon-based HCV treatment [235, 236]. One of them reported a decrease in drug use following HCV treatment [236], whereas the other one found no change [235]. The authors of these investigations did not distinguish among the reasons for non-treatment, potentially explaining the non-significant findings. Altogether, our study suggests that the benefits of HCV assessment and treatment may extend beyond liver-related outcomes to helping PWID modify their injection drug use patterns, at least in the short-term. Additionally, it also indicates that treatment may be only one of several interventions

around HCV care that are likely to positively impact injection drug use behaviours. Among participants who were not eligible to treatment, close monitoring, counselling and care to manage treatment contra-indications (e.g., mental health problems) or to assess spontaneous resolution, may have contributed to decreases in injection drug use [156, 232-234].

Aside for a possible effect of HCV assessment and treatment, it is also possible that the observed associations are, at least partly, attributed to unmeasured confounding, as some individuals may be more likely to make health and behavioural changes in response to acquiring HCV. For example, a higher perceived need for treatment, which has been identified in prior studies as a determinant of treatment initiation [44, 45], could also be linked to a greater inclination to change injection drug use patterns. Inadequate control for a measured covariate could also lead to residual confounding. For example, collapsing the variable duration of injection drug use at the median value could have led to an incomplete adjustment for the estimates of interest if within-category confounding persisted [345]. Finally, socially desirable responding may have also played a role in influencing the effect estimates if participants who received treatment were more inclined to incorrectly indicate cessation of injection drug use (i.e., information bias attributed to differential misclassification of the outcome). However, this risk was diminished in our study by having separate teams involved in providing HCV care and research data collection, and by ensuring patients that their answerers were kept confidential.

More broadly, the generalisability of these findings to the current DAA era is unclear. Indeed, the high side-effect profile of interferon-based regimens required close interaction with health care providers, offering consistent opportunities for interventions aimed at achieving beneficial behavioral change [50]. Because of the high tolerability and simplified treatment, DAA-based therapy is less complex and entails less monitoring, and thus, findings may not be generalizable to the contemporary HCV treatment paradigm.

As a follow-up to this project, in a context where interferon-free DAA regimens had been introduced and become the new standard of care for HCV infection, in Chapter 5, I examined

patterns of drug and alcohol use and injection equipment sharing among PWID during and following DAA-based treatment, capitalizing on data collected as part of SIMPLIFY and D3FEAT. These studies were phase 4 trials evaluating the efficacy of DAA among people with past 6-month injecting drug use or receiving OAT through a network of 25 international sites. In our study, we found that (i) drug and alcohol use remained stable during follow-up or decreased slightly, and (ii) sharing of injection equipment underwent a gradual decline over time. These findings are encouraging, given that sharing behaviors are, ultimately, the main driver of HCV infection among PWID [113]. Importantly, behavioral patterns were not transient but appeared to be sustained during the 2-year follow-up. This was the first and the only study conducted to date to have examined patterns of drug-related behaviours in relation to DAA-based HCV treatment. Not only is this study reflective of the current standard of care in most settings, additional strengths include (i) an assessment of how different types of injected drugs, as well as sharing behaviours, evolve in relation to HCV treatment, (ii) a longer follow-up time, to examine whether drug use patterns are sustained and (iii) a consideration of whether drug use patterns evolved differently for different groups.

A key limitation of this study is the absence of a comparison group of PWID not receiving DAA treatment, preventing our ability to attribute the observed behavioral changes to HCV treatment or any one intervention. In addition, the study was conducted in a selected study population, who has fairly well engaged in care, and may not adequately reflect the broader population of PWID.

It is also important to mention that this study relied on the pooling of two separate studies without accounting for clustering of participants within studies. Typically, pooled analyses should not ignore the heterogeneity across studies, otherwise the estimated confidence intervals could be falsely narrow, leading to misleading results [346]. However, the two studies that were pooled in this case (SIMPLIFY and D3FEAT) were very similar in terms of primary research questions, were implemented by the same research team, in the same settings, and using the same study procedures (e.g., recruitment methods, measures, timing of assessments). Two mentionable

differences exist between the studies: the HCV treatment regimen offered, and patient eligibility criteria related to the recency of injection drug use. The reason for conducting these two studies separately was due to their focus on different treatment regimens, which were developed by different companies for specific HCV infection genotypes; no other patient characteristics determined whether or not one specific treatment was offered. Because the efficacy and safety profile of these medications is remarkably similar (SVR: 94% and 91%; adverse events: 47% and 47%, in SIMPLIFY and D3FEAT, respectively) [294, 295], we did not expect them to have a differential impact on drug use patterns. With respect to patient eligibility criteria for each study, SIMPLIFY only included participants who reported recent injection drug use (defined as injection drug use in the past six months), whereas D3FEAT also included participants who were former PWID (i.e., defined as lifetime) and were currently using OAT. Because our objective with this study was to examine drug use patterns in a population of PWID (regardless of whether or not they were recently injecting), we considered it adequate to pool the two studies.

Each of the two studies presented in Chapters 4 and 5 carries different strengths and limitations, adding different dimensions of evidence to inform the ongoing debate around the potential impact of HCV treatment on drug use and risk behaviours. It is largely acknowledged that HCV treatment engagement creates opportunities to access ancillary health care services and support, receive counselling and discuss behaviour change, all of which have been shown to positively impact drug use patterns in prior studies [156, 232, 233, 278, 280]. Additionally, three of four studies conducted so far, including ours, documented some decreases in drug use following HCV treatment [235, 236, 286, 347]. Collectively, these studies do not support concerns of increasing injection drug use or risk behaviors following HCV treatment [47, 151, 187] and further endorse the removal of barriers to treatment access for all infected PWID, irrespective of ongoing injection drug use. They also suggest that, at least for some PWID, access to HCV treatment and care can prompt motivation to change drug use patterns. Data from Chapter 5 suggests that even in the era of simplified DAA therapies, there may be ways to enhance the delivery of treatment to afford opportunities for harm reduction, as suggested by the decrease in drug use and sharing behaviours observed in some PWID. This finding supports calls to provide counseling, addiction treatment and access to ancillary services alongside HCV treatment to ensure that patients have

access to all the tools necessary to support them in making broader drug use changes [187]. Still, because of competing priorities and concerns [52, 53], the capacity for behaviour change to reduce HCV risk may be limited for some PWID. In this context, in addition to providing access to ancillary health services and support, discussions around the risk for HCV reinfection is key for ongoing monitoring and potential retreatment [157].

As it has been pointed out by Dore et al, "HCV reinfection should not be considered treatment failure, but the inevitable consequence of expanded treatment access and a sign that high-risk individuals are being reached" [157]. Indeed, a key premise of HCV treatment-as-prevention is prioritizing treatment to PWID with ongoing risk behaviours [11]. Modeling studies suggest that, with expanded access to HCV treatment, an increase in the number of cases of HCV reinfection is to be expected within the first few years, before a decline can be observed, as the overall reservoir of HCV infection among PWID diminishes and the full benefits of treatment as prevention emerge [165]. Thus, for PWID who become reinfected, access to retreatment should be provided without stigma and discrimination.

Aside for the need to address providers' concerns around drug use patterns, many other barriers to HCV treatment uptake remain to be addressed. Among patients, misconceptions around available therapies and treatment side-effects leading to refusal or disinterest of treatment underscore a continued need for providers and peers to share up-do-date knowledge and to emphasize the importance of undertaking treatment[9, 44, 45]. At the health system level, liver fibrosis stage restrictions inadvertently send a message that HCV care and cure is not a health care priority [44, 47, 59]. Even in PWID who display high interest in treatment, the often complex steps required for HCV treatment initiation, including delivery of HCV care in tertiary settings, with limited integration of addiction, psychiatric and social care, inflexible appointment policies, lengthy waiting times, feelings of stigma and prejudicial attitudes from providers continue to be important barrier to HCV treatment uptake among PWID [44, 47, 59]. Increased rates of treatment linkage and completion have been shown to occur when patients are offered a variety of support

mechanisms including provision of critical resources such as transportation to appointments, emotional and material support, and peer counselling [348].

Beyond HCV

Although HCV infection is a public health priority among PWID, the high co-morbidity and mortality rate among PWID [1, 84, 85] highlights a need to look beyond HCV-related outcomes and consider contextual forces that render individuals susceptible to injection-related harms. Capitalising once more on data collected in HEPCO (2011-2019), in Chapter 6, I first characterised trajectories of injection frequency in a sample of PWID over 7.5 years, and then examined the extent to which three modifiable factors- housing, income and OAT relate to injection frequencies across distinct trajectories. Overall, long-term patterns of injection could be broadly summarized in five categories: sustained injection (24% infrequent; 20% fluctuating; 14% frequent), gradual decline (12%), and cessation (29%). Furthermore, we found that stable housing, stable income sources and OAT were each independently associated with a lower injection frequency in nearly all trajectory groups (range: 2-14 fewer injection days/month). These findings suggest that despite the observed diversity in trajectories of injection, socioeconomic stability and OAT were consistently associated with a lower injection frequency. Although these findings have potentially important implications for public health interventions, they carry a number of limitations that should be considered.

The extent to which the estimated trajectories are representative of drug use patterns among PWID in the community is unclear, due to i) non-random sampling of study participants, ii) potential misreporting of drug use, iii) possible drug use changes attributed to being enrolled in the study and iv) losses to follow-up over time. First, in the absence of a sampling frame to inform recruitment of PWID into the study, efforts were made to reach participants via diverse strategies, including word-of-mouth and referrals from community-based programmes and addiction centres. Compared to PWID enrolled in a yearly cross-sectional surveillance study between 2009 and 2016 in Montreal[333], our cohort displays similar distributions for

characteristics such as gender, frequency of cocaine and opioid injection and opioid agonist treatment, yet a higher mean age (40 vs 33). Because the recruitment criteria in this surveillance study is restricted to needle-exchange programs[333], it is unclear what the real distribution of these characteristics is in the community, and thus the extent to which our findings are generalisable to PWID in Montreal. Second, self-reported data may have been influenced by participants' tendency to report "positive answers" or by recall errors. That said, interviewers were trained to display a non-judgmental attitude in order to minimize the risk of socially desirable responding, and the recent reference frame of interview questions (i.e., past-month or past three months) minimizes the risk of recall errors. In addition, most studies suggest that self-reported drug-use behaviors of PWID populations are valid [305]. Third, if awareness of being observed, coupled with counselling and access to medical referrals provided as part of the study, lead to decreases in drug use over time (referred to as Hawthorne effect), the estimated prevalence of trajectory groups or their shape could be affected. For instance, it is possible that trajectories of sustained, high-frequency injecting could be under-estimated as a result. Fourth, losses to follow-up may have also played a role, leading to an increasing proportion of lower-risk individuals being retained in the study as time since enrolment elapsed, and this problem may have been differentially affecting certain groups. Given the time period in which the data were collected, when the levels of overdose-related mortality were high [73], it is possible that deaths related to overdose were occurring more in some trajectories (e.g., those who had a trajectory of persistent injecting) than in others (e.g., those who achieved complete cessation). The absence of mortality data within HEPCO prevented us from accounting for this outcome in our analysis. It is reassuring, however, that the median follow-up time was similar across trajectory groups. Finally, it is also worth noting that nearly two-thirds (63%) of participants had already been followed-up in the cohort prior to this study's onset (March 2011), and relative to new enrolees, this group may have had a survival advantage.

While it is difficult to determine how the representativity of trajectories estimated in our study is affected as a result of these drawbacks, it is likely that patterns of sustained, high-frequency injecting were under-estimated. Together, these drawbacks highlight that many of the challenges

typically associated with cohort studies, such as follow-up of participants over time, are amplified when the study population is engaged in an illegal and stigmatized behaviour and has a considerable higher mortality rate relative to the general population [1]. Losses to follow-up are a challenge to all cohort studies focused on PWID, with 25%-35% of enrolled participants often not coming back for a second visit [105, 249]. Despite these limitations, in a context where most studies have focused on short-term injection drug use changes among PWID [240, 242-245, 248-250, 311], evidence from studies such as ours provide some initial insight into how drug use patterns evolve over time in this population and their associated link to specific factors. For example, we found that PWID who achieved cessation in our study were the most likely to report alcohol binges, suggesting a need to carefully consider non-injection drug use patterns among PWID attempting to stop injection drug use.

Of particular importance to public health is the characterization of modifiable factors with potential to shape the course of trajectories. As a second objective in this study, we examined how factors relating to everyday living conditions—stable housing and stable income sources, and OAT relate to injection frequency in the context of different trajectories of injection drug use. Our main finding was that, despite the diversity in injection drug use trajectories among PWID, all three modifiable factors were almost universally related to a lower injection frequency. Although these findings are important and novel, one important limitation must be highlighted. Because modifiable factors were assessed at the same time point as injection frequency, it is not possible to delineate the direction of the associations. While it is likely that OAT led to reductions in injection frequency, given the overwhelming level of evidence supporting this relationship[26-28, 194], whether or not housing and income stability caused changes in injection frequency, or vice-versa, is more complex. Having a regular place to live and access to other basic necessities such as stable employment have been identified as key necessities by PWID attempting to transition away from injection drug use [139]. While a number of observational studies have highlighted a potentially protective effect of the impact of housing and income on drug use [242, 244, 248], evidence from randomised controlled studies is scarce and inconclusive [349]. Yet, it is largely acknowledged

that these factors are closely interlinked, and a bi-directional relationship likely exists in reality [324, 325].

At a time when the needs of the affected community do not seem to align with HCV elimination efforts [52, 53] and mortality unrelated to HCV infection is on the rise [65], our study is timely. The consistency of the observed associations between OAT, housing and income stability, and injection frequency suggests that there are ways to support all PWID in making small behavioral changes that could reduce their risks of injection-related harms, irrespective of whether or not they are in a position to stop injection. An overwhelming level of evidence also supports the positive impact of these factors on broader health outcomes among drug-using populations. OAT has a demonstrated ability to reduce illicit opioid use, risk of HIV and HCV acquisition and involvement in criminal activities, to promote engagement in care and to improve social stability overall [26-28, 194, 350]. Stable housing and income can foster the development of personal choice and agency, and have been shown to improve mental health and quality of life [351, 352]. While access to OAT, stable housing and income is amenable to change, to achieve this, efforts are needed to invest in appropriate social and public health initiatives, such as supportive housing programs, skill-building and employment opportunities and expanding access to low-threshold OAT programs [328-330].

In conclusion, at a time when nearly all countries have embarked on a global effort to eliminate HCV, efforts are needed to ensure that well-evidenced harm-reduction programs are optimised to reduce transmission of HCV, treatment for HCV infection is scaled-up among those who are infected and efforts do not overlook the basic needs and concerns of affected communities. This thesis provided data to help inform (i) optimisation of OAT provision for the prevention of HCV transmission, (ii) expanded access to HCV treatment, and (iii) access to stable housing and income to reduce the risk of injection-related harms among PWID.

7.2 FUTURE RESEARCH DIRECTIONS

Chapter 3 of this thesis suggested that prevention benefit carried by OAT may not apply systematically to everyone. Although findings are in line with prior studies highlighting the importance of OAT dosage in achieving optimal treatment outcomes [26-28, 202, 203], the only other study to have examined this relationship did not find a similar gradient in the effect estimates [208]. Further research is needed to corroborate our observed relationship with HCV infection risk. Additional research is also needed to examine the mechanisms explaining these associations and particularly the factors that may lead PWID who receive suboptimal dosages to have a greater risk of HCV infection relative to those not enrolled in OAT. Such findings could help inform the provision of additional support services to be offered alongside OAT, particularly for PWID among whom higher dose levels are not desired or indicated.

More broadly, research is needed to examine the current levels of OAT coverage and whether or not treatment programs comply with prescribing guidelines and meet patients' needs. Available estimates in Canada indicate a moderate coverage of OAT (i.e., 40 per 100 PWID) [353], yet there is considerable heterogeneity in access to, and the range of pharmacotherapies available by province/ territory and across urban and rural areas, and no estimates are available of the real need for OAT (i.e., how many PWID are eligible for OAT)[2]. Data on prescribing practices at the population level are even more fragmented, perhaps as a result of a dearth of centralized pharmaco-epidemiological data. In the United States, a survey assessing the maintenance dose prescribed in a nationally representative sample of methadone treatment programs found that the proportion of patients who received doses below 60 mg/day- the minimum recommended- declined from 80% in 1998 to 23% in 2011 [32]. Although encouraging, this study suggests that nearly a quarter of patients receiving methadone may still be receiving doses that are generally too low to be effective. In the province of British Columbia, an analysis of a provincial drug dispensation database indicated that compliance to minimally effective dose guidelines fell from 2001 to 2006, and that this decline was mirrored by a decrease in treatment retention across the same time period [31]. Survey assessing the perspectives of PWID on the adequacy of their OAT dose are also needed to ensure that treatment programs meet the needs and preferences of patients.

Furthermore, effective pharmacotherapies for PWID who have stimulant use disorders are urgently needed [354]. An analysis carried by the United Nations Office on Drugs and Crime regarding the global changes in drug manufacture and production suggests that cocaine and amphetamine supply and use might be increasing globally [355]. Canada has a long a long-standing high prevalence of psychostimulant injection, with cocaine being the most commonly injected drug in the country [72]. According to the most recent national surveillance study (2012-2014), approximately two-thirds of PWID inject cocaine or crack, and one-third inject primarily one of these two drugs [71]. Yet, there are no currently approved pharmacological options for the treatment of people with stimulant disorders [354]. Substantial research investment is needed to develop innovative treatment options for this group, especially given then known high risk of HCV infection in cocaine-using PWID [7, 115, 116].

Chapters 4 and 5 of this thesis were concerned with HCV therapy among those infected, and examined the potential of treatment to reduce drug use and risk patterns. Although these two studies are a valuable step forward because they provide much needed evidence to inform the ongoing debate among clinicians and policy-makers on whether drug use and related behaviours would change as a result of HCV treatment, overall, very few studies have investigated this question [47, 151, 187]. The only study conducted so far in the DAA era, presented in Chapter 5, is challenged by the absence of a comparison group and by having been carried out in a selected study population who was fairly well engaged in care at study outset. Carefully-designed studies are therefore needed to examine the evolution of patterns in drug use and sharing behaviours among DAA-treated PWID recruited from the community, who typically have a higher-risk profile for HCV reinfection and are considered a truly "active" PWID population [157]. Additionally, research is also urgently needed in low- and middle-income countries, which carry the greatest burden of HCV infection [183], yet access to harm-reduction and addiction care- and therefore options to provide additional support during HCV treatment- are scarce [104].

Furthermore, a new research agenda should also aim at identifying what works in helping PWID make drug use changes, that is, whether it is the impact of the treatment itself, the intensified counseling, the opportunity to receive addiction treatment or social support services, or a combination of all these actions. The identification of specific interventions that are meaningful for PWID could considerably enhance their impact on the willingness and capacity to initiate changes. There is wide evidence illustrating that the involvement of PWID in the design and delivery of HCV services plays a key role in their response [356-358]. Additionally, exploring these aspects in relation to different trajectories of drug use and sharing behaviours during and following HCV treatment could help clinicians tailor therapeutic actions to optimize health outcomes.

A common theme cutting across Chapters 4, 5 and 6 is the stigma faced by PWID in healthcare settings and the impact it may have on their health outcomes. Although further research is needed to explore reasons leading to low or inadequate dosing of OAT among PWID, prior studies have flagged stigma among providers and treatment settings [30]. Similarly, the low treatment uptake for HCV infection among PWID is a consequence of the stigma the surrounds injection drug use and hepatitis C, and which continues to prevail in medical settings [48]. Indeed, injecting drug use is a highly stigmatized practice, largely due to its illegality and the perception of PWID as being violent, dangerous, and engaging in a criminal activity [342]. It is well acknowledged that most PWID have experienced some form of discrimination within health care settings and that these experiences negatively impact their access to services [359, 360]. Research is needed to develop and implement a substance use curriculum and training among healthcare providers to increase knowledge regarding drug use, HCV and other health and social issued faced by people with substance use disorders.

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