Eliminating hepatitis C among priority populations: Dynamic transmission modelling to inform health policy

Charlotte Lanièce Delaunay, MPH, MA

Department of Epidemiology, Biostatistics and Occupational Health
School of Population and Global Health
McGill University
Montreal, Quebec, Canada
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Abstract

Background

Hepatitis C virus (HCV) spreads via unsterile injection materials, or, less efficiently, via sexual practices. Of 250,000 people living with HCV in Canada, 21,000 are coinfected with HIV, which exacerbates disease severity. The *World Health Organization* (WHO) targets for HCV elimination include reductions of incidence by 80% and mortality by 65% from 2015 to 2030. For Canada to meet these targets, a promising approach, known as micro-elimination, is to tailor elimination strategies to priority populations such as people who inject drugs (PWID), men who have sex with men (MSM), and those living with HIV (LWH). Evidence is needed to inform such locally relevant micro-elimination strategies.

Objectives

My thesis' aim was to identify strategies that can achieve and sustain HCV elimination in Montreal's (Canada) priority groups. I first estimated temporal trends in, and factors associated with, HCV seroprevalence among MSM. Second, I assessed the potential of different interventions to achieve elimination among PWID by 2030. Third, I investigated post-elimination dynamics of HCV transmission among PWID under various scenarios.

Methods

To obtain representative estimates of HCV seroprevalence and its associated factors among MSM, I standardised data from 2005 and 2008 surveys of Montreal MSM to 2018 data collected via respondent-driven sampling. The results informed my modelling work, which focused on HCV transmission via injection drug use (IDU). To assess direct and indirect effects of interventions among Montreal PWID, I developed a dynamic model of HIV-HCV coinfection calibrated to 16 years of surveillance data. I simulated increases in HCV testing, treatment, and coverage of opioid agonist therapy (OAT) and needle and syringe programs (NSP) from 2022 to 2030, varying priority groups (PWID LWH/all PWID; active/ex-injectors). I then assessed the sustainability of HCV elimination targets among

PWID by modelling post-elimination scenarios (2030-2050) scaling down or suspending different combinations of these interventions.

Results

Standardised HCV seroprevalence among MSM remained stable at 8% from 2005 to 2018 and was associated with past IDU and not with sexual behaviours. In my calibrated model, current intervention levels did not achieve elimination among PWID. Increasing testing or OAT and NSP alone made little difference. Reducing time from hepatitis C diagnosis to treatment initiation to 1 year for all PWID led to 95% and 99% reductions in HCV incidence and mortality, respectively, from 2022 to 2030. Post elimination, when scaling down all interventions to current levels, HCV incidence rebounded, doubling from 2 to 4 per 100 PY from 2030 to 2050. High-coverage NSP and OAT were key to either sustain elimination when scaling down testing and treatment or mitigate HCV resurgence when suspending testing and treatment.

Discussion

HCV seroprevalence was high and associated with past IDU among Montreal MSM, showing the need to reduce HCV transmission via IDU in Montreal's priority populations. In a setting with relatively high diagnosis and harm reduction coverage, scaling up treatment is the key to HCV micro-elimination among PWID, and its sustainability relies on access to NSP and OAT. Interventions should reach all PWID, regardless of HIV status or whether people have ceased injecting. Inherent study limitations include challenges in obtaining representative samples of hard-to-reach populations and unaccounted heterogeneity in the modelled population. Strengths include detailed analyses of a wealth of bio-behavioural survey data and the use of a calibrated coinfection model.

Conclusion

HCV care and prevention needs overlap between priority populations and reducing transmission via IDU is key in Montreal. For PWID, HCV micro-elimination is contingent

on scaling up treatment uptake for all, and high-coverage harm reduction can ensure that elimination efforts are sustained and provide long-term benefits.

Resumé

Contexte

Le virus de l'hépatite C (VHC) circule via l'injection de drogues (ID) avec du matériel non-stérile, ou, moins efficacement, par contact sexuel. 21,000 des 250,000 personnes vivant avec le VHC au Canada sont coinfectés par le VIH. Pour éliminer le VHC, l'*Organisation Mondiale de la Santé* cible une réduction de 80% de l'incidence et de 65% de la mortalité entre 2015 et 2030. Au Canada, l'élimination pourrait passer par le développement de stratégies de micro-élimination informées par des données locales et adaptées aux populations prioritaires comme les personnes s'injectant des drogues (PID), celles vivant avec le VIH, et les hommes ayant des relations sexuelles avec d'autres hommes (HARSAH).

Objectifs

Mon objectif était d'identifier des stratégies pour atteindre et pérenniser l'élimination du VHC chez les groupes prioritaires à Montréal. J'ai d'abord estimé les tendances temporelles de la séroprévalence du VHC chez les HARSAH, et les facteurs y étant associés. Puis, j'ai évalué la capacité d'interventions à atteindre l'élimination parmi les PID d'ici à 2030. Enfin, j'ai exploré les dynamiques de transmission du VHC post-élimination chez les PID, selon divers scénarios.

Méthodes

Pour estimer la séroprévalence du VHC chez les HARSAH de manière représentative, j'ai standardisé les données d'études de 2005 et 2008 aux données d'un échantillon conduit par les répondants en 2018. Les résultats m'ont conduite à focaliser mon travail de modélisation sur la transmission du VHC via l'ID. Afin d'étudier l'impact d'interventions chez les PID, j'ai développé un modèle de coinfection VIH-VHC calibré sur 16 ans de données de surveillance. J'ai simulé une augmentation du dépistage du VHC, du traitement, et de la couverture des traitements par opioïdes antagonistes (TOA) et des programmes de

distribution de seringues (PDS) de 2022 à 2030, en variant les groupes prioritaires. J'ai ensuite examiné la pérennité de l'élimination chez les PID en modélisant des scénarios de suspension ou d'allègement des interventions entre 2030 et 2050.

Résultats

La séroprévalence standardisée du VHC est restée stable à 8% chez les HARSAH de Montréal entre 2005 et 2018. Elle était associée avec un passé d'ID et non avec les comportements sexuels. J'ai donc évalué des stratégies d'élimination du VHC chez toutes les PID indépendamment de facteurs sexuels. Maintenir les niveaux actuels d'intervention, ou augmenter le dépistage ou la couverture des TOA et PDS n'a pas permis d'atteindre l'élimination. Augmenter le taux de traitement à 100 pour 100 personnes-années (PA) chez toutes les PID a réduit l'incidence du VHC de 95%, et sa mortalité de 99%, de 2022 à 2030. Post-élimination, le retour aux niveaux d'intervention actuels a généré un rebond de l'incidence de 2 à 4 pour 100 PA entre 2030 et 2050. Une couverture élevée des TOA et PDS était nécessaire pour pérenniser l'élimination.

Discussion

La séroprévalence du VHC est élevée et associée à un passé d'ID chez les HARSAH à Montréal, arguant pour une réduction de la transmission du VHC via l'ID chez les populations prioritaires. Dans un contexte d'accès élevé au dépistage et aux TOA et PDS, l'extension du traitement à tous est cruciale pour la micro-élimination du VHC chez les PID, et sa pérennité repose sur l'accès aux TOA et PDS. Les limitations de mon approche incluent la difficulté à obtenir des échantillons représentatifs de populations difficilement accessibles, et des sources résiduelles d'hétérogénéité dans la population modélisée. Ses forces incluent l'analyse détaillée d'une multitude de données bio-comportementales et l'utilisation d'un modèle calibré de coinfection.

Conclusion

Les besoins des populations prioritaires en matière de prévention et de soins du VHC sont imbriqués, et réduire la transmission via l'ID est essentiel à Montréal. Chez les PID, la micro-élimination du VHC passera par une diffusion du traitement, et sa pérennisation par une couverture élevée des programmes de réduction des méfaits.

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I dedicate this thesis to the two persons who share my life every day. To my life partner, Matthieu Delaunay, for being confident in me when I fail to be. Your love makes me happy and free, and I look forward to our next adventure. And to Louise, who came to the world right on time to make me a mum before I become a doctor, thereby reminding me of life priorities. Watching you grow is the most beautiful gift.

Statement of financial support

I have been fortunate to receive scholarships and prizes from various funding agencies throughout my doctoral studies. I was awarded doctoral training scholarships from the *Department of Epidemiology, Biostatistics, and Occupational Health* at *McGill University* (2017-2018), the *Canadian Network on Hepatitis C* (2018-2022), and the *Fonds de Recherche – Santé du Québec* (2019-2022). I also received prizes for conference presentations from the *Canadian Network on Hepatitis C* (2019) and the *Department of Epidemiology, Biostatistics, and Occupational Health Student Society* at *McGill University* (2020). The *Réseau de Recherche en Santé des Populations du Québec* funded the open access publication of my first thesis manuscript (*"Prix de soutien à la publication d'ouvrages scientifiques")* in 2019. In 2021, I was awarded a *"New investigator scholarship"* to present at the *Conference on Retroviruses and Opportunistic Infections* (CROI), and an *"Academic scholarship"* to present at the *Conference of the Canadian Association for HIV Research* (CAHR). Finally, in 2021, I had the honour of receiving the *"Outstanding graduate student peer mentor award"* from the *Ely and Ezequiel Franco Fellowship*, administered by the *Department of Epidemiology, Biostatistics, and Occupational Health* at *McGill University*.

The data analysed in Manuscript 1 were collected within the *Argus I*, *Argus II*, and *Engage* studies. The *Argus* surveys were funded by the *Institut National de Santé Publique du Québec* and the *Public Health Agency of Canada*. *Engage* is funded by the *Canadian Institutes of Health Research*, the *Canadian Foundation for AIDS Research*, and the *Ontario HIV Treatment Network*. For Manuscript 2 and 3, which were simulation studies, I used secondary data sources. The analyses presented in Manuscript 2 were conducted as part of the study *NoCo: Towards elimination of HCV in HIV-coinfected populations in Canada*, funded by *Gilead Sciences*.

Statement of originality

The work presented in this thesis constitutes original scholarship and informs potential avenues to achieving and sustaining hepatitis C elimination as a public health threat among priority populations in Montreal (Quebec) and the rest of Canada.

Specifically, Manuscript 1 fills knowledge gaps about temporal trends in HCV seroprevalence among MSM living in Montreal, and factors associated with HCV exposure in this population. The modelling study presented in Manuscript 2 provides key information on the potential impact of different HCV elimination strategies for PWID in Montreal. Beyond generating locally relevant information, this is one of few studies examining interventions that focus on PWID LWH. It is also one of the first attempts to model the impact of the COVID-19 pandemic on HCV transmission via IDU. Finally, Manuscript 3 provides key insights on conditions under which HCV elimination targets could be sustained post-elimination among PWID. This study also explores whether HCV prevention and care interventions could yield HIV prevention benefits.

Beyond the work presented as part of this dissertation, a full list of my doctoral training publications is available in Appendix.

Contribution of authors

***Manuscript 1**:* Charlotte Lanièce Delaunay, Joseph Cox, Marina B Klein, Gilles Lambert, Daniel Grace, Nathan J Lachowsky, Mathieu Maheu-Giroux. Trends in hepatitis C virus seroprevalence and associated risk factors among men who have sex with men in Montreal: results from three cross-sectional studies (2005, 2009, 2018). *Sexually Transmitted Infections*. 2020; 97:209-296.

I conceptualised this study with my supervisors Dr. Mathieu Maheu-Giroux and Dr. Marina Klein, and my committee member Dr. Joseph Cox. Dr. Joseph Cox, Dr. Gilles Lambert, Dr. Daniel Grace, and Dr. Nathan J Lachowsky are co-principal investigators of the *Engage* study. I developed the research question and protocol with feedback and support from Dr. Mathieu Maheu-Giroux, Dr. Marina Klein, and Dr. Joseph Cox. I was responsible for conducting all analyses, interpreting the results, drafting the manuscript and editing it with co-authors' contributions, and coordinating the submission, peer-review, and publication process. All authors provided critical feedback and approved the final version of the manuscript.

***Manuscript 2**:* Charlotte Lanièce Delaunay, Marina B Klein, Arnaud Godin, Joseph Cox, Nadine Kronfli, Carla M Doyle, Bertrand Lebouché, Mathieu Maheu-Giroux. Public health interventions, priority populations, and the impact of COVID-19 disruptions on hepatitis C micro-elimination among people who inject drugs in Montreal (Canada): a modeling study. *This manuscript has been submitted to a peer-reviewed journal*.

This analysis was conceived as one of the three objectives of the study *NoCo: Towards elimination of HCV in HIV-coinfected populations in Canada*. Dr. Marina Klein is the principal investigator of this study, and Dr. Mathieu Maheu-Giroux, Dr. Joseph Cox, and Dr. Bertrand Lebouché are co-investigators. Building on the *NoCo* study protocol, I developed the research questions and analysis plan, built, parametrised, and calibrated the model, conducted the analyses, and drafted the manuscript with feedback from Dr. Marina Klein and Dr. Mathieu Maheu-Giroux. I also consulted Arnaud Godin and Carla M Doyle

for model development and revisions. Dr. Nadine Kronfli, Dr. Joseph Cox, and Dr. Marina Klein provided clinical and public health expertise on simulated HCV micro-elimination strategies.

***Manuscript 3**:* Charlotte Lanièce Delaunay, Arnaud Godin, Nadine Kronfli, Dimitra Panagiotoglou, Joseph Cox, Michel Alary, Marina B Klein, Mathieu Maheu-Giroux. Can hepatitis C elimination targets be sustained among people who inject drugs post-2030? *International Journal of Drug Policy*. 2021; 96:103343.

Arnaud Godin and I are co-first authors on this manuscript. I conceived this study and developed the analysis plan with Arnaud Godin, Dr. Mathieu Maheu-Giroux, and Dr. Marina Klein. Arnaud Godin was offered co-first authorship as he developed a preliminary model to tackle the research questions. I was then responsible for developing, parametrising, and calibrating a more complex HIV-HCV coinfection model, with feedback from Arnaud Godin, Dr. Mathieu-Giroux and Dr. Marina Klein. I conducted the simulation analyses and drafted the manuscript conjointly with Arnaud Godin, with feedback from other co-authors. I coordinated the submission, peer-review and publication process. All authors provided critical feedback and approved the final version of the manuscript.

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List of abbreviations

AIDS: acquired immunodeficiency syndrome

ART: antiretroviral therapy

CCC: Canadian Coinfection Cohort

CI: confidence interval

COVID-19: coronavirus disease of 2019

CrI: credible interval

DAA: direct acting antiviral

HCV: hepatitis C virus

HIV: human immunodeficiency virus

IDU: injection drug use

LWH: living with HIV

MSM: men who have sex with men

NSP: needle and syringe programs

OAT: opioid agonist therapy

PLWH: people living with HIV

PWID: people who inject drugs

PY: person-years

RDS: respondent-driven sampling

RNA: ribonucleic acid

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

STBBI: sexually transmitted or blood borne infection

SVR: sustained virologic response

WHO: World Health Organization

1. Chapter 1: General introduction

1.1. Introduction and significance

Chronic HCV infection is a lifelong illness that affects 71 million people worldwide and causes approximately 400,000 deaths annually (1). People LWH are more vulnerable to the consequences of HCV infection, and because the two viruses share routes of transmission, HIV-HCV coinfection is common. Historically, HCV was difficult to treat especially among those LWH. The introduction of new oral treatment regimens called direct-acting antivirals (DAAs) has revolutionised HCV care, and all those chronically infected with HCV can now be cured within a few weeks, with little to no side effects, regardless of HIV status (2). These treatments have generated hope that we could dramatically reduce the global HCV burden, and in 2016 members states of the WHO endorsed global targets for the elimination of HCV as a public health threat (3, 4). These targets include an 80% reduction in chronic HCV incidence, and a 65% reduction in HCV-related mortality, using 2015 as a baseline (3).

Coordinating elimination strategies at the national level can be challenging, especially in federal countries like Canada where each province or territory is responsible for providing health care services to its residents. Further, "twin" HCV epidemics co-exist in Canada, with different HCV-related needs (5). Some population groups, such as people born between 1945 and 1975, or immigrants and newcomers, have a high prevalence of chronic HCV infections but are usually not at risk of transmitting the virus. Diagnosing and curing members of these populations is critical to reduce HCV morbidity and mortality. To prevent incident infections, however, public health efforts should focus on populations at ongoing risk of acquiring and/or transmitting HCV, such as PWID, subgroups of MSM, and people living with HIV (PLWH). Small-scale, tailored interventions, also known as "micro-elimination" strategies, are a promising approach to HCV elimination among these priority populations. Bio-behavioural surveillance data on HCV and its determinants is essential to monitor progress towards elimination targets and inform interventions. With a

wealth of past and ongoing studies conducted among PWID, MSM, and PLWH, Montreal is an appropriate setting to evaluate HCV micro-elimination strategies.

The timeline to the 2030 HCV elimination targets is a short one. Empirically evaluating the population-level impact of several interventions over a short time frame poses a number of challenges. As a way to bypass these barriers to comprehensive evaluations, dynamic models of infectious disease transmission are used for program planning and can inform the design of empirical trials of interventions. When parametrised and calibrated with robust, empirical data, these models allow us to explore direct and indirect effects of HCV micro-elimination strategies. We can vary not only the types of interventions, but also their level of scale-up, and the implications of focusing efforts on subgroups at higher risk of acquiring HCV and/or developing HCV-related complications (6).

In Montreal, HCV and HIV surveillance data have been collected among PWID for more than 15 years, and key epidemiological indicators are published annually (7). Several bio-behavioural surveys have also been conducted among MSM (8, 9), which data should be harmonised to examine trends in HCV prevalence and plausible routes of transmission among this population. For both populations, and when possible, these outcomes should also be stratified by HIV status. Dynamic models should then be used to examine the potential of proven HCV prevention and care strategies to achieve the WHO incidence and mortality reduction targets by 2030 among priority populations. In addition to working toward these ambitious goals, we should identify strategies that ensure that micro-elimination efforts yield long-term public health benefits. There is an urgent need for evidence on the sustainability of HCV elimination targets among populations at ongoing risk of transmission.

1.2. Research objectives

The overarching aim of my thesis is to identify strategies that can achieve and sustain HCV elimination as a public health threat by 2030 among priority populations in Montreal, Quebec, Canada. To this end, I will address three research objectives:

1. To estimate temporal trends in HCV seroprevalence between 2005 and 2018 among Montreal MSM, and to identify socioeconomic, behavioural, and biological factors associated with HCV exposure among this population.
2. To assess the potential of various public health intervention scenarios to achieve HCV elimination among PWID LWH and PWID, by 2030 in Montreal.
3. To investigate the post-elimination dynamics of HCV and HIV transmission among PWID across a variety of harm reduction and HCV testing and treatment scenarios.

1.3. Organisation of thesis

This dissertation is manuscript-based. The three thesis objectives are addressed in three corresponding original research manuscripts, each presented as its own chapter. Manuscript chapters include a preface that briefly presents the study rationale, research questions at stake, the chosen methodological approach, and publication information. Chapter 2 is a comprehensive review of the literature supporting the thesis objectives. Chapter 3 provides general information about data sources used to conduct my doctoral research. Chapter 4 contains Manuscript 1, which estimated HCV seroprevalence trends among MSM subgroups in Montreal from 2005 to 2018, as well as factors associated with HCV seropositivity in this population. Chapter 5 includes Manuscript 2, a mathematical modelling study that evaluated the potential of various interventions to eliminate HCV as a public health threat among all PWID and PWID LWH in Montreal, factoring in the impact of the COVID-19 pandemic. Chapter 6 presents Manuscript 3, which investigated post-HCV elimination dynamics of HCV and HIV transmission among PWID under various intervention scenarios. Finally, the overall findings of this thesis and their implications are discussed in Chapter 7, with reflections on future directions and concluding remarks. All information sources cited along this dissertation are listed in the References section. An exhaustive list of my doctoral training publications is available in Appendix.

2. Chapter 2: Literature review

2.1. Clinical course and epidemiology of HCV

HCV is a blood-borne, highly heterogeneous RNA virus that was discovered in 1989. Seven HCV genotypes and numerous subtypes have since been identified which can influence disease course and management. In Canada, genotypes 1 and 3 are the most common. HCV is transmitted through exposure to infected blood, and in high-income countries, transmission mainly occurs via unsterile needles and drug paraphernalia, or less efficiently, via sexual practices that lead to blood exposure (2). HCV acquisition is followed by acute hepatitis, a six-month phase with little or no symptoms. One out of four people spontaneously clear HCV at this stage, and the others develop chronic hepatitis C. Chronic infection progressively damages the liver and can lead to liver fibrosis, cirrhosis, hepatocellular carcinoma, and death. Disease progression occurs over a period of 20-30 years and early symptoms are non-specific (e.g., fatigue, muscle and joint pain, abdominal discomfort), often resulting in delayed diagnosis and treatment. At the stage of liver decompensation, people face severe symptoms –such as ascites, upper gastrointestinal bleeding, renal failure, and hepatic encephalopathy– and high mortality risk (2).

Approximately 1% of the global population is chronically infected with HCV, representing 71 million people, and 400,000 liver-related deaths were attributed to HCV infection in 2015 (1, 4). In Canada, 250,000 people were estimated to be living with HCV in 2015, corresponding to a 0.7% prevalence in the general population (1). Twin HCV epidemics coexist in Canada: one of recent infections among younger people, where IDU is the main transmission route, and one among “baby boomers” (i.e., people born between 1945 and 1975) who acquired the virus years ago, either via medical or hospital procedures before the introduction of HCV screening of the blood supply in 1992, or via past IDU (5).

Hepatitis C diagnosis typically involves a screening test and a confirmatory test (2, 10). The first one is a serological test, and anti-HCV antibody detection in the blood is a marker of past or present infection. Because those who have spontaneously cleared their infection

or been successfully treated will remain anti-HCV antibody positive, a confirmatory test detecting the presence of HCV RNA (or alternatively HCV core antigen) is necessary to diagnose current HCV infection. For standard HCV testing, venous blood sampling is performed a first time for screening, and, if antibodies are detected, a second time for the confirmatory test. Methods to simplify the hepatitis C testing process have been approved in some Canadian jurisdictions (10). With reflex testing, screening and confirmatory tests are completed with a single blood sample. Rapid or point-of-care testing is an on-site screening test performed via finger prick blood sampling. Finally, both screening and confirmatory tests can be conducted using dried blood spot testing, where blood is sampled via a finger prick and dried on a paper card.

Although there is currently no vaccine to prevent HCV infection, people who have chronic HCV infection (i.e., those HCV RNA positive) can be treated. A successful treatment course is one that leads to sustained virologic response (SVR). SVR is defined as an undetectable HCV RNA test result 12 weeks following treatment completion and is equivalent to a cure. Before 2013, chronic HCV infections were treated with interferon-based regimens, which had suboptimal SVR rates (20-50%) especially in people infected with certain HCV genotypes (including genotype 1) or living with comorbidities such as HIV coinfection (11-13). In addition, these regimens required weekly injections during up to 48 weeks and caused many side effects including muscle and joint pain, fatigue, fever, weight loss, and depression. HCV treatment was revolutionised by the advent of second-generation DAAs. These oral regimens are well-tolerated and can achieve cure rates above 90% in all populations within eight to 12 weeks (2). In the province of Quebec, Canada, DAAs became universally accessible in 2015. Importantly, these treatments do not confer protective immunity against HCV, meaning that reinfection can occur.

2.2. Eliminating HCV as a public health threat

With the introduction of second-generation DAAs, HCV treatment-as-prevention became possible. Treatment-as-prevention is defined as the use of *"treatment as a tool for limiting spread of an infection in generalised epidemics in a particular setting"* (14). This

encouraged the WHO member states to adopt the *Global Health Sector Strategy on Viral Hepatitis 2016-2021*, calling for the elimination of viral hepatitis as a public health threat by 2030 (3). This strategy targets hepatitis A, B, C, D, and E, with a special emphasis on hepatitis B and C viruses which cause the greatest disease burden. Hepatitis C elimination targets include an 80% relative reduction in the incidence of chronic infections and a 65% relative reduction in HCV-related mortality, as compared to their 2015 baseline (4). These targets are ambitious for most settings, and the use of relative endpoints can penalise countries that initiated programs to reduce HCV transmission and mortality prior to 2015 (15). Nevertheless, this resolution has created momentum and several countries (e.g., Georgia, Egypt, Australia) have adopted national plans for HCV elimination (16-18). In 2018, the *Public Health Agency of Canada* published the *Pan-Canadian Sexually Transmitted and Blood-borne Infections Framework for Action* (19). This document is aligned with the WHO targets and relevant to all sexually transmitted and blood-borne infections (STBBIs). Nevertheless, because HCV elimination will require specific, concerted actions, experts and members from the *Canadian Network on Hepatitis C*, a national, multidisciplinary research and training network, have joined efforts to publish a *Blueprint to Inform Hepatitis C elimination Efforts in Canada* (5). The *Blueprint* defines high-level objectives for HCV prevention, testing and diagnosis, and care and treatment, that should be met to reach elimination by 2030. This document also recognises that optimal elimination strategies will vary across settings and populations, and therefore offers a "*menu of options, suggested activities, and evidence-based good practices for provinces and territories to develop their own HCV action plans to meet those targets*" (5).

Disease progression models informed by data on chronic HCV prevalence, diagnosis, and treatment have been used to assess countries' progress towards the WHO HCV elimination targets. In 2021, Canada was added to the list of countries that could be on track for HCV elimination by 2030, assuming that current levels of diagnosis and treatment are maintained (20-22). Rapid increases in treatment rates have been observed since DAAs became universally accessible in Canada, partly because many people already engaged in care were awaiting these low-toxicity, highly efficacious regimens (23). Now that these patients have

been cured, sustaining high treatment rates could be increasingly challenging as those remaining to be cured face multiple barriers to HCV treatment and prevention.

2.3. HCV micro-elimination

The HCV elimination agenda was adopted under the premise that universal DAA treatment for people living with HCV would be the primary tool for reducing HCV incidence and mortality. Yet eliminating HCV at the global, or even national level is a broad, complex, and costly undertaking. This is especially true when the definition of elimination refers to the removal of the public health threat as opposed to a reduction of the incidence to zero. We must accept that, despite tremendous public health efforts required for elimination, HCV could not completely disappear in the next few decades and continue to affect vulnerable people, albeit in much smaller numbers. As infections become rarer, reaching and treating these people will also become more challenging. Arguing that global elimination of a disease's threat is achieved by successively eliminating it from defined populations or regions, Lazarus and colleagues conceptualised the HCV micro-elimination approach. This pragmatic method recommends "*break[ing] down national elimination goals into smaller goals for individual population segments, for which treatment and prevention interventions can be delivered more quickly and efficiently using targeted methods*" (24). Among other principles, micro-elimination entails tailoring case finding strategies, HCV care models, and surveillance to the realities of a specific group. The scale of intervention can vary but region- or city-levels are considered appropriate. The availability of robust data on the epidemiology of HCV in the population of interest is essential and planning and implementation should involve multiple stakeholders including public health authorities, healthcare providers, community organisations and members of the population. The authors also suggest the use of mathematical modelling to determine the type and level of interventions required to achieve elimination by 2030, and recommend that essential HCV outcomes are monitored and reported annually (25).

Strategically, a small-scale program may appear less daunting to policy-makers and be more likely to gain their support. Successful HCV micro-elimination among a specific

group can also build momentum for more ambitious efforts at the general population level (24). In Canada, HCV infections are concentrated in specific populations with disparate unmet prevention and treatment needs. The country's response is also made challenging by important geographic differences in both HCV epidemiology and provincial healthcare systems. In this context, developing micro-elimination approaches suitable for each setting and priority population is a promising avenue to country-level HCV elimination.

2.4. Priority populations

The *Blueprint* summarises information on priority populations for the elimination of hepatitis C as a public health threat in Canada. They are defined as "*groups that are disproportionately affected by HCV and/or have challenges in accessing HCV services*" (5). Mirroring the twin HCV epidemics described above, some populations groups such as the 1945-1975 birth cohort, or immigrants and newcomers from countries where HCV is endemic, have high rates of past or current infection and are therefore exposed to HCV morbidity and mortality. Diagnosing and treating these people is a priority to alleviate their HCV burden, yet efforts to prevent new infections should focus on populations at risk of acquiring and transmitting the virus, such as PWID or subgroups of MSM.

Immigrants and newcomers from countries where HCV is endemic

In 2011, foreign-born people were estimated to represent 35% of those seropositive to HCV in Canada (26). Although they can be part of other priority populations (e.g., PWID), the majority of immigrants acquired HCV via unsafe medical or dental practices in countries they previously lived in or transited through. Most foreign-born people do not engage in behaviours that are associated with HCV transmission risk (e.g., IDU). This means that despite bearing a disproportionate share of the HCV burden in Canada, incident infections rarely occur among these populations. National recommendations include voluntary screening for HCV upon arrival in Canada. Yet immigrants and newcomers face multiple barriers to healthcare services, including cultural and linguistic obstacles, racism, fear of deportation, and competing priorities (5) so screening is often not carried out. Diagnosis is often delayed until late in disease course and morbidity and mortality are high (27, 28).

People born between 1945 and 1975 (baby boomers)

People from the 1945-1975 birth cohort represent between 66% and 75% of people living with HCV in Canada (29-31). The majority of baby boomers acquired HCV years ago, via medical or hospital procedures pre-1992, or via past IDU. Due to the advanced stage of their HCV infections, as well as their older age, these people are at increased risk of developing cirrhosis, hepatocellular carcinoma, and dying from liver causes. Nevertheless, few of them have been tested for HCV, partly because their healthcare providers may not be aware of remote exposures to the virus, and due to stigma surrounding HCV infection and risk factors (5). Similarly to foreign-born people, baby boomers bear an excessive share of the HCV burden in Canada but new infections rarely occur among this population in the absence of exposing behavioural factors.

People who inject drugs

Approximately 85% of new HCV infections occur among PWID in Canada, and this group has the highest HCV incidence and prevalence. For example, 69% of PWID in Montreal had been previously exposed to HCV in 2018, and seroincidence (i.e., the incidence of anti-HCV seroconversions) reached 21 per 100 PY in 2017 (7, 32). Not only can PWID acquire HCV via the use of unsterile needles and drug paraphernalia, but they are also exposed to high rates of incarceration (and re-incarceration) due to drug criminalisation (33), unstable housing, poverty, multiple forms of violence, stigma, and competing health priorities. All these factors act to increase HCV acquisition and transmission risks and create barriers to prevention and care services (5). The needs of PWID have been neglected historically, and the current opioid death epidemic is among North America's most severe public health crises. Close to 27,000 apparent opioid toxicity deaths occurred between January 2016 and September 2021 in Canada (34). The COVID-19 pandemic and its response have further exacerbated this crisis. From April 2020 to March 2021, opioid-related deaths increased by 95% compared to the year before in Canada, and death rates have remained high since then (34).

People living with HIV

HIV is transmitted via body fluids such as blood, semen, vaginal secretions, and breast milk. Due to shared routes of transmission, HCV infection is common among PLWH. A global systematic review and meta-analysis estimated HCV seroprevalence among different groups of PLWH: 2% of the general population, 6% of MSM, and 82% of PWID LWH had previously been exposed to HCV (35). PLWH had six times higher odds of past HCV exposure than their HIV-negative counterparts.

HIV attacks the immune system –including through the destruction of CD4+ cells. Its natural course is divided into three stages (36). Acute HIV infection starts within two to four weeks of virus acquisition, lasts between a few days and a few weeks, and can be asymptomatic or cause non-specific, flu-like symptoms. In this phase, HIV viral load increases rapidly, putting people at increased risk of transmitting the virus. Following acute infection, people progress to chronic infection, which can last more than a decade. People may not experience symptoms during this phase, yet the virus is still active and can be transmitted. The end of the chronic infection phase is marked by a sudden increase in viral load and depletion of CD4+ cells below 200 cells/mm^3, when people develop acquired immunodeficiency syndrome (AIDS). At this stage of infection, the immune system is so damaged that people are highly exposed to opportunistic infections, have a high risk of transmitting HIV, and typically survive around three years (36). HIV cannot be cleared nor cured, yet the infection can be effectively managed with antiretroviral therapy (ART), which suppresses viral replication and allows the immune system to recover from the damage caused by HIV infection. Importantly, once PLWH achieve viral suppression, they are no longer infectious. Further, the life expectancy of PLWH who are on ART approaches that of HIV-negative people (37).

PLWH are however more vulnerable to the consequences of HCV infection: they are less likely to spontaneously clear HCV, have higher HCV viral loads, experience faster liver disease progression, and have higher mortality rates (38). Before the advent of second-generation DAAs, PLWH were considered difficult to treat for HCV infection. They

required longer treatment courses, experienced severe side effects more frequently, were exposed to adverse health outcomes such as neutropenia (reduced white blood cell count that increases the risk of bacterial infections), and had lower SVR rates (39). Drug-drug interactions between HIV and HCV treatment regimens posed additional challenges. As a result, very few HIV-HCV coinfected people were successfully treated for HCV in the interferon era (40).

Fortunately, HIV-HCV coinfected people have not been left out of the HCV treatment revolution: second-generation DAAs show similarly high SVR rates in this population, and treatment uptake has increased (23, 41, 42). Current clinical guidelines therefore recommend that all HCV RNA-positive people initiate HCV treatment, regardless of HIV status (43). Taken together, PLWH are a candidate population for HCV micro-elimination because they can be more vulnerable to the consequences of HCV infection, and their HCV infection can now be treated with short-duration, safe, and efficient treatments. Furthermore, most of them can be reached by public health interventions since they are already engaged in HIV care (41, 44). Priority populations overlap, and PLWH can be part of other priority groups such as PWID and MSM. These intersections should be considered when developing HCV elimination interventions.

Men who have sex with men

The epidemiology of hepatitis C among MSM is multifactorial and context-specific. A global systematic review and meta-analysis published in 2021 estimated HCV seroprevalence among MSM at 3%, three times higher than that in the general population (45). HCV seroprevalence is also higher among MSM LWH (6%) than among HIV-negative MSM (1.5%). Importantly, HCV reinfection rates are up to 10 times higher than those of primary infection among MSM, highlighting the importance of preventing new exposures to the virus post-SVR (46, 47). Factors associated with HCV exposure in MSM vary across geographical settings, and uncertainty persists regarding the mechanisms at play in viral transmission. IDU is more commonly reported by MSM, and a major risk factor for HCV transmission. It is estimated that 30% of MSM with a history of IDU are

seropositive to HCV globally (compared with less than 3% of those who have never injected drugs) (45).

Sexual transmission of HCV is unusual in heterosexual relationships, yet in certain contexts –including in Europe, the US, and Vancouver (British Columbia, Canada)– evidence of sexual transmission has been reported among MSM LWH since the early 2000s (48-51). It was hypothesised that HIV infection was the main facilitator of sexual transmission (46, 52): MSM LWH could be more exposed to HCV acquisition due to weaker immunity, and at higher risk of transmitting the virus due to higher HCV viral loads in semen (45). Yet several studies published after 2010 show that sexual transmission of HCV can also occur among HIV-negative MSM who are eligible for, or use, HIV pre-exposure prophylaxis ("PrEP") (48, 49, 53). In addition, phylogenetic evidence demonstrates that HIV-negative MSM can sexually acquire HCV strains previously circulating among MSM LWH. Sexually transmitted infections (e.g., syphilis, lymphogranuloma venereum) and mucosal traumatic practices such as brachio-anal sex (i.e., fisting), group sex, and chemsex (i.e., sexualised drug use) have been identified as possible risk factors for HCV exposure (54).

Not all studies of HCV transmission among MSM have found evidence of sexually acquired HCV (55). Molecular approaches have also shown that the characteristics of HCV transmission networks vary. In Australia, MSM and PWID transmission networks overlap, suggesting that injecting and sexual risk factors co-exist (56). Contrarily, separate networks have been described for these two populations in the Netherlands (57). Trends in HCV prevalence and incidence also differ across geographical settings: for example, incidence seems to have stabilised in Western Europe, but continues to increase in Northern European countries (58). These disparities highlight the need to obtain localised data on the prevalence and determinants of HCV infection in MSM subgroups, to tailor micro-elimination strategies to local transmission dynamics.

Indigenous peoples

First Nations, Inuit, and Métis peoples –collectively referred to as Indigenous peoples– have been identified as a priority population for HCV elimination in Canada (5). Although epidemiological data on HCV infection among Indigenous peoples are scarce, it is estimated that HCV incidence is five times higher among Indigenous people than among non-Indigenous people (59-62). Overall, HCV is more present in middle-aged men, yet young Indigenous people, and young women in particular, are disproportionately affected by HCV (63). In a review of Indigenous perspectives on HCV etiology and care paradigms, Fayed and colleagues (59) advocated for the recognition of Indigenous people as a central population affected by HCV rather than an additional, parallel priority population. This approach acknowledges that Indigenous people share behavioural or circumstantial determinants of HCV acquisition with other groups (e.g., PWID), and are over-represented in populations affected by HCV. It also presents colonialism, *"an umbrella term for all past and contemporary processes of oppressive colonial systems, including colonization, neo-colonialism, and racism"* (59), as the major risk factor for HCV infection among Indigenous people. The authors introduce the historic trauma pathway, demonstrating the colonial aetiology of HCV infection among Indigenous people, and calling for responsive anticolonial and wellness-based approaches to HCV care for Indigenous people (59). One of these approaches is Indigenous healing, where mainstream HCV care (e.g., treatment with DAAs) is only one component of a response structured by three principles: historic trauma prevention, historic trauma harm reduction, and wellness promotion.

Compared with other provinces, Indigenous people represent small proportions of HCV priority populations in Quebec. For instance, among PWID engaged in the *Canadian Coinfection Cohort* (CCC), a prospective study of HIV-HCV coinfected people in Canada, 3% of those recruited in Quebec self-identify as Indigenous, compared with 39% in British Columbia and 82% in Saskatchewan (42). Micro-elimination strategies developed for the majority of PWID –or other priority groups– may therefore miss key components of an adequate response for Indigenous PWID. Tailored models of care are needed and should be designed by and for Indigenous people living with or at risk of acquiring HCV.

2.5. Sampling hard-to-reach populations

Developing appropriate interventions to eliminate the public health threat posed by an infection in a defined population requires knowledge of the infection prevalence and routes of transmission in this population. PWID and MSM are priority populations for the micro-elimination of HCV in Canada, and both groups have been described as "hidden" because no sampling frame exists for them, or "hard-to-reach" because they engage in behaviours that can be socially stigmatised or illegal (e.g., possession and/or consumption of illicit drugs). As a result, conventional infectious disease surveillance activities are not best suited to monitor transmission among these groups (64). It is difficult to directly measure the size of these populations, and obtaining representative samples and thereafter generalisable estimates of outcomes of interest is challenging. Sampling strategies have been developed to conduct infectious disease bio-behavioural surveillance for STBBIs in these groups. These methods aim to minimise bias in the estimates, while factoring in feasibility and scarcity of resources. Examples include snowball sampling, facility-based sampling, targeted sampling, time-location sampling, and respondent-driven sampling. Two of these approaches –time-location and respondent-driven sampling– are relevant to this dissertation.

The principles of time-location sampling are based on the observation that members of priority populations tend to gather at certain locations (64). For MSM, examples include bars, saunas, or sports centres (8). A list of locations is generated from preliminary formative assessment and community mapping, and a number of locations is then sampled from this list (via probability sampling) to serve as recruitment sites. People encountered at these sites during a pre-defined time interval (e.g., a randomly chosen 4-hour period, on a randomly chosen weekday) and who meet the study eligibility criteria are invited to participate in the study. Selection probabilities can be estimated, and individual weights are generated as the inverse of a participant's probability of selection into the study. These weights are based on the sampling strategy and participation rates at both venue and individual levels, and can be used to generate tentatively representative estimates (64). Nevertheless, time-location sampling presents major disadvantages. First, resource-

intensive field work is required to not only map but also visit potential study venues and obtain authorisations to recruit from these venues. In addition, venues where members of the priority population congregate can change over time, meaning that the sampling frame development must be updated at each round of data collection. Second, because the behaviours and health outcomes studied can be stigmatised, and recruitment occurs in spaces exposed to scrutiny –even if questionnaires are then administered anonymously and in a safe space– refusal rates may be high, or answers may be prone to social desirability bias. Finally, and perhaps most importantly, time-location sampling can suffer from selection bias if members who do not visit the chosen locations differ from those who do in terms of behaviours and risks of STBBIs —something that even the use of sampling weights cannot remediate. Non-venue-based socialising has become prominent, for example through the widespread use of geosocial networking mobile applications by MSM to meet other men, and this trend has accelerated since the beginning of the COVID-19 pandemic (65). For these reasons, time-location sampling no longer constitutes a first-choice sampling method for hidden and hard-to-reach populations.

One alternative approach is respondent-driven sampling (RDS), which involves chain referral sampling. This technique has the advantage of being able to theoretically, and under certain conditions, yield representative samples. This design can be used under four assumptions: 1) the population is well-networked, 2) recruiters and recruits have reciprocal, personal relationships, 3) recruiters randomly invite members of their networks to participate in the study, and 4) sampling occurs with replacement. The process starts with a formative assessment and community mapping is conducted to identify an initial group of participants who represent the diversity of the priority population, and are referred to as "seeds" (64). Seeds are provided a fixed number of recruitment coupons, each with a unique serial number. They are encouraged to recruit peers from their network by giving them a coupon. The newly recruited participants can then come to the study site, return the coupon they were recruited with, have their data collected, and receive new coupons (the same fixed number) to further recruit peers from their own networks. Several recruitment "waves" are conducted until the required sample size and/or sample "equilibrium" are

reached. Equilibrium refers to a stage where the distributions of chosen variables (e.g., HCV seroprevalence, age, sexual orientation, income) remain stable though successive recruitment waves. Typically, both participation and recruitment are incentivised. RDS does not limit recruitment to specific sites, and recruitment chains can access people through their social networks. Using coupons to limit the number of people recruited by the same person both minimises the influence of initially chosen seeds and enables long recruitment chains that can reach hidden pockets of the priority population (64). Furthermore, investigators keep track of recruitment chains and relationships between recruiters and recruits, and information is collected on the network size of each study participant. At the analysis stage, individual weights inversely proportional to the respondent's probability of selection into the study can thus be used to obtain representative estimates (66). One advantage of RDS over time-location sampling is that initial community mapping does not determine the sampling frame, which is built incrementally by recruitment waves. In addition, financial incentivisation as well as "peer-pressure", from being invited to participate by a friend/peer, can reduce the risk of non-response bias (64).

2.6. Dynamic models to evaluate the impact of interventions

HCV prevalence among priority populations can be estimated using cross-sectional data collected via robust sampling strategies. Yet, assessing other key outcomes such as incidence and HCV-related mortality can be challenging. Dynamic models of infectious disease transmission can triangulate information from multiple empirical sources to estimate such outcomes. Further, these models can be instrumental in evaluating the impact of public health interventions on the course of an HCV epidemic. Interventions utilise scarce resources; their potential population-level impact thus needs to be assessed before they are implemented at scale. Evaluating the effect of interventions on population-level infectious disease transmission through empirical studies is challenging for several reasons. First, the cost and time required to conduct large community-based randomised controlled trials (the gold standard) is prohibitive and frequently poses ethical dilemmas –a control group without intervention is often unacceptable, which can also be the case if there is no clinical equipoise for the intervention. Second, only a few interventions can be empirically

compared in a given setting and timeframe. Third, the time horizon of these trials is often too short to fully capture the indirect effects of interventions (e.g., the public health benefits accrued by individuals not directly targeted by the intervention but benefiting from reduced risk of HCV acquisition through decreased population-level prevalence).

As a way to bypass these barriers to comprehensive evaluations, dynamic mathematical models of disease transmission are increasingly used for program planning and provide valuable information to effectively design trials to test interventions in real-life settings (67). They simulate the onward transmission of disease based on a conceptual framework that traces causality links between risk factors, interventions, infections, and disease distribution within a population. When combined with robust data, these dynamic simulations allow us to make predictions about the course of an epidemic under various scenarios, including the implementation of public health interventions. Also, both direct and indirect effects of interventions can be estimated (68). In contrast with models of disease progression –also referred to as burden of disease models or static models– the force of infection in dynamic models depends on the time-varying prevalence of infectious individuals, as well as demographic, biological, behavioural, and policy-level factors (6, 69).

Types of mathematical models

Dynamic models of infectious diseases transmission can be categorised between agent-based models and compartmental models. In agent-based models, each person is represented separately with their characteristics (e.g., age, sex, disease status). These models are inherently stochastic and can incorporate multiple sources of heterogeneity as well as complex contact patterns (69). For instance, the sexual transmission of an infection can be modelled according to relationship duration and concurrency, types of sexual practices, and sexual network structure. However, these models can be challenging to parametrise and calibrate to empirical data. Alternatively, compartmental models of infectious diseases transmission can be developed. With this approach, the modelled population is compartmentalised according to disease status and further stratified by key

determinants of infection (i.e., age, sex). Parameter values are homogeneous within compartments and represent averages of individual trajectories (e.g., the average annual HIV testing rate among women under 30 years old). Compartmental models can be deterministic or stochastic. The chosen model structure reflects the research questions at hand and the evidence available on the natural course of infection, its distribution in the studied population, and its determinants.

Dynamic models of disease transmission are a valuable tool to evaluate and compare HCV micro-elimination strategies for priority populations: the type, scale, and duration of intervention(s) can vary, as well as the population group(s) receiving the intervention. Multiple outcomes (e.g., incidence, prevalence, mortality, number of infections averted) can be compared across strategies, for different population subgroups (e.g., people who currently inject drugs versus those who have a history of IDU). In a model, the implementation of an intervention is quantified by changing the related parameter values. Evidence is therefore needed to inform the magnitude of change associated with each studied intervention. Several strategies are susceptible to reduce HCV incidence and mortality and have been evaluated using dynamic models.

2.7. Interventions to reduce HCV transmission and morbidity

Harm reduction programs

The WHO defines harm reduction as "*a set of policies, programs, services, and actions that aim to reduce the harm to individuals, communities, and society related to drugs*", including HCV and HIV infection (70). Harm reduction programs include NSP; these services were introduced in the late 1980s-early 1990s in Canada and vary in scope, yet they now generally provide unlimited access to needles, syringes, and other drug preparation and consumption material (e.g., filters, spoons, containers) (71). NSP models are plural and range from service points such as pharmacies, to mobile outreach units or community organisations. With NSP, the probability that people inject with previously used material is lower, and the individual risk of HCV acquisition can thereby be reduced by approximately 20% (72). OAT was introduced around the same time as NSP in Canada

and consists in the prescription of long-acting opioid agonists such as methadone or buprenorphine to treat opioid dependency. These medications aim to reduce drug cravings and prevent withdrawal syndromes for people who wish to reduce or cease their consumption of opioids. Because people receiving OAT tend to inject less frequently, OAT can reduce the risk of HCV acquisition by approximately 50% (72). NSP and OAT coverage among PWID were estimated at 82% and 33%, respectively, in Montreal in 2018 (7).

Although NSP and OAT have proven effective at reducing HCV transmission, modelling studies show that increasing the coverage of harm reduction alone is unlikely to achieve HCV elimination targets among PWID (6). Specifically, one modelling study conducted in the UK indicated that relatively high coverage of NSP and OAT (above 50%) likely prevents a high number of infections, but that incremental prevention benefits decrease as coverage increases (73). Although modelling findings are context-specific, these results could be relevant to the city of Montreal, where HCV seroprevalence and incidence are particularly high among PWID, and a relatively large proportion of PWID already engage in harm reduction programs. Persistently high HCV incidence rates could be fuelled by sustained transmission among "pockets" of PWID who have not been reached by harm reduction programs and engage in high-risk injection practices (74).

HCV treatment-as-prevention

Various modelling studies, and a few empirical ones, have examined the population-level impact of HCV treatment-as-prevention strategies among priority groups.

<u>People who inject drugs</u>

Emerging empirical evidence suggests that increasing DAA treatment rates can lead to substantial reductions in HCV prevalence and incidence among PWID (75, 76). Yet most knowledge on the potential impact of HCV treatment scale-up among PWID comes from modelling studies. Treatment-as-prevention strategies have been modelled in various contexts, with disparate treatment rates. In several settings, "modest" treatment rates

(below 10 per 100 PY) could be sufficient to achieve HCV elimination among PWID, especially if combined with increases in access to harm reduction programs (6). In Montreal, DAAs are universally covered and HCV treatment was initiated at a rate of 12 per 100 PY in a cohort of PWID in 2017 (77), and 31 per 100 PY among HIV-HCV coinfected PWID in 2014-2019 (42). Despite relatively high HCV testing and treatment uptake, and good coverage of NSP and OAT, HCV seroincidence and seroprevalence remain high among PWID in Montreal (7). Substantial increases in DAA uptake may therefore be necessary to meet the WHO HCV elimination targets. Modelling evidence suggests that increasing HCV treatment rates to 200 per 100 PY among PWID in high-incidence settings like Montreal, London (UK), or France could be cost-effective if combined with enhanced testing and harm reduction (78). Treatment rates of this magnitude (150 per 100 PY) have been observed empirically, for example in Iceland with the implementation of a national treatment-as-prevention plan to eliminate HCV before 2030 (75, 79). Considering this evidence and the short timeframe to the WHO HCV elimination goals, treatment rates of at least 100 per 100 PY could be reachable and required to substantially reduce HCV incidence among PWID in Montreal.

Although several HIV-HCV coinfection models (i.e., modelling the transmission of both viruses dynamically) have been developed, we know little about strategies that could eliminate HCV among PWID LWH. Further, it is unclear whether implementing HCV treatment-as-prevention among PWID LWH, who are often engaged in care, could achieve HCV elimination targets among all PWID through indirect effects. One modelling study investigated the impact of HCV treatment scale-up among PWID LWH in Andalusia, Spain (80). Their results suggest that this strategy would not achieve the WHO HCV incidence reduction target by 2030, neither among all PWID nor among PWID LWH, due to ongoing circulation of HCV from HIV-negative PWID to PWID LWH. Further research is needed to examine the impact of treatment-as-prevention, as well as other public health interventions, on HCV-related mortality targets among PLWH with a history of IDU.

Men who have sex with men

The epidemiology of HCV among MSM varies by HIV status, and studies evaluating strategies for HCV elimination have often focused on MSM subgroups. Empirical studies have shown dramatic decreases in HCV incidence among MSM LWH following generalised DAA uptake in this population (81, 82). Several modelling studies have also explored the potential for DAA scale-up to eliminate HCV as a public health threat among MSM living with HIV (83, 84), and their results have been synthesised by Martin and colleagues (85). HCV incidence, prevalence, and observed routes of transmission among MSM vary across geographical settings, resulting in the simulation of different epidemic characteristics. High reinfection rates –up to 12 per 100 PY (86-88)– have been observed across settings, which could compromise elimination. Yet, MSM LWH represent small populations, and in high-income countries most of them are engaged in HIV care and can therefore be offered HCV testing and treatment. Based on modelling results, the scale of DAA uptake required to eliminate HCV among MSM LWH depends on pre-existing trends in HCV incidence (85). In settings with increasing incidence, boosting treatment rates may not be sufficient to achieve elimination, and reductions in the frequency of HCV-exposing behaviours, for instance via behavioural interventions, may be required (84).

Little evidence exists regarding the potential for HCV treatment-as-prevention to reach elimination targets among HIV-negative MSM, or all MSM. One modelling study conducted by MacGregor and colleagues (89) explored combined HCV screening and treatment strategies for MSM LWH and/or HIV-negative MSM using PrEP (who are also engaged in care and can therefore be reached by interventions). The authors also quantified the additional screening and treatments efforts that should be deployed among HIV-negative MSM not on PrEP to reach HCV elimination by 2030. They concluded that in contexts with low PrEP coverage among HIV-negative MSM, screening and treatment should be increased among all MSM for elimination targets to be reached. In contexts with high PrEP coverage, these interventions could focus on PrEP users and those LHW (89).

2.8. Impact of the COVID-19 pandemic on HCV prevention and care

In March 2020, Montreal declared a state of public health emergency due to cases of COVID-19 (90). As of April 2022, Quebec has experienced six transmission waves of SARS-CoV-2, with close to 292,000 cumulative confirmed cases and 5,350 deaths in the greater Montreal region (91). Pandemic response measures have included social distancing or isolation, travel restrictions (including within the province), curfews, closure of services deemed non-essential, postponing non-urgent care, and vaccine passport mandates (90). To date, 91% of the Quebec population aged 12 years and above is considered adequately vaccinated (92).

The COVID-19 pandemic has disrupted HCV surveillance and research activities. Yet accumulating evidence points towards increases in drug-related harms and reductions in access to HCV prevention and care –although these services were considered essential and could remain open. In Quebec, the overall number of HCV treatments prescribed decreased by approximately 25% in 2020 compared to 2019 (93). Across Canada, the majority of STBBI prevention, testing, and treatment services experienced a decrease in either the demand for their services or their ability to deliver these services (94). Harm reduction programs saw an increase in demand for their services, and over 60% of them reported little change in their ability to respond to this demand (94). Members of community organisations offering services to PWID in Montreal observed substantial reductions in HCV testing and treatment. They reported that the capacity of harm reduction services had been less impacted. Finally, as previously mentioned, the number of overdose-related deaths has skyrocketed in the past two years (34, 95). It is urgent to investigate the impact of these changes on HCV incidence and other health outcomes among PWID.

2.9. Research gaps

The aim of this dissertation was to identify public health strategies that can achieve and sustain HCV elimination in priority groups in Montreal. In this setting, two population groups, PWID and MSM, can be at higher risk of acquiring and/or transmitting HCV. These priority populations intersect with a third one: PLWH.

In a micro-elimination perspective, one preliminary step is to review local epidemiological data on the prevalence and determinants of HCV infection in the populations of interest. In Montreal, these outcomes have been measured on a regular basis among PWID through a bio-behavioural surveillance network (7). Among MSM, the need for representative data is all the more compelling since HCV prevalence estimates and trends, as well as associated risk factors, are highly variable across settings. Several cross-sectional, bio-behavioural surveys of STBBIs have been conducted among MSM in Montreal (9, 96). These studies used various sampling methods and eligibility criteria, and there is a need for comparable, representative estimates of HCV prevalence trends among MSM subgroups over time. Factors associated with HCV infection should also be investigated to better understand plausible routes of transmission in this population.

Secondly, locally valid modelling inputs should be generated to identify interventions that have the potential to eliminate HCV as a public health threat among priority populations in Montreal. Depending on presumable HCV transmission routes among MSM (via sexual transmission and/or IDU), interventions could be investigated conjointly or separately for MSM and PWID. Evidence on the influence of HIV dynamics on HCV elimination strategies is scarce, hence the model(s) developed should explicitly represent both epidemics and their synergies. Promising interventions include but are not limited to treatment-as-prevention, and these should be assessed with comprehensive epidemiological outcomes comprising HCV incidence and mortality.

Finally, little is known regarding efforts that will be required to sustain the WHO targets post-elimination among populations at ongoing risk of HCV reinfection. This question should be investigated, first because it is crucial that selected HCV elimination strategies ensure long-term individual and collective public health benefits. Moreover, reaching elimination will require significant investments and the sustainability of their impact is of interest to public health decision-makers.

3. Chapter 3: Data sources

To inform local micro-elimination efforts, I leveraged several survey and data sources. This section provides an overview of their main characteristics and population samples.

3.1. Argus I and II

Argus is a two-wave cross-sectional study of STBBIs and associated risk behaviours that was conducted among Montreal MSM in 2005 (*Argus I*) and 2009 (*Argus II*) as part of *M-Track*, the Canadian enhanced surveillance system for MSM (96). To be eligible for participation, men had to have ever had sex with a man, be at least 18 years old, and live on the island of Montreal in 2005 and in the province of Quebec in 2009. Both HIV-negative MSM and MSM LWH were eligible to participate. Venue-based sampling methods were used to recruit 1,957 men from 40 locations in 2005 and 1,873 men from 42 locations in 2009. The investigators selected venues using convenience sampling in 2005, and time-location sampling in 2009. Recruitment was conducted in locations where gay men socialise (e.g., bars, coffee houses, saunas). These surveys combined infection surveillance using biological tests and behavioural monitoring through a self-administered questionnaire. The majority of respondents (99% in 2005 and 98% in 2009) provided dried blood spot samples for serological testing for HIV, HCV, and syphilis. The questionnaires investigated respondents' socio-demographic characteristics, the composition of their social network, the public places they visited to seek sexual encounters, their sexual activities with regular and casual partners, their consumption of alcohol and drugs, health history and screening for STBBIs, and their attitudes and knowledge regarding HIV, HCV, and other STBBIs (96). Slight differences existed between the 2005 and 2009 questionnaires. For instance, some questions about the participants' sexual partners, drug consumption, or sexualised drug use were framed differently.

3.2. Engage

Initially, *Engage* was a two-cycle bio-behavioural RDS-designed cross-sectional study that was conducted among MSM in Montreal, Toronto (Ontario, Canada), and Vancouver (9).

The first round of data was collected in 2018, and in 2019 the *Canadian Institutes for Health Research* allocated funding to extend the study into a longitudinal cohort by inviting the participants to return every six months for six additional follow-up visits. The overarching study objective is to examine factors that influence HIV transmission among MSM. For this dissertation, I used the first round of data collected at the Montreal site. To be eligible, participants must self-identify as a man, be 16 years of age or older, report sexual activity with a man in the past six months, live in the greater Montreal area, and receive an RDS voucher for participation in the study or be invited to be an initial seed. Both HIV-negative MSM and MSM LWH are eligible to participate. In 2018, a community-based sample of MSM was recruited using RDS: after formative assessment and community mapping, 25 seeds were purposively selected to represent the diversity (e.g., ethnicity, language, HIV status) of MSM living in Montreal. Each seed was provided invitation coupons to recruit their MSM peers, and each successive recruit was also encouraged and incentivised to recruit their peers. The resulting recruitment chains were tracked. Participants received $C50 for completing the study, and an additional $C15 for each peer recruited. They were also invited to participate in draws to win either a prepaid card ($C250) or a travel voucher ($C2,000). A total of 1,179 participants completed a questionnaire with six sections: RDS recruitment, socio-demographics, service access and use, relationships, community and societal context, sexual behaviours, knowledge and attitudes, and individual characteristics. Blood samples were collected for HIV, HCV (serology and RNA), hepatitis B virus, and syphilis testing.

3.3. SurvUDI

SurvUDI is a bio-behavioural network established in 1995 in Quebec for the epidemiological surveillance of HIV among PWID (7). HCV surveillance was added to the study objectives in 2003. In 2002, *SurvUDI* became part of *I-Track*, the enhanced surveillance system among PWID in Canada. Continuous recruitment is conducted at various sites including sterile injection equipment access centres, rehabilitation centres, detention centres, shelters, clinics, and hospital emergency departments. To be eligible to participate, people must report IDU in the past six months. PWID can complete only one

study visit within a six-month period. Individual identifiers allow the investigators to track participation across longer time periods, and to estimate annual HIV incidence and HCV seroincidence among repeated testers. Information on socio-demographic characteristics, consumption and injection behaviours (e.g., use of harm reduction programs), sexual behaviours, and HIV and HCV testing and management (e.g., testing in the past six months, HIV and HCV treatment) are collected through interviewer-administered questionnaires. Serological tests for HIV and HCV are performed on gingiva exudate samples. In Montreal, a total of 14,036 questionnaires were administered to PWID between 1995 and 2018.

3.4. The Canadian Coinfection Cohort

The CCC is a prospective longitudinal cohort study launched in 2003, with ongoing recruitment and follow-up (97). This multidisciplinary project aims to address the multifaceted nature of HIV-HCV-coinfection and has served as a research network for studying coinfection and related health outcomes. As of December 2021, 2,056 participants had been recruited from 18 HIV centres in both major urban centers and smaller cities across six Canadian provinces, to obtain a representative sample of the Canadian epidemic. Recruitment has been designed and conducted to reach marginalised populations who access diverse models of care and have various risk profiles (e.g., PWID, MSM, women, Indigenous people). Participants must be 16 years of age or older, have a documented HIV infection, and chronic HCV infection or evidence of HCV exposure (i.e., be anti-HCV antibody positive, or HCV RNA positive). All eligible participants are approached to participate, and refusals are kept track of. Follow-up visits are scheduled every six months. A questionnaire is used to collect socio-demographic, medical, behavioural, and quality of life data. At baseline, demographic information, as well as risk factor and behavioural information is obtained, diagnoses are collected, and medical conditions that may impact liver function are investigated (e.g., alcohol consumption, hepatitis B virus infection, auto-immune diseases). At follow-up visits, information on risk behaviours, medical treatments, and diagnoses is updated. Blood tests performed at each visit include the following: HIV RNA, CD4 and CD8 T-cell counts, HCV RNA, and HCV genotype (at baseline only). Information on clinical endpoints and causes of death are collected and linked to provincial

vital statistics bureaus to determine if patients lost to follow-up are deceased and, when required, the cause of death.

3.5. Ethics

The research ethics board of the *Research Institute of the McGill University Health Centre* approved the *Argus I* and *II* (ethics committee number: A10-M66-04B) and *Engage* (ethics committee number: MP-CUSM-15-632) studies. The data analysis request form submitted to perform the analyses presented in this dissertation was approved by the *Engage Analysis Committee*.

The *Canadian Coinfection Cohort* was approved by the research ethics boards of all participating institutions and the community advisory committee of the *Canadian HIV Trials Network*. My thesis work did not involve primary analysis of the CCC data therefore no additional ethics approval was required. Similarly, only secondary data analysis was performed using *SurvUDI* results. The *SurvUDI* study protocol was approved by the research ethics boards of all institutions involved.

4. Chapter 4: Temporal trends in HCV seroprevalence and associated factors among men who have sex with men

4.1. Preface to Manuscript 1

Reliable estimates of HCV prevalence can serve as a benchmark to monitor progress towards HCV elimination. Along with factors associated with HCV exposure, these estimates can also inform dynamic models to simulate the impact of HCV micro-elimination strategies. I capitalised on data from three bio-behavioural surveys conducted among MSM in Montreal to provide retrospective estimates of HCV seroprevalence trends spanning over a decade. I also assessed social, behavioural, and biological factors associated with HCV seropositivity in this population.

In 2019, I received an award titled "*Soutien à la Publication d'Ouvrages Scientifiques"* from the *Réseau de Recherche en Santé des Populations du Québec* to publish this manuscript open access. The article was published in *Sexually Transmitted Infections* (June 2021, Volume 97, Issue 4) (98).

4.2. Manuscript 1: Trends in hepatitis C virus seroprevalence and associated risk factors among men who have sex with men in Montreal: results from three cross-sectional studies (2005, 2009, 2018)

Charlotte Laniece Delaunay[1,2], Joseph Cox[1,2,3], Marina B. Klein[1,2], Gilles Lambert[3,4], Daniel Grace[5], Nathan Lachowsky[6], Mathieu Maheu-Giroux[1§]

[1] *Department of Epidemiology, Biostatistics and Occupational Health, School of Population and Global Health, McGill University, Montréal, Canada*

[2] *Department of Medicine, McGill University Health Centre, Montréal, Canada*

[3] *Direction Régionale de Santé Publique, Centre Intégré Universitaire de Santé et de Services Sociaux du Centre-Sud-de-l'Île de Montréal, Montréal, Canada*

[4] *Direction des Risques Biologiques et de la Santé au Travail, Institut National de Santé Publique du Québec, Montréal, Canada*

[5] *Social and Behavioural Health Sciences Division, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada*

[6] *School of Public Health and Social Policy, University of Victoria, Victoria, Canada*

§ Corresponding author:

Mathieu Maheu-Giroux

Purvis Hall

1020 Pine Avenue West

Montréal, QC, Canada H3A 1A2

(+1) 514-398-5110

mathieu.maheu-giroux@mcgill.ca

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Keywords: hepatitis C elimination; gay, bisexual, and other men who have sex with men; bio-behavioural surveillance; prevalence study; key population; respondent-driven sampling.

Abstract

Objectives

To eliminate hepatitis C (HCV) by 2030, Canada must adopt a micro-elimination approach targeting priority populations, including gay, bisexual, and other men who have sex with men (MSM). Accurately describing HCV prevalence and risk factors locally is essential to design appropriate prevention and treatment interventions. We aimed to estimate temporal trends in HCV seroprevalence between 2005-2018 among Montréal MSM, and to identify socio-economic, behavioural, and biological factors associated with HCV exposure among this population.

Methods

We used data from three cross-sectional surveys conducted among Montréal MSM in 2005 (n=1,795), 2009 (n=1,258), and 2018 (n=1,086). To ensure comparability of seroprevalence estimates across time, we standardized the 2005 and 2009 time-location samples to the 2018 respondent-driven sample. Time trends overall and stratified by HIV status, history of injection drug use (IDU), and age were examined. Modified Poisson regression analyses with generalized estimating equations were used to identify factors associated with HCV seropositivity pooling all surveys.

Results

Standardized HCV seroprevalence among all MSM remained stable from 7% (95% confidence interval (CI): 3-10%) in 2005, to 8% (95%CI: 1-9%) in 2009, and 8% (95%CI: 4-11%) in 2018. This apparent stability hides diverging temporal trends in seroprevalence between age groups, with a decrease among MSM <30 years old, and an increase among MSM aged ≥45 years. Lifetime IDU was the strongest predictor for HCV seropositivity, and no association was found between HCV seroprevalence and sexual risk factors studied (condomless anal sex with men of serodiscordant/unknown HIV status, number of sexual partners, group sex).

Conclusions

HCV seroprevalence remained stable among Montréal MSM between 2005-2018. Unlike other settings where HCV infection was strongly associated with sexual risk factors among MSM, IDU was the preeminent risk factor for HCV seropositivity. Understanding the intersection of IDU contexts, practices, and populations is essential to prevent HCV transmission among MSM.

Key messages

- Standardized hepatitis C virus (HCV) seroprevalence remained stable at approximately 8% among Montréal men who have sex with men (MSM) from 2005-2018.
- We observed diverging temporal trends in HCV seroprevalence across age groups, with a decrease among men <30, and an increase among men aged ≥45 years.
- Lifetime history of injection drug use was the preeminent risk factor for HCV seropositivity among MSM living in Montreal.
- Sexual behaviors did not exhibit strong associations with HCV exposure in our population.

Introduction

Canada is not on track to eliminate the hepatitis C virus (HCV) as a public health threat by 2030.[1, 2] Gay, bisexual, and other men who have sex with men (MSM) have been identified as a priority population for HCV micro-elimination.[3-5] Since 2000, HCV epidemics have been reported among MSM living with HIV in industrialized countries.[6] In this population, global HCV incidence has increased from 2.6/1,000 person-years pre-2000 to 8.1/1,000 person-years post-2010,[7] with high reinfection rates,[6] and global HCV seroprevalence was estimated at 6.4% from 2002-2015.[8] Comparatively, the HCV burden has remained stable among HIV-negative MSM, with estimates of seroprevalence ranging from 0.0-3.4%,[9-13] and a global incidence of 0.4/1,000 person-years.[14] Nevertheless, acute HCV infections have recently been reported among HIV-negative MSM without a history of injection drug use (IDU) in Europe,[15] the United States (US),[16] and Vancouver, British Columbia (Canada).[17] These data may mask variations across geographical settings, highlighting the importance of local contexts and related risks.

In industrialized countries, most HCV infections have been attributed to the use of unsterile needles and drug paraphernalia, and receipt of blood or blood products before the introduction of HCV screening.[18] In parallel, evidence from Europe, the US, and Vancouver shows that sexual transmission can account for a substantial proportion of incident HCV infections among MSM.[6, 17, 19-21] Two other overlapping population groups may be at increased risk of being chronically infected with HCV: individuals born between 1945-1975, due to exposures to HCV-contaminated blood and blood products before 1990,[22] and immigrants originating from HCV endemic countries.[23] Socio-economic factors such as education and income can also influence the risk of acquiring HCV among MSM.[19, 24-26] The impact of these factors on HCV transmission among MSM subgroups is context-dependent, and may vary by HIV status. Additionally, sexual and injecting behaviours may interact, for example through the practice of chemsex, a form of sexualized drug use associated with a higher risk of HCV infection among MSM.[27, 28] To date, there is little evidence of sexual transmission of HCV among MSM in

Canada.[12, 13, 17, 29, 30] Between 312,681-426,384 MSM live in Canada, representing approximately 2.6% of the adult male population.[w1] The size of this key population, the variability in HCV incidence and prevalence among MSM populations, as well as the diversity of potential routes of transmission reflect the importance of using locally-valid epidemiological evidence to inform tailored interventions targeting micro-elimination.

Scarce evidence exists on HCV prevalence and risk factors among MSM subgroups in Canadian cities. In Vancouver, HCV seroprevalence among all MSM was estimated at 4.9% in a cross-sectional study conducted in 2008-2009.[12] In this city, 16.8% of MSM living with HIV tested HCV seropositive, against 10.4% in a similar study conducted in Toronto, Ontario in 2010-2012.[13] Temporal trends in HCV seroprevalence among MSM have not been assessed in Canada, and available cross-sectional data suggest potential within-country variability in seroprevalence. In Montréal, Québec (Canada), recent and comprehensive information is required to inform HCV elimination interventions among MSM.

In this study, we aimed to 1) investigate temporal trends in HCV seroprevalence among MSM living in Montréal from 2005-2018, overall and stratified by HIV status, IDU status, and age group; and 2) identify the social, behavioural, and biological factors associated with HCV exposure among this heterogeneous population.

Methods

Data sources and harmonization

Three cross-sectional surveys of sexually transmitted and blood-borne infections were conducted among Montréal MSM in 2005, 2009, and 2018: Argus 1, Argus 2, and the first wave of the Engage cohort study, respectively. These surveys have been previously described.[w2, w3] Briefly, they combined HIV, HCV, and syphilis surveillance and behavioural monitoring through self-administered questionnaires. In 2005 (N=1,957) and 2009 (N=1,873), locations where MSM can be found were identified. In 2005, venues were selected using convenience sampling, and in 2009 time-location sampling was used, where

sampling probabilities are generated at the location- and individual-level.[w4, w5] In 2018, a community-based sample of 1,179 MSM was recruited using respondent-driven sampling (RDS), a link-tracing method that uses information about participants' social networks to estimate their probability of being recruited and adjust for the biases associated with over/under-sampling of certain groups.[w6] Eligibility criteria varied slightly across the three surveys (Table 4.3).

To compare the three surveys, we first harmonized the eligibility criteria across datasets. Our analyses were restricted to cis-gender men aged ≥18 years who reported sexual activity with a man in the past six months (P6M) and resided in Montréal. The sensitivity and specificity of the assays used for anti-HCV antibody detection in the three surveys were comparable (sensitivity: 100% in 2005, 2009, and 2018; specificity: 99.95% in 2005 and 2009, and 99.69% in 2018).[w2, w3, w7]

Temporal trends in HCV seroprevalence

We estimated HCV seroprevalence in 2005, 2009, and 2018, among all MSM, stratified by HIV status, lifetime history of IDU, and age group, and among HIV-negative MSM without a history of IDU. To ensure comparability of the samples across time, regression-based standardization was performed. The RDS-weighted 2018 survey was used as the standard and the other surveys were adjusted to yield the same distribution of age, sexual orientation, annual income, and first language. This was achieved by first fitting multivariable logistic regression models with HCV seropositivity as the outcome (defined as a positive anti-HCV antibody test) to the 2005 and 2009 data, separately. Age was modeled using a restricted cubic spline,[w8] and we investigated the presence of multiplicative statistical interaction between each pair of covariates. For the stratified analyses, the same model was fitted separately among each subgroup of interest. Using these models, we then predicted the individual probability of testing HCV seropositive using the covariate patterns observed in the 2018 standard sample, among all MSM and by subgroup. Finally, we computed the weighted mean of these individual probabilities using Volz-Heckathorn weights[w9] to estimate standardized HCV seroprevalence among the different groups at all time points.

We obtained 95% confidence intervals (CIs) using cluster-level block bootstrap, with clusters corresponding to the recruitment site in 2005 (n=40 sites) and 2009 (n=39 sites) and to the initial seed of the recruitment chain in 2018 (n=27 seeds). We performed complete case analyses as only 5% of observations had any missing value for the variables used in these estimations.[w10]

Factors associated with HCV seropositivity

Pooling data from the three surveys, we examined potential determinants of HCV seropositivity using prevalence ratios. We used univariable and multivariable modified Poisson regression models with generalized estimating equations (with exchangeable correlation structures), accounting for clustering.[w11-w13] The following predictors were selected a priori based on their potential association with HCV: survey year, lifetime history of IDU, HIV seropositivity, history of syphilis (defined as a reactive serological test), age (categorical), birth outside of Canada, annual income ≥30,000 Canadian dollars (CAD), education level higher than high school, sexual orientation other than gay/homosexual, self-identification as Indigenous, first language other than French/English, and specific sexual practices reported in the P6M: transactional sex (defined as having given/received money, drugs, or other goods or services in exchange for sex), condomless anal sex (CAS) with a man of serodiscordant/unknown HIV status, >5 male sexual partners, and group sex. We used multiple imputation by chained equations for missing values as 33% of observations had at least one missing value for these variables, principally information regarding (23%) CAS.[w14, w15]

We also investigated whether the impact of sexual practices on HCV varied by HIV status, and quantified the joint association of lifetime IDU and sexual behaviours with the outcome. We assessed the presence of additive and multiplicative interactions between the following terms: i) HIV seropositivity and four sexual risk factors reported in the P6M (i.e., transactional sex, CAS with a man of serodiscordant/unknown HIV status, number of sexual partners, and group sex) and ii) history of IDU and the same four factors. To evaluate multiplicative interaction, we included the product term of each selected pair of factors in

the main analysis model separately and examined the estimate and CI of each product term coefficient.[w16] Additive interaction was assessed by obtaining the relative excess risk due to interaction (RERI) and its CI.[w17, w18] All analyses were conducted using R 3.5.3,[w19] with the *RDS*,[w20] *geepack*,[w21] *mice*,[w15] and *dplyr*[w22] packages.

Ethical considerations

The research ethics board of the *Research Institute of the McGill University Health Center* approved all three surveys, and written informed consent was obtained from all participants.

Results

Characteristics of participants (pre-standardization)

A total of 4,139 MSM were included in our analyses (1,795 in 2005; 1,258 in 2009; 1,086 in 2018) (Figure 4.1). The pre-standardized proportion of participants living with HIV was 13% (95%CI: 11-14%) in 2005, 15% (95%CI: 13-17%) in 2009, and 18% (95%CI: 16-21%) in 2018 (Table 4.1). Unadjusted HCV antibody prevalence was 5% in 2005, 4% in 2009, and 5% in 2018. The raw percentage of participants with a history of IDU was 7% in 2005 (95%CI: 6-8%), 12% (95%CI: 10-14%) in 2009, and 10% (95%CI: 8-12%) in 2018.

Table 4.1. Description of participants included in three cross-sectional bio-behavioural surveys of men who have sex with men conducted in Montréal, Québec (Canada; 2005-2018; before any standardization).

Characteristic	2005 (N = 1,795) n (%)	2009 (N = 1,258) n (%)	2018 (N = 1,086) n (%)
HCV seropositivity	95 (5%)	49 (4%)	58 (5%)
HIV seropositivity	224 (13%)	193 (15%)	200 (18%)
Reactive syphilis serology	93 (5%)	116 (9%)	194 (18%)
Age	38 (28-47)†	40 (30-47)†	34 (28-49)†
Income ≥30,000 CAD in the past year	891 (50%)	763 (61%)	461 (42%)
Education level higher than high school	1,217 (68%)	537 (43%)	806 (74%)
Sexual orientation other than gay/homosexual	336 (19%)	107 (9%)	205 (19%)
Born outside of Canada	244 (14%)	194 (15%)	348 (32%)
Self-reported ethnicity or family background			
Indigenous	33 (2%)‡	16 (1%)	9 (1%)
English Canadian	146 (8%)‡	108 (9%)	103 (9%)
French Canadian	1,219 (68%)‡	865 (69%)	537 (49%)
European	105 (6%)‡	119 (9%)	157 (14%)
Asian	31 (2%)‡	14 (1%)	40 (4%)
Arab or North-African	28 (2%)‡	20 (2%)	44 (4%)
Sub-Saharan African	3 (<1%)‡	3 (<1%)	9 (1%)
Latin, South or Central American	60 (3%)‡	29 (2%)	92 (8%)
Caribbean	20 (1%)‡	7 (1%)	9 (1%)
Oceanian (e.g., Australian, Pacific Islander)	2 (<1%)‡	0	1 (<1%)
Other	84 (5%)‡	61 (5%)	74 (7%
First language other than French/English	125 (7%)	101 (8%)	74 (7%)
Transactional sex in the P6M§	329 (18%)‡	187 (15%)‡	108 (10%)
CAS with a man of serodiscordant/unknown HIV status in the P6M¶	200 (11%)‡	251 (20%)‡	395 (36%)‡

Characteristic	2005 (N = 1,795) n (%)	2009 (N = 1,258) n (%)	2018 (N = 1,086) n (%)
> 5 male sexual partners in the P6M	664 (37%)	569 (45%)	533 (51%)
Group sex in the P6M	479 (27%)	407 (32%)‡	252 (23%)
History of injection drug use¥	128 (7%)‡	147 (12%)	110 (10%)

CAD: Canadian dollars, CAS: condomless anal sex, P6M: past six months.

† Median (interquartile range).

‡ More than 2% of observations were missing for this variable, in this dataset.

§ Transactional sex was defined as having given/received money, drugs, or other goods or services in exchange for sex in the past 6 months.

¶ Male sexual partners included both oral and anal sexual partners.

¥ Lifetime injection of any non-prescribed drug was considered as a previous experience of injection drug use.

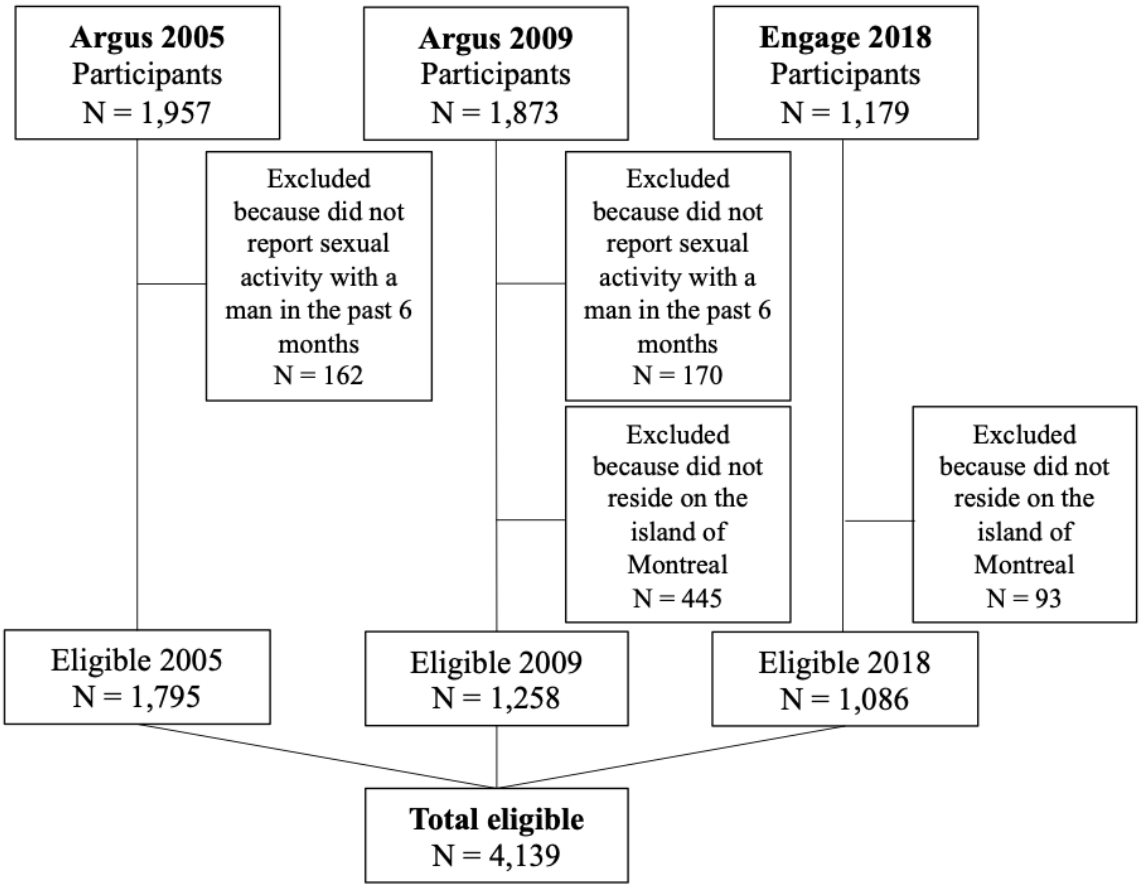

Figure 4.1. Study eligibility flowchart.

Figure legend: Study eligibility flowchart. Individuals missing values on any eligibility criterion were excluded from our analyses.

Temporal trends in HCV seroprevalence (post-standardization)

Standardized HCV seroprevalence among all MSM remained stable, ranging from 7% (95%CI: 3-10%) in 2005, to 8% (95%CI: 1-9%) in 2009, and 8% (95%CI: 4-11%) in 2018 (Figure 4.2, Table 4.4).

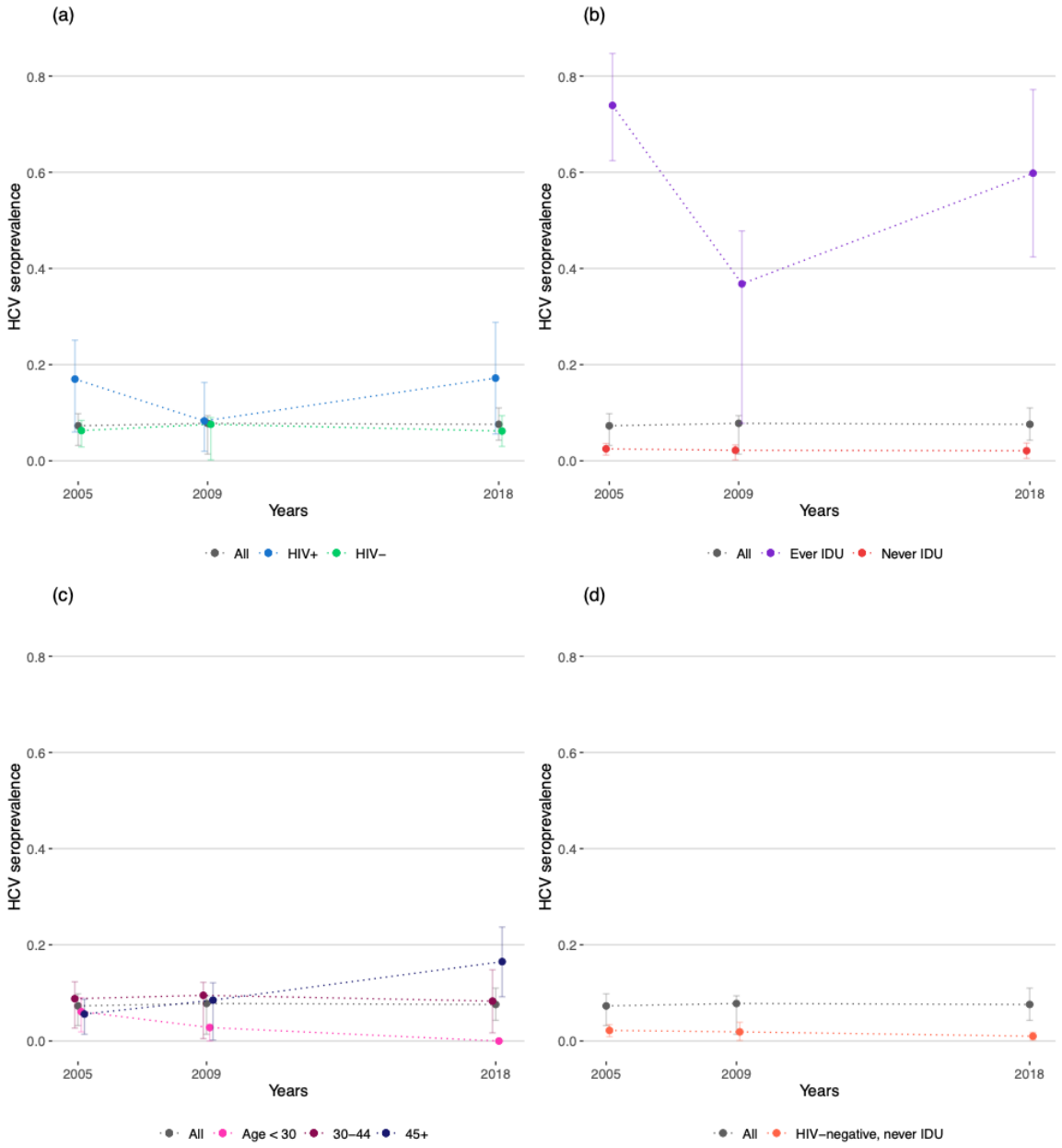

Figure 4.2. Standardized HCV seroprevalence estimates.

Figure legend: HCV seroprevalence estimates among gay, bisexual, and other men who have sex with men (MSM) overall, stratified by (a) HIV status, (b) lifetime history of injecting drug use (IDU), and (c) age group, and among (d) HIV-negative MSM without a history of IDU in 2005, 2009, and 2018 in Montréal, Québec (Canada).

Stratification by HIV and IDU status did not reveal consistent temporal trends in HCV seroprevalence among these subgroups. We observed a drop in estimates for MSM living with HIV and MSM with a history of IDU in 2009 and obtained relatively wide CIs among these two groups due to smaller numbers of observations. The highest HCV seroprevalence point estimates were obtained among participants with a history of IDU, with 74% (95%CI: 62-85%) in 2005, 37% (95%CI: 8-48%) in 2009, and 60% (95%CI: 42-77%) in 2019. In contrast, HCV seroprevalence among MSM without a history of IDU was estimated at 3% (95%CI: 1-4%) in 2005, 2% (95%CI: 0-3%) in 2009, and 2% (95%CI: 1-4%) in 2018. HCV seropositivity was also far more common among MSM living with HIV at 17% (95%CI: 6-25%) in 2005, 8% (95%CI: 2-16%) in 2009, and 17% (95%CI: 6-29%) in 2018, than among HIV-negative MSM at 6% (95%CI: 3-8%) in 2005, 8% (95%CI: 0-9%) in 2009, and 6% (95%CI: 3-9%) in 2018. Finally, HCV seroprevalence remained relatively stable among HIV-negative MSM without a history of IDU at 2% (95%CI: 1-3%) in 2005, 2% (95%CI: 0-4%) in 2009, and 1% (95%CI: 0-2%) in 2018.

When stratifying by age group, we observed a decrease in HCV seroprevalence among MSM <30 years old over time, from 6% (95%CI: 2%-9%) in 2005, to 3% (95%CI: 0-3%) in 2009, and 0% (95%CI: 0-1%) in 2018. We noted no clear temporal trend in HCV seroprevalence among MSM aged 30-44 years (9%; 95%CI: 3-12% in 2005, 10%; 95%CI: 1-12% in 2009, and 8%; 95%CI: 2-15% in 2018). Among MSM aged ≥45 years, HCV seroprevalence increased from 6% (95%CI: 1-9%) in 2005 to 9% (95%CI: 0-12%) in 2009 and to 17% (95%CI: 9-24%) in 2018.

Factors associated with HCV seropositivity

Lifetime history of IDU was the strongest predictor of HCV seropositivity in our population (Table 4.2). Increased age, recent transactional sex, HIV seropositivity, and sexual orientation other than gay/homosexual were also associated with increased HCV seroprevalence. Our results suggest an association between socio-economic factors and the outcome: MSM with higher income and education level were less likely to test HCV-seropositive. Being born outside of Canada was also associated with lower HCV

seroprevalence. Few participants identified as Indigenous (1-2% across surveys), leading to wide uncertainty around the aPR for this population group. We found no association between recent sexual behaviours studied and HCV seropositivity. Finally, first language other than French/English was not associated with a variation in the outcome.

Table 4.2. HCV seroprevalence ratios obtained by pooling three cross-sectional surveys of men who have sex with men conducted in Montréal, Québec (Canada) (2005, 2009, 2018).

Covariates	Univariable prevalence ratio (95% confidence interval)	Multivariable prevalence ratio (95% confidence interval)
History of IDU	18.2 (12.2-27.2)	8.0 (5.5-11.5)
Age		
<30	1.00	1.00
30-44	2.1 (1.4-3.2)	2.2 (1.5-3.3)
≥45	1.9 (0.9-4.1)	2.5 (1.6-3.9)
Transactional sex (P6M)	4.6 (3.0-7.1)	2.1 (1.7-2.5)
HIV seropositivity	2.9 (1.8-4.8)	1.7 (1.3-2.3)
Sexual orientation other than gay/homosexual	5.4 (3.2-9.2)	1.6 (1.3-2.1)
Income ≥30,000 CAD in the past year	0.3 (0.2-0.4)	0.5 (0.4-0.7)
Born outside of Canada	0.2 (0.0-0.6)	0.5 (0.3-0.9)
Year of data collection		
2005	1.0	1.0
2009	0.4 (0.2-0.8)	0.5 (0.3-0.8)
2018	0.9 (0.3-2.4)	1.0 (0.7-1.4)
Education level higher than high school	0.2 (0.1-0.3)	0.4 (0.3-0.6)
Self-identified Indigenous ethnicity or family background	1.1 (0.1-23.7)	1.4 (0.4-4.5)
Reactive syphilis serology	0.9 (0.4-1.9)	1.1 (0.7-1.6)
1st language other than French/English	0.4 (0.1-1.0)	1.0 (0.5-2.0)
> 5 male sexual partners (P6M)	0.8 (0.5-1.4)	1.0 (0.7-1.3)
Group sex in the P6M	0.8 (0.5-1.2)	0.8 (0.6-1.2)
CAS with a man of serodiscordant/ unknown HIV status (P6M)	0.7 (0.3-1.6)	0.7 (0.5-1.1)

CAD: Canadian dollars; CAS: condomless anal sex; IDU: injecting drug use; P6M: past 6 months.

Sensitivity analyses

We detected negative additive and multiplicative interactions between HIV seropositivity and transactional sex in the P6M (Table 4.5). The presence of negative additive and multiplicative interactions means that the association with HCV seropositivity when both factors are present is smaller than, respectively, the sum and product, of the individual associations of the two factors with the outcome. We also identified negative additive interactions between history of IDU and each sexual risk factors studied, separately, and a positive multiplicative interaction between history of IDU and group sex in the P6M. A positive multiplicative interaction indicates that the association when both factors are present is stronger than the product of the individual associations.

Discussion

Standardizing and pooling three large cross-sectional surveys of MSM from 2005-2018, our results suggest that HCV seroprevalence has remained stable around 8% in Montréal, at a higher level than in other North American settings (3-5%).[12, w23, w24] Despite this overall stability, we observed diverging trends among age groups. Monitoring changes in HCV seroprevalence among young adults has been used to gauge trends in HCV incidence in the general population.[3] The decrease observed in HCV seroprevalence among younger participants may therefore indicate a decline in new HCV infections among MSM from 2005-2018. In contrast, the increase in HCV seroprevalence among MSM aged ≥45 years may reflect birth cohort effects (i.e., males born between 1945-1975[22]), temporal changes in injecting and/or sexual behaviours among older MSM, or changes in inter-generational transmission of HCV over time.

HCV seroprevalence was particularly high among MSM living with HIV, and MSM with a history of IDU. The drop in seroprevalence observed in 2009 among these groups could indicate temporal changes in injecting behaviours (e.g., increased number of new injectors never exposed to HCV). However, these results could reflect remaining differences in the composition of the samples post-standardization. HCV seroprevalence among HIV-

negative MSM in Montréal ranged from 6-8% between 2005-2018, on the high end of estimates from Canada,[13] the US,[w24] and Europe.[10] The seroprevalence estimated among MSM without a history of IDU (2-3%) was also twice as high as that estimated in Vancouver for the same group.[12] These numbers are greater than the 1% HCV seroprevalence estimated for the general Canadian population.[w25] Yet, the seroprevalence observed among HIV-negative MSM without a history of IDU (1-2%) was comparable to that among the general population, in line with previous findings from Argus 1.[w26] The relatively high HCV seroprevalence observed among all MSM may therefore reflect frequent exposure to the virus among subgroups with particular vulnerabilities (e.g., HIV infection) or risk behaviours (e.g., IDU).

Reporting a history of IDU was the strongest predictor of HCV seropositivity among Montréal MSM between 2005-2018. This is concerning given that the proportion of MSM who reported lifetime IDU in Engage (6%[w3]) is twelve times that reported among the general population in Montréal (0.5%[w27]). Aside from recent transactional sex, which encompasses having given/received drugs in exchange for sex, we observed no association between sexual behaviours and HCV seroprevalence. These results are consistent with those obtained in Toronto,[13] and a study conducted in 2001 among Montréal MSM.[29] However, they contrast with emerging evidence from Vancouver[17] and with studies conducted in Europe[6] and the US,[14] where sexual risk factors were strongly associated with new HCV infections among MSM.

We observed no positive interactions between HIV-positivity and sexual behaviours. One potentially important risk factor that we could not directly investigate is chemsex. Nevertheless, the positive multiplicative interaction observed between group sex and IDU could partly capture the association of chemsex practices with HCV seroprevalence, although we could not measure the concomitance of injecting and sexual behaviours. No positive interaction was observed between history of IDU and other sexual risk factors.

Altogether, higher socio-economic status (i.e., income and education) was associated with lower HCV seroprevalence. Our data did not allow us to specifically examine the

relationship between birth in HCV endemic countries and HCV seropositivity. In this regard, interpreting the negative association between birth outside of Canada and HCV seroprevalence is challenging. Having a first language other than French/English, another proxy for country of origin, was not associated with the outcome. Reporting a sexual orientation other than gay/homosexual was positively associated with HCV seropositivity. Because data on sexual orientation were categorized differently across our three surveys, the "other" category represents varied self-reported sexual orientations (bisexual, heterosexual, and queer). Few studies have examined the distribution of sexually transmitted and blood-borne infections by sexual orientation among MSM populations. [w28-w30] Understanding these complex links remains challenging and studies did not consistently identify groups most at risk or with unmet prevention needs.

Our results should be interpreted considering the study's main limitations. First, cross-sectional data render the interpretation of observed associations challenging due to a temporality bias. However, pooling the available data allowed us to produce robust, comparable estimates of HCV exposure across time, and to investigate the plausibility of different modes of transmission of the virus among these groups. Second, we could not investigate the relationship between lifelong sexual practices and HCV seropositivity due to data limitations. Yet, we could quantify the adjusted association of numerous recent sexual behaviours with HCV exposure.

Strengths of this study include its large sample size, resulting from the pooling of three comparable surveys. To maximize internal validity, we standardized our three samples on variables whose distributions should have remained relatively stable over time. Although generalizability to the target population cannot be directly assessed, we used the community-based, RDS-adjusted Engage sample as a standard. Additionally, recent epidemiological data on HCV exposure and determinants among MSM living in Montréal is lacking, and very few population-based studies have examined HCV prevalence trends among MSM subgroups globally. As such, our work provides a unique opportunity to inform local public health interventions. Canadian guidelines recommend HCV screening among people born from 1945-1975, with a history of IDU, and/or living with HIV, and

treatment for all chronically infected people.[w31] In addition, specific efforts should be directed towards understanding and reducing harms associated with IDU practices among MSM.

Conclusions

HCV seroprevalence remained high among Montréal MSM between 2005-2018, likely reflecting frequent exposure to the virus among MSM living with HIV and MSM with a history of IDU. Unlike other settings where HCV infection was strongly associated with sexual risk factors among MSM subgroups, history of IDU was the preeminent risk factor for HCV seropositivity among Montréal MSM. Understanding the intersection of IDU contexts, practices, and populations is essential to prevent HCV transmission among these overlapping populations.

Competing interests

C.L.D., G.L., D.G., and N.L. have no conflicts of interest to declare. J.C. has received research grant funding from Gilead Sciences, Merck Canada, and ViiV Healthcare. He also received travel support and honoraria for advisory work from Gilead Sciences, Merck Canada and ViiV Healthcare. M.K. reports grants for investigator-initiated studies from ViiV Healthcare, Merck, and Gilead; research grants from Janssen; personal fees from ViiV Healthcare, Bristol-Myers Squibb, AbbVie, and Gilead, all outside the submitted work. M.M.-G. reports grant funding from Gilead Sciences.

Authors' contributions

C.L.D., J.C., M.K., and M.M.-G. conceived and designed the study. J.C. and G.L. were involved in the study design and data collection of the Argus 1 and 2 surveys. J.C., G.L., D.G., and N.L. were involved in the study design and data collection of the Engage study. C.L.D. administered and processed the different databases. C.L.D. performed the statistical analyses with inputs from M.K. and M.M.-G. All authors contributed to results interpretation. C.L.D. drafted the manuscript and all authors critically reviewed it for important intellectual content. All authors approved the final version.

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4.3. Manuscript 1 – Appendix

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Table 4.3. Eligibility criteria for participating in the Argus 1 (2005), Argus 2 (2009), and Engage (2018) studies conducted in Montréal, Québec (Canada).

Study	Eligibility criteria
Argus 1 (2005)	- Gender-identify as a man - Have ever had sex with a man - Be 18 years of age or older - Speak French or English - Reside on the island of Montréal - Be able to provide informed consent
Argus 2 (2009)	- Gender-identify as a man - Have ever had sex with a man - Be 18 years of age or older - Speak French or English - Reside in the province of Quebec - Be able to provide informed consent
Engage (2018)	- Gender-identify as a man - Report sexual activity with a man in the past 6 months - Be 16 years of age or older - Be able to complete a computer-based questionnaire in French or English - Reside in the greater Montréal region - Be able to provide informed consent - Receive a voucher for participation in the study, or be purposively invited to be an initial "seed"

Table 4.4. Standardized HCV seroprevalence among all men who have sex with men (MSM) and stratified by HIV status, by injection drug use status, and by age group, in 2005, 2009, and 2018 in Montréal, Québec (Canada).

	Standardized HCV seroprevalence (95% confidence interval)		
Group	**2005**	**2009**	**2018**
All MSM	7% (3-10)	8% (1-9)	8% (4-11)
MSM living with HIV	17% (6-25)	8% (2-16)	17% (6-29)
HIV-negative MSM	6% (3-8)	8% (0-9)	6% (3-9)
MSM with a history of IDU	74% (62-85)	37% (8-48)	60% (42-77)
MSM without a history IDU	3% (1-4)	2% (0-3)	2% (1-4)
MSM aged <30 years old	6% (2-9)	3% (0-3)	0% (0-1)
MSM aged 30-44 years old	9% (3-12)	10% (1-12)	8% (2-15)
MSM aged ≥45 years old	6% (1-9)	9% (0-12)	17% (9-24)
HIV-negative MSM without a history of IDU	2% (1-3)	2% (0-4)	1% (0-2)

IDU: injection drug use; MSM: men who have sex with men.

Table 4.5. Adjusted prevalence ratios of multiplicative interaction terms and relative excess risk due to interaction of selected potential risk factors for HCV seropositivity pooling three cross-sectional surveys of men who have sex with men in Montréal, Québec

Interaction studied	Exponentiated coefficient of the multiplicative interaction term (95% confidence interval)	Relative excess risk due to interaction (95% confidence interval)
HIV infection; CAS with a man of serodiscordant/ unknown HIV status (P6M)	1.0 (0.4; 2.3)	-0.5 (-1.5; 0.9)
HIV infection; >5 male sexual partners (P6M)	0.9 (0.5; 1.6)	-0.8 (-1.7; 0.1)
HIV infection; transactional sex (P6M)	0.6 (0.4; 0.9)	-3.3 (-4.6; -2.3)
HIV infection; group sex (P6M)	0.9 (0.5; 1.7)	-0.8 (-1.7; 0.2)
History of IDU; CAS with a man of serodiscordant/ unknown HIV status (P6M)	1.0 (0.5; 1.9)	-6.7 (-10.2; -4.1)
History of IDU; >5 male sexual partners (P6M)	1.1 (0.7; 1.8)	-6.5 (-10.6; -3.8)
History of IDU; transactional sex (P6M)	0.9 (0.6; 1.6)	-8.9 (-13.9; -5.6)
History of IDU; group sex (P6M)	2.0 (1.1; 3.7)	-4.6 (-7.9; -1.7)

CAS: condomless anal sex; IDU: lifetime injection drug use; P6M: past 6 months.

These interaction terms were included in the multivariable model described in table 4, separately.

All the variables used in the interaction terms are binary (coded 0,1).

5. Chapter 5: Strategies to achieve HCV micro-elimination among people who inject drugs by 2030

5.1. Preface to Manuscript 2

Findings from Manuscript 1 suggest that HCV elimination strategies for MSM should be evaluated with a model that represents HCV transmission via IDU and incorporates HIV transmission dynamics. Therefore, I used a single model to evaluate HCV elimination strategies for PWID and MSM. Because all individuals represented in the model have a history of IDU, they are further referred to as PWID.

I developed a dynamic, compartmental model of HCV and HIV transmission among PWID living in Montreal. This model served for both studies presented in Manuscripts 2 and 3, and Manuscript 3 was published first. Full model details are therefore presented in the main text and supplementary material of Manuscript 3. In Manuscript 2, I first generated evidence on the type of intervention(s) to prioritise if we want to eliminate HCV as a public health threat among all PWID and among PWID LWH by 2030 in Montreal. Second, I investigated the implications of focusing these interventions on PWID LWH and active injectors. Third, these simulations accounted for reduced access to HCV prevention and care services in the context of the COVID-19 pandemic. This manuscript has been submitted to a peer-reviewed journal.

5.2. Manuscript 2: Public health interventions, priority populations, and the impact of COVID-19 disruptions on hepatitis C micro-elimination among people who inject drugs in Montreal (Canada): a modeling study

Charlotte Lanièce Delaunay[1,2], Marina B Klein[1,2,3,4], Arnaud Godin[3], Joseph Cox[1,2,3], Nadine Kronfli[1,2,3], Bertrand Lebouché[2,3,5], Carla Doyle[1], Mathieu Maheu-Giroux[1,§]

[1] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

[2] Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

[3] Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada

[4] CIHR Canadian HIV Trials Network, Vancouver, British Columbia, Canada

[5] Department of Family Medicine, McGill University, Montreal, Quebec, Canada

[§] Corresponding author: Mathieu Maheu-Giroux

2001 Avenue McGill College

Montréal, Québec H3A 1G1, Canada

Phone: 001 514-398-5110

Email: mathieu.maheu-giroux@mcgill.ca

Keywords: people who inject drugs; people living with HIV; mathematical modeling; hepatitis C; elimination; COVID-19.

Abstract

Introduction: In Montreal (Canada), high hepatitis C virus (HCV) seroincidence (21 per 100 person-years in 2017) persists among people who have injected drugs despite relatively high testing rates and coverage of needle and syringe programs and opioid agonist therapy. HCV seroprevalence is higher among people who have injected drugs living with HIV (86% in 2018) than among all people who have injected drugs (69%). We assessed the potential of interventions to achieve HCV elimination (80% incidence reduction and 65% reduction in HCV-related mortality between 2015 and 2030) in the context of COVID-19 disruptions among all people who have injected drugs and people who have injected drugs living with HIV.

Methods: Using a dynamic model of HIV-HCV co-transmission, we simulated increases in needle and syringe programs (from 82% to 95%) and opioid agonist therapy (from 33% to 40%) coverage, HCV testing (every 6 months), or treatment rate (100 per 100 person-years) starting in 2022 among all people who have injected drugs and those living with HIV. We also modeled treatment scale-up among active injectors only. We reduced intervention levels in 2020-2021 due to COVID-19-related disruptions. Model outcomes included HCV incidence, prevalence, and mortality, and proportions of averted HCV infections and deaths.

Results: COVID-19-related disruptions could have caused temporary rebounds in HCV transmission. Further increasing coverage of needle and syringe programs/opioid agonist therapy, or HCV testing had little impact. Scaling-up treatment among all people who have injected drugs achieved incidence and mortality targets among all people who have injected drugs and those living with HIV. Increasing HCV treatment rates among people who have injected drugs living with HIV led to substantial progress towards elimination but was insufficient to achieve it. Finally, focusing treatment on active injectors could achieve elimination, yet fewer projected deaths were averted over 2022-2030 (36% versus 48%).

Conclusions: HCV treatment scale-up among all people who have injected drugs will be required to eliminate HCV in high-incidence and prevalence settings. Achieving elimination by 2030 will entail concerted efforts to restore and enhance pre-pandemic levels of HCV prevention and care.

Introduction

If untreated, chronic hepatitis C virus (HCV) infection can cause cirrhosis, liver cancer, and death [1]. Direct-acting antivirals (DAAs) cure HCV in over 95% of those treated, regardless of co-infection with HIV [2]. The *World Health Organization* (WHO) targets for HCV elimination as a public health threat include reductions of 80% in chronic HCV incidence and 65% in HCV-related mortality between 2015 and 2030 [3]. In Canada, 85% of new HCV infections are diagnosed among people who have injected drugs (PWID) –a priority population for elimination [4, 5]. PWID living with HIV are less likely to spontaneously clear HCV and experience faster liver disease progression [6]. By the time they develop end-stage liver disease, most people PWID have ceased injecting [1, 7]. Hence, ex-injectors should be considered for preventing HCV-related deaths. In Montreal (Quebec, Canada), 82% of active injectors (i.e., people who report injecting in the past six months) use needle and syringe programs (NSP) and 33% are on opioid agonist therapy (OAT) –close to the 40% recommended coverage [8]. They are tested for HCV every 14 months on average (annual testing is recommended) [9, 10], and DAAs are universally accessible. Yet, HCV seroincidence is high among active injectors (21 per 100 person-years [PY] in 2017), and seroprevalence is higher among active injectors living with HIV (86% in 2018) than among all active injectors (69%) [9]. However, those living with HIV are mostly engaged in care, and thus more easily reached by interventions [11].

Traditionally, HCV prevention for PWID has relied on harm reduction programs such as NSP and OAT [12]. Following the introduction of DAAs, studies have suggested that HCV "treatment-as-prevention" can reduce HCV incidence and prevalence among PWID [13-15]. Results are context-dependent, but regular testing, broad DAA access, and high-coverage harm reduction programs are likely essential to any HCV elimination response [14]. However, few studies have explored elimination strategies implemented among and for PWID living with HIV specifically. One modeling study conducted in Spain showed that increasing DAA uptake among PWID living with HIV was unlikely to achieve the WHO incidence reduction target due to ongoing HCV transmission from HIV-negative PWID [16]. Further, the effects of focused interventions on active and/or ex-injectors on

HCV-related mortality are unknown. Finally, starting in 2020, the COVID-19 pandemic has disrupted HCV prevention and care services for PWID across Canada and exacerbated the pre-existing overdose crisis [17-19]. The impact of these disruptions could have compromised recent progress towards elimination.

Informed by robust data, dynamic models of disease transmission can simulate the course of an epidemic under different "what if" scenarios and estimate direct and indirect effects of interventions [20]. Our overall objective was to assess the potential of various intervention scenarios to achieve HCV elimination among all PWID and PWID living with HIV by 2030 in Montreal. Multiple local initiatives aim to eliminate HCV and we can leverage population-based surveys to inform elimination efforts [9, 21, 22]. To strengthen the evidence base for elimination strategies we: 1) examined strategies for PWID subgroups (all PWID or PWID living with HIV; active and/or ex-injectors); 2) evaluated both incidence and mortality reduction targets; and 3) explored COVID-19-related disruptions.

Methods

Model structure

We used a dynamic, compartmental model of HCV and HIV transmission via injection drug use among PWID. The model's full description, including its parameterization and calibration can be found elsewhere [23]. Briefly, seven compartments represent HCV infection and care cascade: 1) susceptible to HCV infection (HCV-seronegative); 2) acute infection (primary infection); 3) susceptible to HCV re-infection (HCV-seropositive); 4) acute infection (re-infection); 5) undiagnosed chronic HCV infection; 6) diagnosed chronic HCV infection; 7) under treatment. Seven compartments describe HIV infection and care cascade: 1) susceptible to HIV infection; 2-4) living with HIV, not on antiretroviral treatment (ART), stratified by CD4 cell counts (>350 cells/mm^3, 200-350 cells/mm^3, <200 cells/mm^3), and 5-7) living with HIV, on ART, stratified by CD4 cell counts. Injecting behaviour dynamics are modeled through three compartments: 1) active injectors not on

OAT; 2) active injectors on OAT; 3) ex-injectors (regardless of OAT status). People enter the model upon first injection and exit upon death (HCV-related, AIDS-related, or from other causes).

For both viruses, we used time-varying forces of infection that depend on prevalence among injecting contacts (depending on mixing by sex, HIV status, and injecting behaviours), NSP and OAT coverage, and treatment status of injecting partners [23]. We also modeled the impact of HIV infection and linkage-to-care on HCV natural history and care: people living with HIV are less likely to spontaneously clear HCV [24]; those not on ART have higher HCV-related mortality rates [25]; and those on ART have facilitated access to HCV testing and treatment [11].

Model parametrization and calibration

To inform model parameters, we used data from *SurvUDI*, the HIV/HCV bio-behavioural surveillance network among active injectors in Quebec [9] and the *Canadian Co-infection Cohort*, a prospective study of HIV-HCV co-infected people [21]. We retrieved complementary information from the literature –primarily from systematic reviews and meta-analyses. We used the Bayesian sampling importance resampling algorithm for model calibration [23, 26]. Specifically, we included the following annual empirical targets (*SurvUDI*; 2003-2018): HCV seroprevalence, HCV seroincidence, HIV prevalence, HIV incidence, joint prevalence of anti-HCV antibodies and HIV, and ART coverage among those living with HIV. As the last calibration data available were in 2018, we assumed constant parameter values from 2018 to March 2020. From March 2020 to May 2021, we modeled COVID-19-related disruptions by reducing access to HCV services. Based on emerging Canadian literature and information provided by local community organizations, we modeled a 50% reduction in HCV testing and treatment rates and a 15% reduction in NSP and OAT coverage [17, 18, 27, 28]. We assumed that pre-COVID-19 intervention levels (i.e., 2018 parameter values) were restored in June 2021.

Intervention scenarios and model outcomes

Between 2022 and 2030, we simulated eight intervention scenarios, including a *status quo* scenario with unchanged intervention levels. In other scenarios, intervention levels increased linearly to reach values provided in Table 5.1 in 2024, and then remained constant until 2030. We set a limit of 95% for HCV diagnosis and treatment coverage because existing interventions make it difficult to reach higher coverage. To isolate the impact of each intervention, we modeled them separately in the main analyses. We obtained intervention parameter values by triangulating information about current intervention levels in Montreal, Canadian public health guidelines, results from empirical and modeling studies, and consulting HCV care providers [8, 9, 29-31]. For each scenario, we generated point estimates using medians and 95% credible intervals (95%CrIs) for all outcomes described in Table 5.2.

Table 5.1. Public health intervention scenarios modeled from 2022 to 2030 among different subgroups of people who have injected drugs in Montreal, Quebec, Canada.

Scenario number	Intervention description	Priority population	Intervention parameter values			
			Opioid agonist therapy coverage	Needle and syringe program coverage	Baseline HCV testing rate	Baseline HCV treatment rate†
1	Status quo	-	33%	82%	85 per 100 PY	10 to 30 per 100 PY
2	Increased harm reduction coverage	Active injectors‡ living with HIV	40%	95%	85 per 100 PY	10 to 30 per 100 PY
3	Increased HCV testing rates	People who have injected drugs living with HIV	33%	82%	200 per 100 PY	10 to 30 per 100 PY
4	Increased HCV treatment rates	People who have injected drugs living with HIV	33%	82%	85 per 100 PY	100 per 100 PY
5	Increased harm reduction coverage	All active injectors	40%	95%	85 per 100 PY	10 to 30 per 100 PY

6	Increased HCV testing rates	All people who have injected drugs	33%	82%	200 per 100 PY	10 to 30 per 100 PY
7	Increased HCV treatment rates	All people who have injected drugs	33%	82%	85 per 100 PY	100 per 100 PY
8	Increased HCV treatment rates	All active injectors	33%	82%	85 per 100 PY	100 per 100 PY

†People living with HIV who are on antiretroviral treatment have higher HCV testing and treatment rates. The range of "*10 to 30 per 100 PY*" corresponds to the calibrated baseline treatment rate.

‡People who report injecting drugs in the past six months.

HCV: hepatitis C virus; PY: person-years.

Table 5.2. Model outcome definitions, populations, and timeframes

Outcome definition	Populations	Timeframe†
Relative reduction in chronic HCV incidence	- All active injectors‡ - Active injectors living with HIV	2015-2030
Relative reduction in HCV-related mortality	- All people who have injected drugs - People who have injected drugs living with HIV	2015-2030
Relative reduction in chronic HCV prevalence	- All active injectors - Active injectors living HIV	2015-2030
Cumulative proportion of incident chronic infections averted as compared to status quo scenario	- All active injectors - Active injectors living HIV	2022-2030
Cumulative proportion of HCV-related deaths averted as compared to status quo scenario	- All people who have injected drugs - People who have injected drugs living with HIV	2022-2030

†All intervention scenarios were modeled from 2022 to 2030. The *World Health Organization*'s targets for HCV incidence and mortality reductions are defined over the 2015-2030 timeframe.

‡People who report injecting drugs in the past six months.

HCV: hepatitis C virus.

Sensitivity analyses

We modeled scenarios combining previously described interventions. We also simulated the eight scenarios described above assuming no COVID-19 disruptions in HCV services in 2020-2021.

Ethics

This study was approved by the *McGill University Health Centre Research Ethics Board* (REB#: MP-37-2019-4700). Our analyses were conducted using publicly available data sources. Hence, consent was not necessary for this study.

Results

Model calibration and pre-intervention period

Our calibrated model was able to reproduce survey estimates (Additional file 1; Figure 5.3) [23]. In 2015, year of reference for HCV elimination targets, the median chronic HCV incidence was 12 per 100 PY (95%CrI: 10-15) among all active injectors, and 17 per 100 PY (95%CrI: 14-19) among those living with HIV. The median HCV-related mortality rate was 5 per 1000 PY (95%CrI: 4-8) among PWID, and 9 per 1000 PY (95%CrI: 7-14) among PWID living with HIV. Fifty-one percent (95%CrI: 45-59) of all active injectors and 77% (95%CrI: 70-84) of those living with HIV were chronically infected with HCV. Following universal coverage of DAAs in 2015, HCV incidence, prevalence, and mortality started decreasing (Figure 5.1). In 2022, the modeled population size consisted of an estimated 5,300 active injectors –14% living with HIV– and 18,000 ex-injectors.

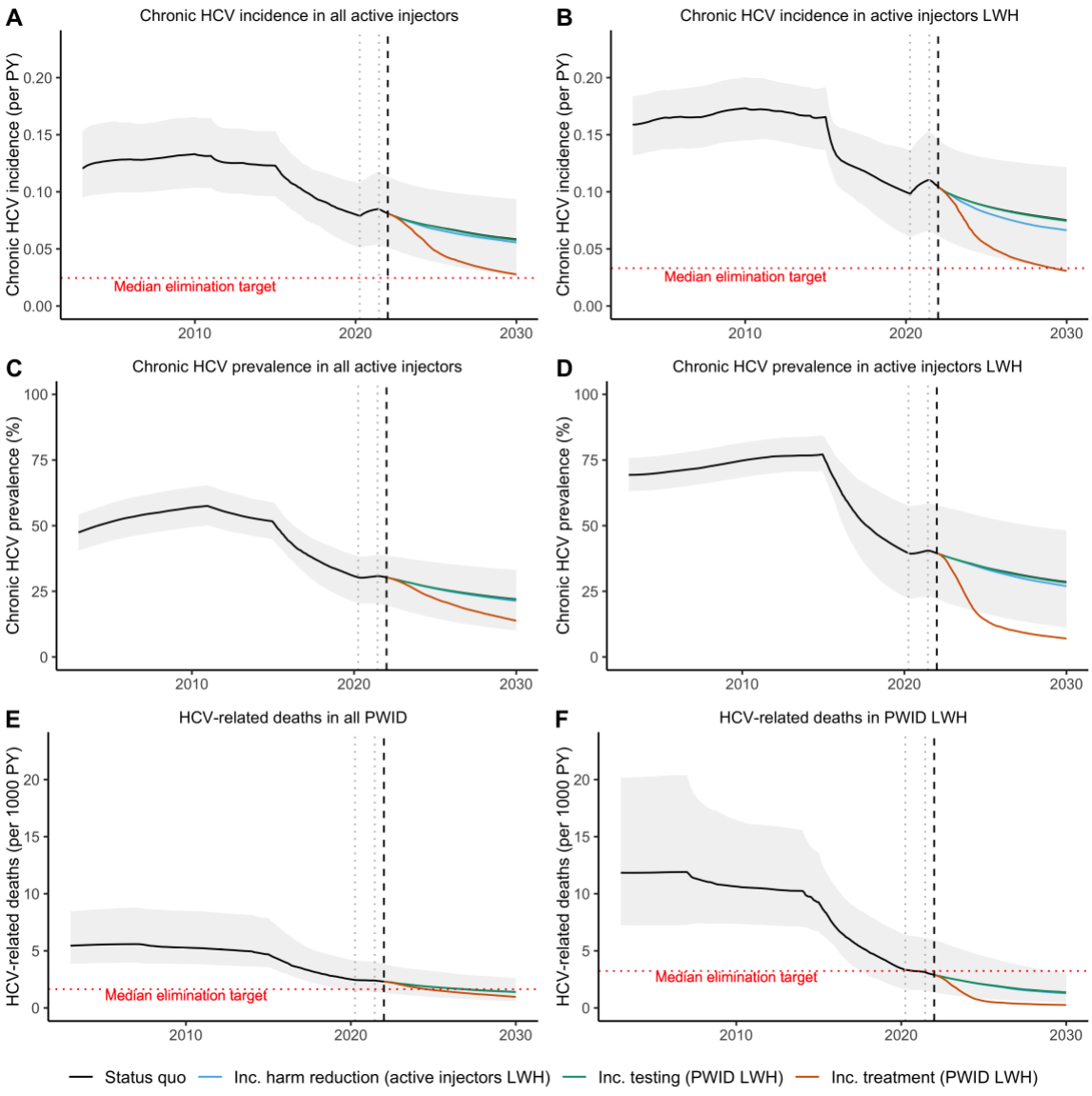

Figure 5.1. HCV outcomes among PWID and PWID living with HIV when implementing interventions among PWID living with HIV

Figure legend: Simulated chronic HCV incidence among all active injectors (i.e., people who report injecting in the past six months) (A) and active injectors living with HIV (B), chronic HCV prevalence among all active injectors (C) and active injectors living with HIV (D), and HCV-related mortality among all PWID (E) and PWID living with HIV (F) under various intervention scenarios implemented among PWID living with HIV in

Montreal, Canada, from 2003 to 2030. The grey ribbons represent 95% credible intervals around estimates for the status quo scenario. The grey dotted vertical lines represent the start (March 2020) and stop (May 2021) dates of modeled disruptions in HCV care and prevention services due to the COVID-19 pandemic. The black dashed vertical line represents the start date (January 2022) of modeled intervention scenarios. ***Abbreviations****: HCV: hepatitis C virus; Inc.: increased; LWH: living with HIV; PWID: people who have injected drugs.*

Impact of COVID-19 disruptions

Between March 2020 and May 2021, reductions in access to HCV services led to temporary increases in median chronic HCV incidence (from 8 to 8.5 per 100 PY) and prevalence (from 30% to 31%).

Status quo

When keeping all intervention levels constant post-2022, the HCV incidence reduction target was met in 1% of simulations among all active injectors and 3% among those living with HIV. The posterior probabilities of achieving the mortality reduction target were 68% and 98% for PWID and PWID living with HIV, respectively. Between 2015 and 2030, chronic HCV prevalence decreased by a median of 58% (95%CrI: 47-69) among all active injectors and by 62% (95%CrI: 52-73) among those living with HIV. Nevertheless, 2,080 (95%CrI: 1,760-2,330) PWID became chronically infected with HCV between 2022-2030, including 270 (95%CrI: 220-330) living with HIV. During the same period, 300 (95%CrI: 230-410) PWID died of HCV-related causes, of whom 50 (95%CrI: 40-70) were living with HIV.

Interventions among PWID living with HIV

Increasing harm reduction coverage (scenario 2) or HCV testing (scenario 3) among those living with HIV made little additional difference compared to status quo: incidence targets

were not met more frequently among all active injectors or those living with HIV, and it was uncertain whether the mortality target could be achieved among all PWID (Figure 5.1). Decline in chronic HCV prevalence was also similar to that observed under the status quo. Negligible proportions of cumulative chronic HCV cases and HCV-related deaths were averted between 2022 and 2030 in comparison to status quo (Table 5.3).

Table 5.3. Hepatitis C infections and deaths under various intervention scenarios among people who have injected drugs from 2022 to 2030 in Montreal, Canada.

Scenario number	Intervention description	Priority population	Median proportion of cumulative chronic HCV infections averted from 2022 to 2030 (95%CrI)		Median proportion of cumulative HCV-related deaths averted from 2022 to 2030 (95%CrI)	
			Among active injectors living with HIV	Among all active injectors	Among people who have injected drugs living with HIV	Among all people who have injected drugs
1	Status quo	-	Referent	Referent	Referent	Referent
2	Increased harm reduction coverage†	Active injectors‡ living with HIV	7% (2-13)	3% (1-6)	2% (0-4)	1% (0-2)
3	Increased HCV testing rates	People who have injected drugs living with HIV	0% (0-1)	0% (0-1)	0% (0-1)	0% (0-0)
4	Increased HCV treatment rates	People who have injected drugs living with HIV	19% (0-41)	24% (8-38)	55% (42-65)	15% (9-20)
5	Increased harm reduction coverage[1]	All active injectors	11% (6-17)	12% (7-18)	4% (1-7)	3% (2-5)
6	Increased HCV testing rates	All people who have injected drugs	1% (0-4)	1% (0-4)	1% (0-3)	2% (1-5)

7	Increased HCV treatment rates	All people who have injected drugs	40% (32-48)	44% (38-50)	60% (50-68)	58% (49-64)
8	Increased HCV treatment rates	All active injectors	40% (32-48)	44% (38-50)	39% (28-46)	36% (31-40)

†Joint increase in the coverage of (1) needle and syringe programs, and (2) opioid agonist therapy.

‡People who report injecting drugs in the past six months.

CrI: credible interval; HCV: hepatitis C virus.

When increasing treatment among PWID living with HIV (scenario 4), the posterior probability of reaching incidence targets was 40% among all active injectors and 60% among those living with HIV (Figure 5.1). Under this scenario, mortality targets were achieved in most simulations (94%) among all PWID and all of them among PWID living with HIV. Chronic HCV prevalence decreased by 73% (95%CrI: 65-80) between 2015 and 2030 among active injectors and by 91% (95%CrI: 88-93) among those living with HIV. Approximately one in four cumulative chronic HCV infections was averted between 2022 and 2030 among all active injectors, and one in five among those living with HIV, as compared to the status quo (Table 5.3). One in six HCV-related deaths projected under status quo was prevented among all PWID, and over half among PWID living with HIV.

Interventions among all PWID

Extending enhanced harm reduction (scenario 5) or testing (scenario 6) to all did not substantially impact chronic HCV incidence, prevalence, or mortality (Figure 5.2). Yet, compared to status quo, increasing NSP and OAT coverage prevented 12% of cumulative chronic infections between 2022 and 2030 among all active injectors and 11% among those living with HIV (Table 5.3). Higher harm reduction coverage also prevented 3% of cumulative HCV-related deaths among PWID and 4% among PWID living with HIV.

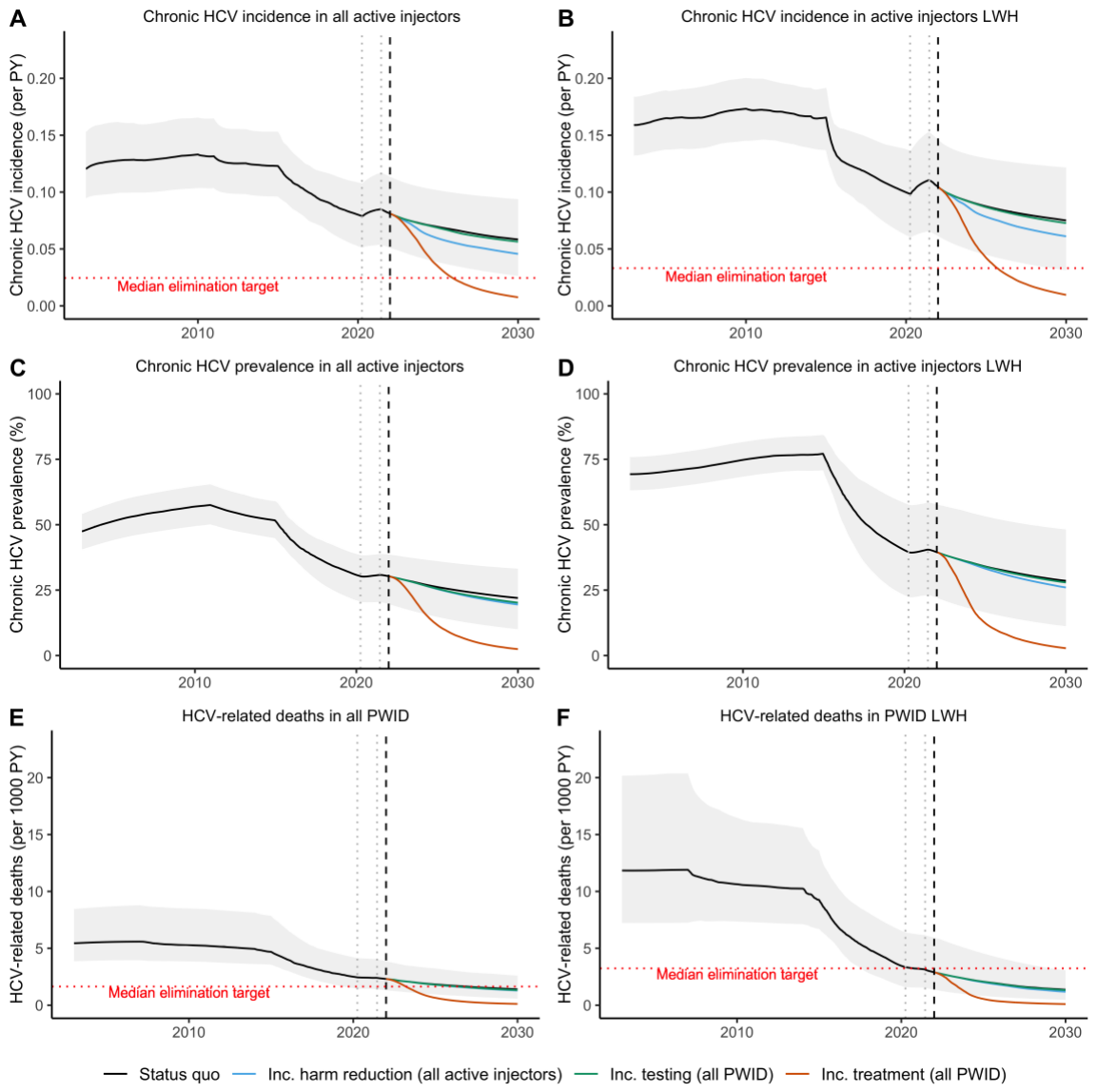

Figure 5.2. HCV outcomes among PWID and PWID living with HIV when implementing interventions among all PWID.

Figure legend: Simulated chronic HCV incidence among all active injectors (i.e., people who report injecting in the past six months) (A) and active injectors living with HIV (B), chronic HCV prevalence among all active injectors (C) and active injectors living with HIV (D), and HCV-related mortality among all PWID (E) and PWID living with HIV (F)

under various intervention scenarios implemented among all PWID in Montreal, Canada, from 2003 to 2030. The grey ribbons represent 95% credible intervals around estimates for the status quo scenario. The grey dotted vertical lines represent the start (March 2020) and stop (May 2021) dates of modeled disruptions in HCV care and prevention services due to the COVID-19 pandemic. The black dashed vertical line represents the start date (January 2022) of modeled intervention scenarios. ***Abbreviations****: HCV: hepatitis C virus; Inc.: increased; LWH: living with HIV; PWID: people who have injected drugs.*

When increasing treatment for all PWID (scenario 7), HCV incidence and mortality reduction targets were met in all simulations, for both PWID and PWID living with HIV (Figure 5.2). Between 2015 and 2030, chronic HCV prevalence was reduced by 95% (95%CrI: 94-96) among active injectors and by 96% (95%CrI: 95-97) among those living with HIV. This scenario also prevented a median of 44% cumulative incident chronic infections between 2022 and 2030 among PWID and 40% of these among PWID living with HIV (Table 5.3). Finally, over half of HCV-related deaths projected to occur under status quo were prevented: 58% among PWID and 60% among PWID living with HIV.

Increased treatment among active injectors

With regards to HCV incidence and prevalence, increasing treatment among active injectors only (scenario 8) yielded the same results as scenario 7 (scaled-up treatment for all PWID). This intervention achieved HCV elimination targets for both PWID and PWID living with HIV. Yet, smaller fractions of HCV-related deaths were prevented between 2022 and 2030: 36% among PWID and 39% among PWID living with HIV.

Sensitivity analyses

Jointly modeling interventions did not affect our results: sizeable effects were consistently driven by increased treatment and increases in testing or harm reduction coverage had little impact (Additional file 1; Figures 5.4 and 5.5). Assuming no disruption in HCV services

during the COVID-19 pandemic did not affect the qualitative ranking of scenarios (Additional file 1; Figures 5.6 and 5.7).

Discussion

Principal findings

DAA scale-up to levels beyond those reached in 2020 among all PWID diagnosed with HCV, irrespective of HIV status or time since last injection, was key to reaching HCV elimination targets by 2030 in Montreal. Focusing treatment efforts on PWID living with HIV –who can be reached by interventions and have high HCV acquisition and transmission risks– prevented many HCV-related deaths, especially among those living with HIV. This strategy led to substantial progress towards elimination but was insufficient to achieve it. Ex-injectors no longer contribute to HCV transmission via injection drug use. Yet, including them in treatment efforts is important to prevent HCV-related deaths. HCV transmission is high in Montreal and COVID-19-related reductions in access to HCV services led to rapid epidemic resurgence among PWID. In addition to scaling-up treatment, it is therefore essential that pre-COVID-19 levels of HCV testing and harm reduction are rapidly restored to ensure elimination by 2030.

Contextualization of results

Harm reduction coverage and HCV testing rates are already relatively high in Montreal. It is therefore not surprising that further increases in coverage had little impact. Previous modeling studies have also concluded that harm reduction strategies alone were unlikely to eliminate HCV among PWID [14]. Nevertheless, NSP and OAT are cost-effective, prevent multiple drug-related harms, and may be instrumental to sustaining HCV elimination targets post-2030 among PWID [23, 32]. Harm reduction should therefore remain at the core of elimination strategies for PWID. Bottlenecks can form at different stages of the HCV care cascade. In settings where few PWID are aware of their HCV

infection, increasing testing can reduce HCV prevalence [33]. In settings like Montreal, where most PWID know their HCV status, further reducing time from infection to diagnosis may have little impact on HCV incidence or mortality [31]. These differences advocate for tailoring HCV elimination strategies to local challenges.

Evidence from modeling studies suggests that HCV treatment rates below 10 per 100 PY could achieve elimination among PWID in several settings [14]. In Montreal, however, HCV seroincidence and seroprevalence remain high despite relatively high engagement in HCV prevention and care: higher treatment uptake would be necessary to reduce transmission. A modeling study suggests that HCV treatment rates of 200 per 100 PY could be cost-effective among PWID in high-incidence settings like Montreal [31]. In real-world programs like Iceland, treatment rates above 150 per 100 PY have been attained among PWID [34]. We used a treatment rate of 100 per 100 PY as it was deemed achievable in our setting based on existing literature. Nevertheless, extensive public health efforts will be required to massively engage PWID in DAA treatment given current rates are approximately 10-30 per 100 PY. Local empirical data are warranted to determine how to reach and sustain this level of treatment.

Few studies have examined interventions to eliminate HCV among PWID while incorporating HIV transmission dynamics [16, 35]. Our results suggest that while not sufficient to meet the WHO incidence reduction target among all PWID, increasing HCV treatment among PWID living with HIV could lead to substantial progress toward this goal. Because our model followed ex-injectors until death, we could additionally show that focusing treatment efforts on PWID living with HIV could achieve the WHO mortality reduction target for all PWID.

Potential implications

Scaling-up DAA uptake among PWID is necessary to eliminate HCV in this population, and this could be achieved by macro-level policies such as funding health services, care models offering alternatives to hospital-based specialized HCV care, interventions

facilitating health service utilization by patients and providers, and HCV education [36]. HCV treatment-as-prevention has generated optimism that we can reach and sustain HCV elimination as a public health threat among PWID [23]. Yet, the COVID-19 pandemic and its response could delay HCV elimination in many countries [37]. Disruptions in harm reduction, HCV testing, and HCV treatment services have been observed across Canada [17, 28]. In Montreal, HCV incidence among active injectors is high but declining. Nevertheless, our results show that reduced access to HCV services could have reversed this trend. In Germany, models also showed that COVID-19-related disruptions in HCV care may cause an increase in HCV incidence and compromise elimination among men who have sex with men living with HIV [38]. Staying on track for HCV elimination will require refocusing public health efforts towards HCV prevention and care, which may prove difficult in the context of an aggravated overdose crisis and the emergence of new SARS-CoV-2 variants [27].

Strengths and limitations

Our results need to be interpreted considering some limitations. First, potential sources of heterogeneity in HCV risks and unmet prevention needs are not explicitly modeled, which could lead to underestimating efforts required for HCV elimination [39]. For instance, Indigenous peoples, who are disproportionately affected by HCV in Canada, are not represented [8]. A minority of PWID self-identify as Indigenous in Montreal, nevertheless, their health needs should be addressed in a tailored, anti-colonial healing framework [29, 40]. Second, we used conservative estimates to quantify COVID-19-related disruptions in HCV services and assumed that access was restored as of April 2021. We may thus have underestimated the efforts needed to stay on track for HCV elimination by 2030.

Our findings help understand how heterogeneity in HCV acquisition/transmission risk (by HIV status) and needs (between active and ex-injectors) can be factored in the design and implementation of strategies to reduce HCV burden among PWID. These results can inform HCV elimination strategies in settings comparable to Montreal, and our model can be parametrized with empirical data from any context. This is one of few studies to explore

the implications of the COVID-19 pandemic on the HCV elimination agenda for priority populations.

Conclusions

In settings with elevated HCV incidence and prevalence, high DAA uptake by all PWID will be required to eliminate HCV as a public health threat among all PWID and PWID living with HIV. Ex-injectors should be included in treatment efforts to avoid preventable HCV-related deaths. The COVID-19 pandemic has impacted HCV prevention and care services for PWID, and concerted efforts to restore and scale-up treatment are urgently needed to ensure that HCV elimination is reached by 2030.

Competing interests

This work was supported by the investigator-initiated study funded through the *Gilead Sciences LEGA-C Program* [grant number IN-US-334-4492, June 1st, 2018]. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. CLD, AG, BL, and CD have no conflict of interest to declare. MK reports grants for investigator-initiated studies from *ViiV Healthcare*, *Abbvie*, and *Gilead*; research grants from *Janssen*, and consulting fees from *ViiV Healthcare*, *AbbVie*, and *Gilead*, all outside the submitted work. JC has received institutional funding for investigator-sponsored research from *ViiV Healthcare* and *Gilead Sciences*. He has also received remuneration for advisory work and/or travel support from *ViiV Healthcare*, *Gilead Sciences* and *Merck Canada*. NK reports research funding from *Gilead Sciences*, *McGill Interdisciplinary Initiative in Infection and Immunity*, *Canadian Institutes of Health Research*, and *Canadian Network on Hepatitis C*; reports advisory fees from *Gilead Sciences*, *ViiV Healthcare*, *Merck*, and *AbbVie*; and reports speaker fees from *Gilead Sciences*, *AbbVie*, and *Merck*, all outside of the submitted work. MM-G reports grants from the *Canadian Institutes of Health Research* and the *Canadian Foundation for AIDS Research*, and contractual arrangements from both the *World Health Organization* and the *Joint United Nations Programme on HIV/AIDS* (UNAIDS), all outside of the submitted work.

Authors' contributions

MK, MM-G, JC, and BL conceived this study. CLD developed the research questions and analysis plan, built, parametrized, and calibrated the model, conducted the analyses, and drafted the manuscript with feedback from MK and MM-G. AG and CD were also consulted for model development and revisions. NK, JC, and MK provided clinical and public health expertise on simulated HCV micro-elimination strategies. All authors have read and approved the final manuscript.

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Additional files

Additional file 1: Additional results

This Word document provides model calibration fits as well as results from sensitivity analyses.

List of abbreviations

ART: antiretroviral treatment

DAA: direct acting antiviral

HCV: hepatitis C virus

NSP: needle and syringe programs

OAT: opioid agonist therapy

PWID: people who have injected drugs

PY: person-years

WHO: World Health Organization

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5.3. Manuscript 2 – Appendix

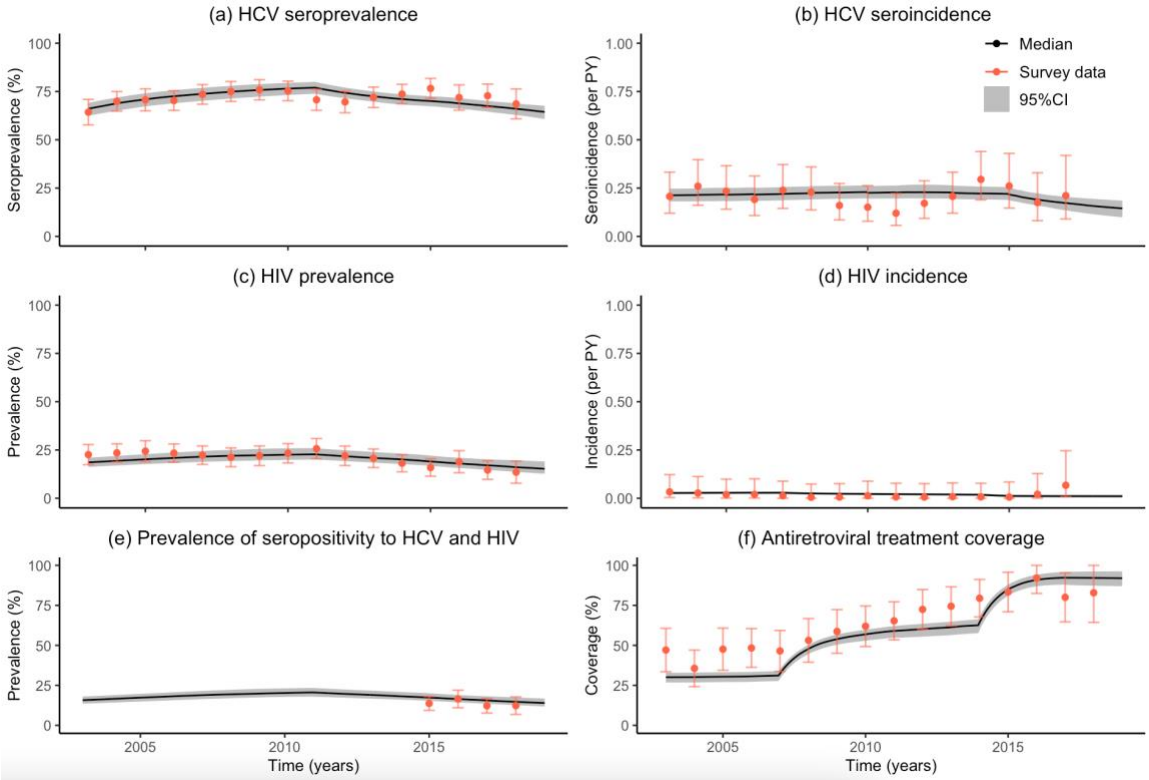

Figure 5.3. Model calibration to HCV and HIV survey estimates.

Figure legend: Model calibration to (a) annual hepatitis C (HCV) seroprevalence (2003-2018), (b) annual HCV seroincidence (i.e., anti-HCV seroconversions) (2003-2017), (c) annual HIV prevalence (2003-2018), (d) annual HIV incidence (2003-2017), (e) joint prevalence of anti-HCV antibodies and HIV infection (2015-2018), and (f) self-reported antiretroviral treatment coverage among people living with HIV (2003-2018). The empirical data points and confidence intervals were extracted from reports of the SurvUDI network surveys (a design effect of 2 is used to calculate standard errors) [1]. Prevalence (a), (c), and (e) are estimated among participants at their first visit to the network. Incidence (b) and (d) are estimated among repeated testers. The calibration targets correspond to the confidence intervals of all estimates when a design effect of 10 is applied.

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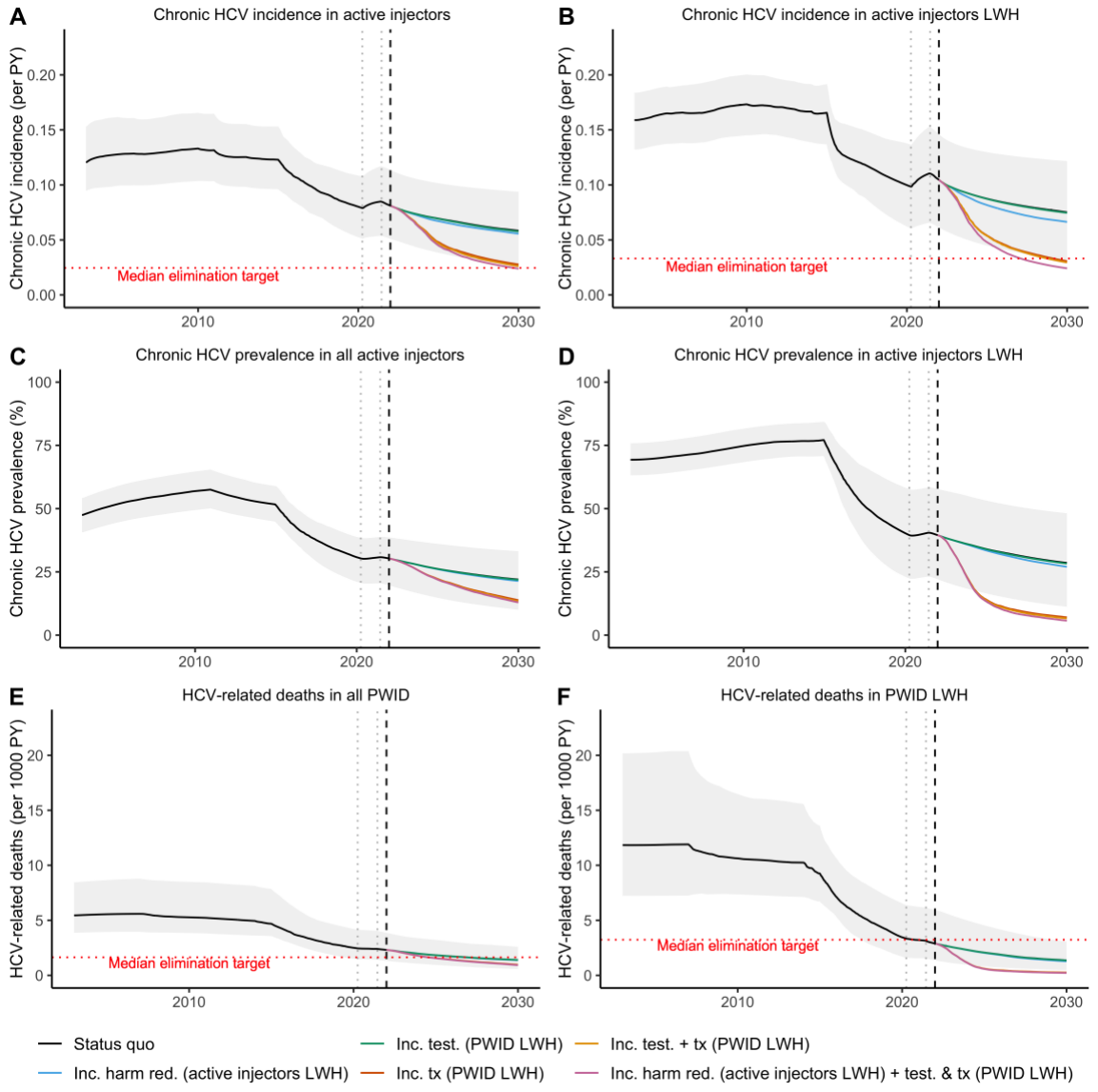

Figure 5.4. HCV outcomes among PWID and PWID living with HIV when implementing single and combined interventions among PWID living with HIV.

Figure legend: Simulated chronic hepatitis C virus (HCV) incidence among all active injectors (i.e., people who report injecting in the past six months) (A) and active injectors living with HIV (B), chronic HCV prevalence among all active injectors (C) and active injectors living with HIV (D), and HCV-related mortality among all PWID (E) and PWID living with HIV (F) under single- or combined-intervention scenarios implemented among PWID living with HIV in Montreal, Canada, from 2003 to 2030. The grey ribbons represent 95% credible intervals around estimates for the status quo scenario. The grey dotted vertical lines represent the start (March 2020) and stop (May 2021) dates of modeled disruptions in HCV care and prevention services due to the COVID-19 pandemic. The black dashed vertical line represents the start date (January 2022) of modeled intervention scenarios. ***Abbreviations****: Inc.: increased; LWH: living with HIV; PWID: people who have injected drugs; red.: reduction; test.: testing; tx: treatment.*

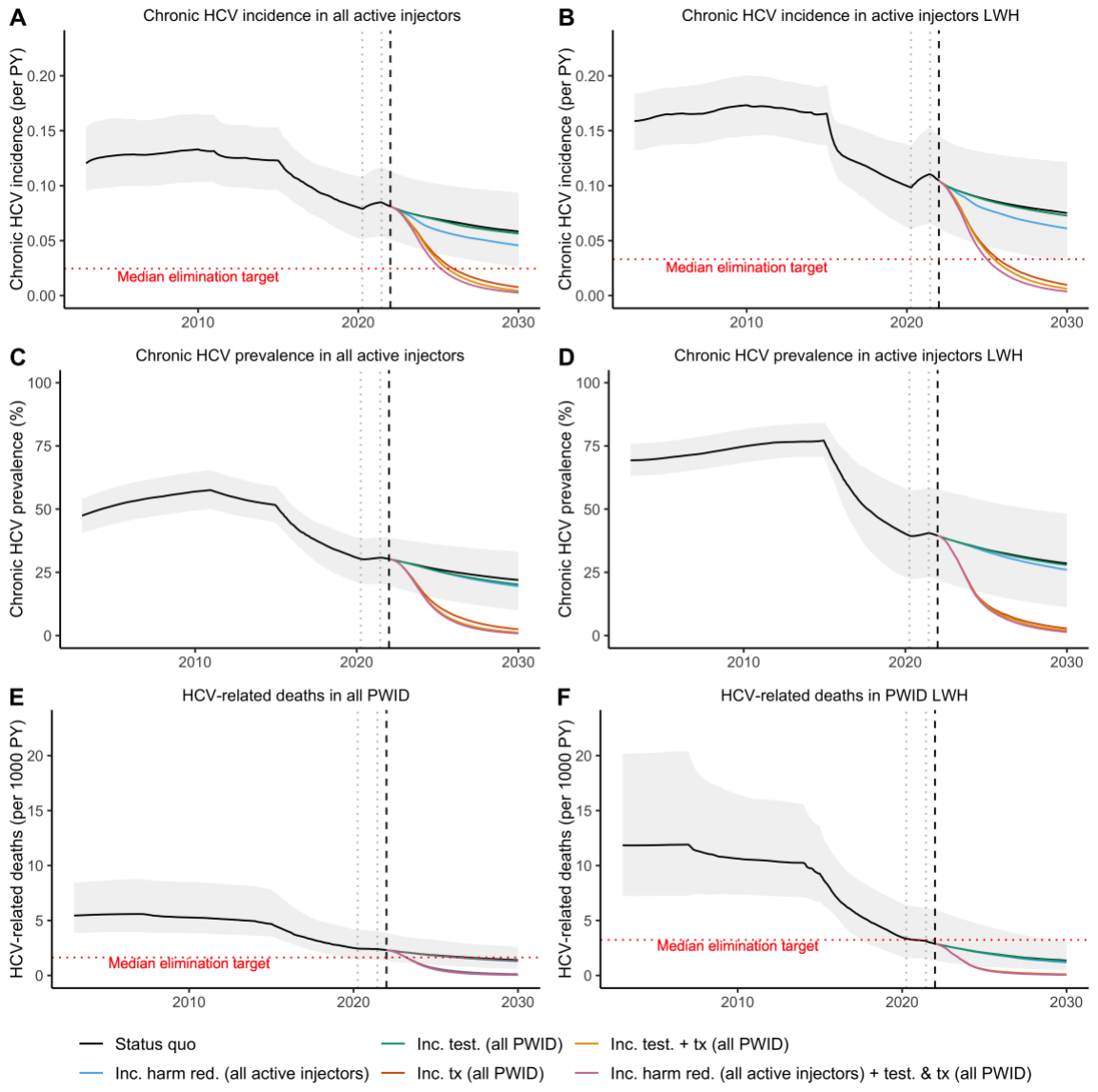

Figure 5.5. HCV outcomes among PWID and PWID living with HIV when implementing single and combined interventions among all PWID.

Figure legend: Simulated chronic hepatitis C virus (HCV) incidence among all active injectors (i.e., people who report injecting in the past six months) (A) and active injectors living with HIV (B), chronic HCV prevalence among all active injectors (C) and active injectors living with HIV (D), and HCV-related mortality among all PWID (E) and PWID living with HIV (F) under single- or combined-intervention scenarios implemented among

all PWID living in Montreal, Canada, from 2003 to 2030. The grey ribbons represent 95% credible intervals around estimates for the status quo scenario. The grey dotted vertical lines represent the start (March 2020) and stop (May 2021) dates of modeled disruptions in HCV care and prevention services due to the COVID-19 pandemic. The black dashed vertical line represents the start date (January 2022) of modeled intervention scenarios. ***Abbreviations****: Inc.: increased; LWH: living with HIV; PWID: people who have injected drugs; red.: reduction; test.: testing; tx: treatment.*

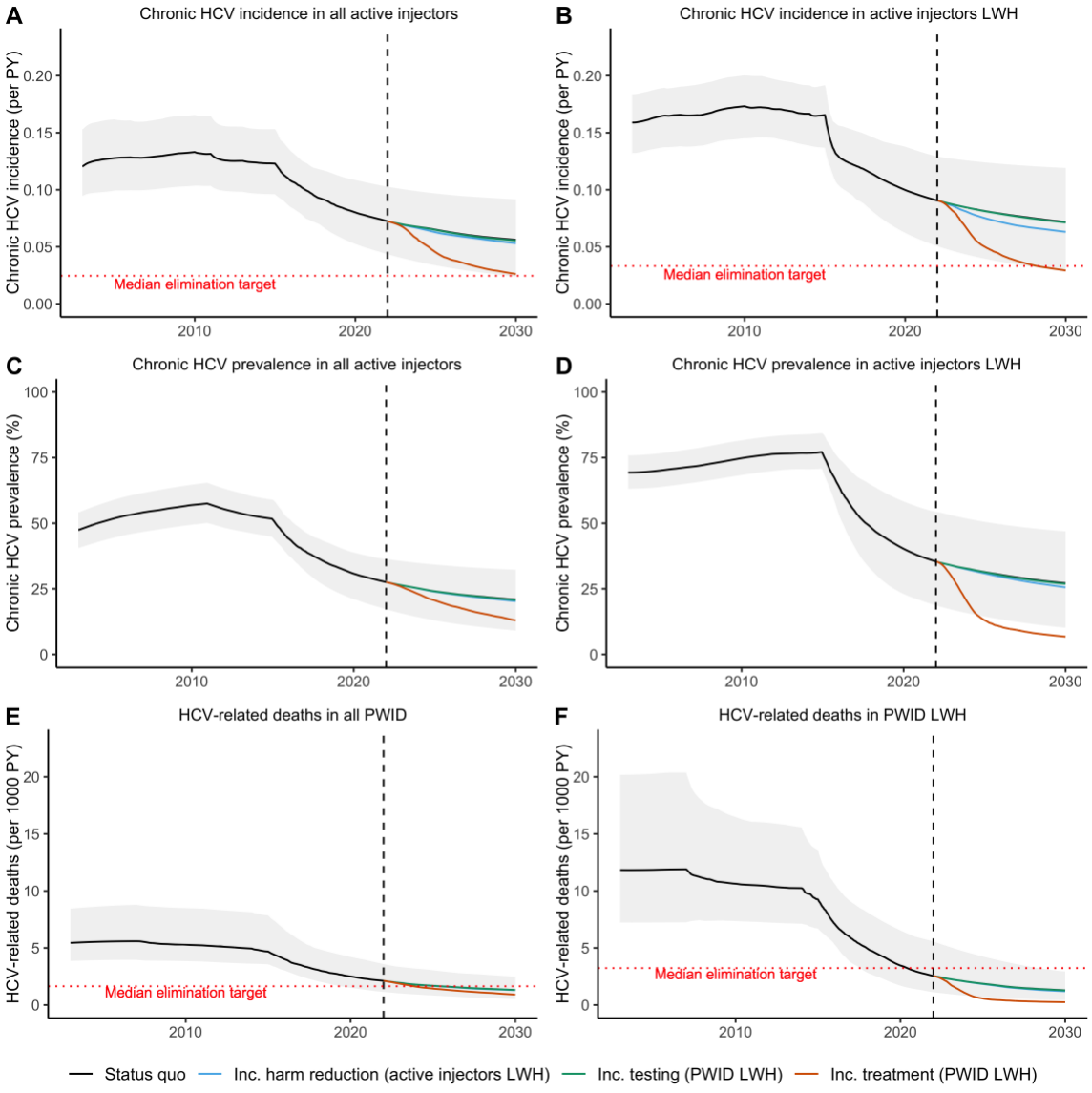

Figure 5.6. HCV outcomes among PWID and PWID living with HIV when implementing interventions among PWID living with HIV and assuming no COVID-19-related disruptions in HCV services.

Figure legend: *Simulated chronic hepatitis C virus (HCV) incidence among all active injectors (i.e., people who report injecting in the past six months) (A) and active injectors living with HIV (B), chronic HCV prevalence among all active injectors (C) and active injectors living with HIV (D), and HCV-related mortality among all PWID (E) and PWID*

living with HIV (F) under intervention scenarios implemented among PWID living with HIV in Montreal, Canada, from 2003 to 2030. Simulations were run assuming constant model parameter values from 2018 to 2022. The grey ribbons represent 95% credible intervals around estimates for the status quo scenario. The black dashed vertical line represents the start date (January 2022) of modeled intervention scenarios. ***Abbreviations****: Inc.: increased; LWH: living with HIV; PWID: people who have injected drugs.*

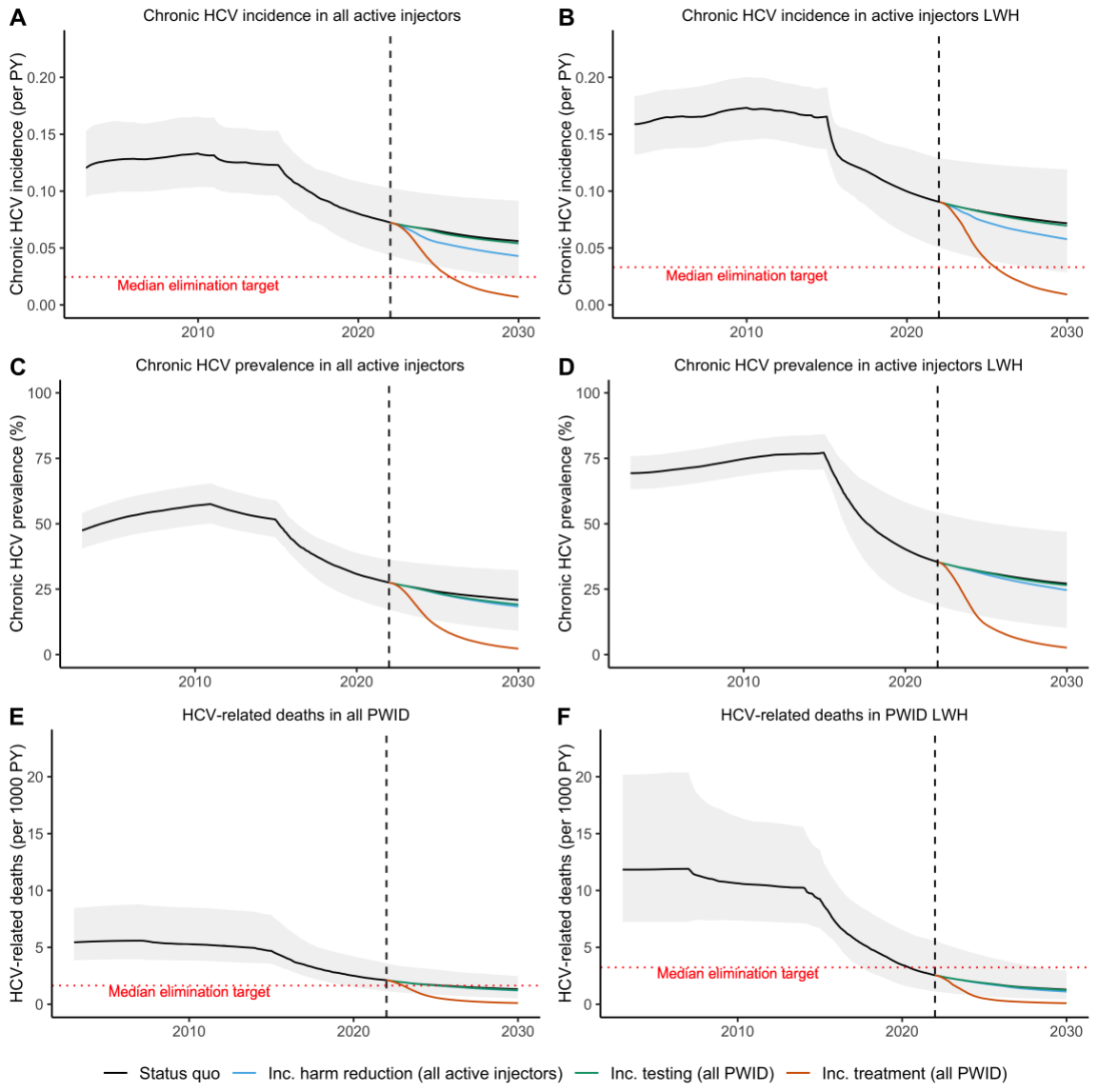

Figure 5.7. HCV outcomes among PWID and PWID living with HIV when implementing interventions among all PWID and assuming no COVID-19-related disruptions in HCV services.

Figure legend: Simulated chronic hepatitis C virus (HCV) incidence among all active injectors (i.e., people who report injecting in the past six months) (A) and active injectors living with HIV (B), chronic HCV prevalence among all active injectors (C) and active injectors living with HIV (D), and HCV-related mortality among all PWID (E) and PWID

living with HIV (F) under intervention scenarios implemented among all PWID living in Montreal, Canada, from 2003 to 2030. Simulations were run assuming constant model parameter values from 2018 to 2022. The grey ribbons represent 95% credible intervals around estimates for the status quo scenario. The black dashed vertical line represents the start date (January 2022) of modeled intervention scenarios. ***Abbreviations****: Inc.: increased; LWH: living with HIV; PWID: people who have injected drugs.*

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6. Chapter 6: Can HCV elimination targets be sustained among PWID after 2030?

6.1. Preface to Manuscript 3

Eliminating hepatitis C as a public health threat among PWID is a key component of drug-related harm prevention (99), and evidence presented in the previous chapter can inform the selection of micro-elimination strategies. Nevertheless, if we reduce chronic HCV incidence by 80% and HCV-related mortality by 65%, some level of HCV prevention and care services will be needed to avoid epidemic resurgence among PWID. Manuscript 3 provides timely insight into long-term strategies to ensure sustainable elimination of hepatitis C as a threat to the health of PWID in high-incidence and prevalence settings. This analysis also demonstrates how prevention efforts targeting HCV can impact HIV dynamics at the population-level.

We were invited to publish this manuscript in the special issue *"Progress and remaining challenges to address hepatitis C, other infectious diseases, and drug-related harms to improve the health of people who use drugs"* of the *International Journal of Drug Policy* (October 2021, Volume 96) (100).

6.2. Manuscript 3: Can hepatitis C elimination targets be sustained among people who inject drugs post-2030?

Charlotte Lanièce Delaunay[a,c,§], Arnaud Godin[a,§], Nadine Kronfli[b,c], Dimitra Panagiotoglou[a], Joseph Cox[a,b], Michel Alary[d,e,f], Marina B. Klein[a,b,c], and Mathieu Maheu-Giroux[a,*]

[§] *Contributed equally*

[a] *Department of Epidemiology, Biostatistics, and Occupational Health, School of Population and Global Health, Faculty of Medicine, McGill University, 1020 Avenue des Pins Ouest, H3A 1A2, Montréal (QC), Canada*

[b] *Department of Medicine, Division of Infectious Disease and Chronic Viral Illness Service, McGill University Health Centre, 1001 Boulevard Décarie, H4A 3J1, Montréal (QC), Canada*

[c] *Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, 5252 Boulevard de Maisonneuve Ouest, H4A 3S5, Montréal (QC), Canada*

[d] *Département de Médecine Sociale et Préventive, Université Laval, 1050 Avenue de la Médecine, G1V 016, Québec (QC), Canada*

[e] *Axe Santé des Populations et Pratiques Optimales en Santé, Centre de recherche du CHU de Québec-Université Laval, 1050 Chemin Sainte-Foy, G1S 4L8, Québec (QC), Canada*

[f] *Institut National de Santé Publique du Québec, 945 Avenue Wolfe, G1V 5B3, Québec (QC), Canada*

*** Corresponding author:**

Mathieu Maheu-Giroux

1020 Avenue des Pins Ouest, Rm. 43

Montréal (QC), Canada, H3A 1A2

Email: mathieu.maheu-giroux@mcgill.ca

Telephone: +1 (514) 398-5110

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Abstract

Background

In high-income countries, people who inject drugs (PWID) are a priority population for eliminating hepatitis C virus (HCV) by 2030. Despite evidence informing micro-elimination strategies, little is known regarding efforts needed to maintain elimination targets in populations with ongoing acquisition risks. This model-based study investigates post-elimination transmission dynamics of HCV and HIV among PWID under different scenarios where harm reduction interventions and HCV testing and treatment are scaled-down.

Methods

We calibrated a dynamic compartmental model of concurrent HCV and HIV transmission among PWID in Montréal (Canada) to epidemiological data (2003-2018). We then simulated achieving the *World Health Organization* elimination targets by 2030. Finally, we assessed the impact of four post-elimination scenarios (2030-2050): 1) scaling-down testing, treatment, opioid agonist therapy (OAT), and needle and syringe programs (NSP) to pre-2020 levels; 2) only scaling-down testing and treatment; 3) suspending testing and treatment, while scaling down OAT and NSP to pre-2020 levels; 4) suspending testing and treatment and maintaining OAT and NSP coverage required for elimination.

Results

Scenario 1 leads to a modest rebound in chronic HCV incidence from 2.4 to 3.6 per 100 person-years by 2050 (95% credible interval – CrI: 0.8-7.2). Under scenario 2, chronic HCV incidence continues to decrease. In scenarios 3 and 4, HCV incidence and mortality rapidly increase to 11.4 per 100 person-years (95%CrI: 7.4-15.5) and 3.2 per 1000 person-years (95%CrI: 2.4-4.0), respectively. All scenarios lead to decreases in the proportion of reinfections among incident cases and have little impact on HIV incidence and HIV-HCV coinfection prevalence.

Conclusion

Despite ongoing transmission risks, HCV incidence rebounds slowly after 2030 under pre-2020 testing and treatment levels. This is heightened by maintaining high-coverage harm reduction interventions. Overall, sustaining elimination would require considerably less effort than achieving it.

Introduction

Hepatitis C virus (HCV) infection can lead to cirrhosis, liver failure, and hepatocellular carcinoma, causing more than 500,000 deaths per year globally (Thrift, El-Serag, & Kanwal, 2017). Member states of the *World Health Organization* (WHO) have set ambitious objectives for HCV elimination as a public health threat by 2030, including an 80% reduction in the incidence of chronic infections, and a 65% reduction in HCV-related mortality, using 2015 as the baseline year (World Health Organization, 2016). Recent modelling studies suggest that, although few high-income countries are currently on track to achieve these targets on time (Razavi, Sanchez Gonzalez, Yuen, & Cornberg, 2020), Canada could eliminate HCV by 2030 if high treatment rates are sustained (Binka et al., 2020). Micro-elimination approaches have been identified as key to achieving WHO targets in high income countries. In several settings, unmet prevention needs mean that people who inject drugs (PWID) bear most of the HCV burden (Lazarus, Wiktor, Colombo, & Thursz, 2017).

Between 0.3 and 1% of 15–64-year-old people in North America report injecting drugs in the past year (Degenhardt et al., 2017; Jacka et al., 2020; Lansky et al., 2014). Roughly 9% of these people are living with HIV, and 55% have previously been exposed to HCV (Degenhardt et al., 2017). It is estimated that 10% of the HIV burden and 81% of the HCV burden can be attributed to injection drug use in North America (Degenhardt et al., 2016). Among PWID, those living with HIV are more vulnerable to the consequences of HCV infection due to higher levels of chronicity, accelerated liver disease progression, and higher mortality rates (Chen & Morgan, 2006; Shepard, Finelli, & Alter, 2005; Valle Tovo et al., 2007). Yet, HIV-HCV coinfected PWID tend to be engaged in HIV care and can therefore be reached by HCV prevention and care interventions (Sacks-Davis et al., 2018). PWID have been identified as a priority population for HCV micro-elimination and the HIV-HCV syndemic exacerbates the morbidity and mortality burden in this group.

The investments required to achieve elimination over the next decade will be important and could be compromised by epidemic resurgence. Assuming successful micro-

elimination strategies, little is known regarding the efforts needed to avoid a post-elimination resurgence in populations with ongoing transmission risks. Using an uncalibrated model, Gountas and colleagues explored the potential sustainability of HCV elimination among PWID if HCV treatment stopped in 2030. They concluded that high coverage of harm reduction interventions would be key to prevent a post-elimination rebound in HCV incidence (Gountas, Sypsa, Blach, Razavi, & Hatzakis, 2018). Scott and colleagues found that post-elimination outbreaks would be unlikely among PWID in Iceland (Scott et al., 2018). Yet, due to its insular location and relatively small PWID population (approximately 400 people in 2018), the example of Iceland cannot be transposed to most geographical settings.

We have less than ten years to mobilise resources for HCV elimination. There is a time-sensitive need for modelling to evaluate the sustainability of HCV incidence and mortality reductions among PWID. Leveraging two decades of empirical data from bio-behavioural surveys of PWID in Montréal (Canada), this model-based study aims to investigate the post-elimination dynamics of HCV and HIV transmission across a variety of harm reduction, testing, and treatment scenarios.

Methods

Setting

Using an HIV-HCV co-infection model, we simulated the transmission dynamics of HCV and HIV among PWID in Montréal (Canada), where 1.3% (95% confidence interval – CI: 1.0-1.7%) of the population aged 15 years and above reported ever injecting drugs (Camirand, Traoré, Baulne, & Courtemanche, 2016) and where HCV seroprevalence among PWID is greater than 60% (Leclerc, Roy, Morissette, Alary, & Blouin, 2021).

Model structure

We developed a dynamic, deterministic, sex-stratified compartmental model of HCV and HIV transmission among PWID living in Montréal, starting in 2003. The model structure

was adapted from the work of Godin and colleagues (Godin, Kronfli, Cox, Alary, & Maheu-Giroux, 2020). Three concurrent dynamics were considered in a single model: 1) HCV transmission and care continuum, 2) HIV transmission and care continuum, and 3) injecting behaviours (Figure 6.1). People can therefore progress through different dynamics simultaneously (e.g., someone could be infected with HCV and HIV at the same time, and then move through the continuum of care for both infections). People enter the model upon first drug injection at a recruitment rate that was chosen to replicate the observed decline in population size of active PWID in Montréal from 1996 (Remis et al., 1998) to 2010 (Leclerc et al., 2014). At first injection, everyone is assumed to be HCV and HIV seronegative. People exit the model upon death, which can result from three causes: background mortality among PWID, liver-related mortality among people infected with HCV, and AIDS-related mortality among people living with HIV (PLHIV). Each model dynamic is briefly described below, and full model details are available in the supplementary materials.

HCV transmission dynamics

HCV acquisition and transmission occur through injection drug use. People can acquire HCV at a time-varying force of infection that depends on chronic HCV prevalence among injecting contacts (as a function of mixing by sex, HIV status, and injecting behaviours) and the coverage of harm reduction programs – opioid agonist therapy (OAT) and needle and syringe programs (NSP). Following infection with HCV, people experience an acute phase (Westbrook & Dusheiko, 2014) in which individuals either spontaneously clear the infection or progress to chronic disease. Males and PLHIV are less likely to spontaneously clear HCV (Grebely et al., 2014; Smith, Jordan, Frank, & Hagan, 2016). Left untreated, people with chronic HCV infection can ultimately die of HCV-related causes, with a higher mortality rate among PLHIV who are not on antiretroviral therapy (ART) (Hayashi et al., 2014; Trickey et al., 2019). If diagnosed, they can be linked to care and treated; and are assumed to be non-infectious over the treatment's course. Second-generation direct acting antivirals (DAAs) became universally accessible in 2015 in the province of Québec, resulting in increased uptake and effectiveness among PWID, as well as shorter treatment

durations (Rodriguez-Torres et al., 2012; Saeed et al., 2017; Torriani et al., 2004). According to current clinical practice, all PLHIV should be tested for HCV. Because PLHIV who are on ART are already engaged in HIV care, they are tested immediately for HCV in our model, and rapidly treated if chronically infected with HCV. Following successful treatment, people become HCV susceptible again (but remain antibody-positive) and can be re-infected at a rate assumed equal to that of primary infection (Hajarizadeh et al., 2020). If treatment does not result in sustained virologic response (SVR), the natural disease progression follows its course unless treatment is re-initiated (Figure 6.1). In line with current Canadian guidelines, people who are re-infected can be treated at the same rate as people with primary infection (Shah et al., 2018).

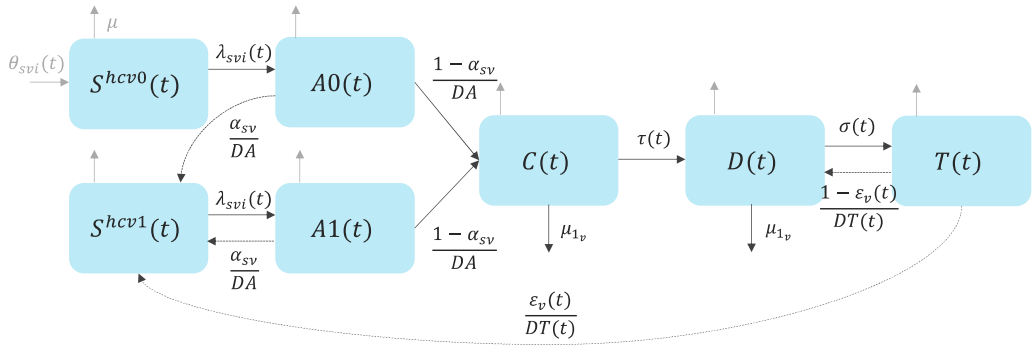
HIV transmission dynamics

Similarly to HCV, we modelled HIV transmission through injection drug use. The force of infection varies according to HIV prevalence within the population of injecting contacts (as a function of mixing by sex, HIV status, and injecting behaviours), the coverage of harm reduction interventions, and ART status of injecting partners. Following HIV acquisition, people progress through three CD4 cell count stages (>350 cells/mm^3; 200-350 cells/mm^3; <200 cells/mm^3) and, if left untreated, ultimately die of AIDS-related causes (Cori et al., 2015). PLHIV are assumed to test for HIV at the same rate regardless of CD4 cell count, and they can initiate ART at a time-varying rate that is consistent with past eligibility criteria for ART (Richardson, Grant, & Zolopa, 2014; Tseng, Seet, & Phillips, 2015). Robust evidence shows that PLHIV who are on ART and have an undetectable viral load cannot transmit HIV sexually (Rodger et al., 2016). Nonetheless, because a fraction of PWID on ART may not be virally suppressed (Lesko, Tong, Moore, & Lau, 2017; Westergaard, Hess, Astemborski, Mehta, & Kirk, 2013), and due to increased transmission risk via parenteral exposures (Baggaley, Boily, White, & Alary, 2006; Degenhardt et al., 2010), we assumed that treated PWID living with HIV could transmit the virus, albeit at a much reduced rate than untreated PLHIV. If treatment is discontinued, PLHIV return to their pre-ART CD4 cell count category and disease can progress further (Figure 6.1).

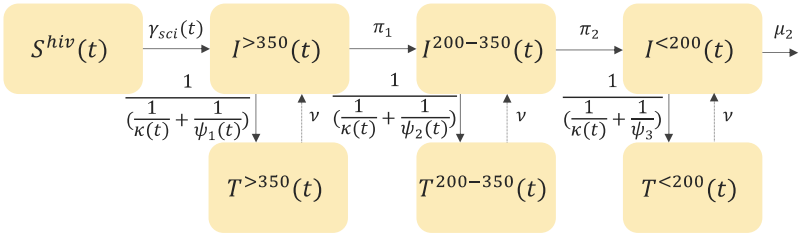
Injecting behaviour dynamics

When PWID who inject opioids engage in OAT, their injection frequency decreases, thereby reducing their risk of acquiring and/or transmitting blood-borne infections. We used efficacies of 50% (Platt et al., 2017) and 54% (MacArthur et al., 2012) for the reduction of HCV and HIV transmission, respectively, among PWID on OAT. Regardless of OAT engagement, PWID cease to inject after an average of fourteen years (Montain et al., 2016). People who have ceased to inject are no longer at risk of acquiring or transmitting HCV and HIV, but progress through the different HCV and HIV disease stages if left untreated. Information about NSP coverage was extracted from surveillance data collected among PWID in Montréal (Leclerc et al., 2021), and NSP was assumed to reduce HCV and HIV transmission by approximately 20% and 34%, respectively (Aspinall et al., 2014; Platt et al., 2017).

(a) HCV natural history and continuum of care



(b) HIV natural history and continuum of care



(c) Injection dynamics

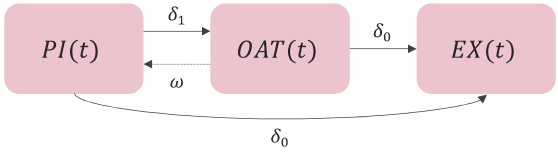


Figure 6.1. Model structure and intercompartmental flowchart.

Figure legend: (a) Hepatitis C (HCV) natural history and continuum of care. The model population is open, and people enter the model upon first injection (PI), as seronegative to HCV (S^{hcv0}) and HIV (S^{hiv}). They can become acutely infected with HCV at a time-dependent force of infection $\lambda(t)$, and either spontaneously clear the virus or progress to chronic infection (C). If diagnosed (D), chronically infected people can initiate HCV treatment (T). In the absence of treatment, the disease progresses, and liver-related death can occur. When treatment is successful, people remain anti-HCV antibody-positive (S^{hcv1}) and can be reinfected. (b) HIV natural history and continuum of care. HIV

susceptible people can acquire HIV at a time-dependent force of infection $\gamma(t)$. Once infected, they progress through disease stages, represented by three decreasing CD4 cell count categories ($I^{>350}$, $I^{200-350}$, $I^{<200}$). AIDS-related death can occur when the CD4 cell count is inferior to 200 cells/mm^3. Antiretroviral therapy can be initiated among eligible individuals, and the model allows for treatment interruptions. (c) Injection dynamics. A fraction of people who inject drugs can initiate opioid agonist therapy (OAT). They are then assumed to inject at lower frequencies and are therefore less likely to acquire and transmit HCV and HIV. Opioid agonist therapy can also be interrupted. After an average duration of 14 years, people who inject drugs cease to inject permanently (EX).

Parametrisation

Model parameters were informed by data from the Montréal sites of *SurvUDI*, a bio-behavioural surveillance network for HIV (1995-) and HCV (2003-) among PWID in the province of Québec. HCV and HIV testing rates, NSP coverage, and OAT engagement were estimated from this source (Blouin et al., 2016; Campeau et al., 2018; Leclerc et al., 2021; Roy et al., 2011). These were complemented by analyses of data from the *Canadian Co-infection Cohort*, an ongoing prospective study of HIV-HCV coinfected individuals across Canada (Klein et al., 2010). The cohort was used to parameterise HCV treatment uptake and effectiveness among PLHIV (manuscript in preparation). Other parameter values were drawn from the scientific literature, prioritising systematic reviews and meta-analyses when available (Table 6.1). More details on the above-mentioned surveys and parameter estimations are provided in the supplementary materials.

Table 6.1. Model parameter descriptions, values, prior distributions, and sources

Parameters	Symbols	Values or prior distributions	Units	Source
Demography				
Yearly reduction in active PWID[a] population size[c]	$dPWID(t)$		%	(Leclerc et al., 2014; Remis et al., 1998)
≤2010		Beta(476, 9524)		
>2010		0		Assumption
Background mortality rate	μ	1/46	per PY[a]	(Mathers et al., 2013)
HCV natural history				
Spontaneous HCV[a,b] clearance rate	α_{sv}		%	(Smith et al., 2016)
Among HCV+/HIV-		Beta(19, 55)		
Among HCV+/HIV+		Beta(60, 310)		
Relative increased spontaneous HCV clearance among females	rr^{α}	2.16	−	(Grebely et al., 2014)
Acute phase duration	DA	0.5	year	(Westbrook & Dusheiko, 2014)
Liver-related mortality rate	μ_{1_v}	1/57	per PY	(Trickey et al., 2019)
Increased liver-related mortality among PLHIV[a] not on ART[a]	rr^{μ_1}	LGN(log(2.29), 0.44)	−	(Hayashi et al., 2014)
HIV natural disease progression				
Progression rate from >350 CD4 cell count to 200-350 CD4 cell count	π_1	LGN(log(1/5.9), 0.05)	per PY	(Cori et al., 2015)
Progression rate from 200-350 CD4 cell count to <200 CD4 cell count	π_2	LGN(log(1/5.6), 0.08)	per PY	(Cori et al., 2015)
AIDS-related mortality rate	μ_2	Beta(19.8, 80.2)	per PY	(Cori et al., 2015)
HCV transmission				
Baseline HCV transmission rate	β^{HCV}	U(0.4, 0.8)	per PY	Calibration
Reduced HCV transmission and acquisition among people on OAT[a]	rr_i^{oatHCV}	0.5	−	(Platt et al., 2017)

Parameters	Symbols	Values or prior distributions	Units	Source
HIV transmission				
Baseline HIV transmission rate	β^{HIV}	U(0.1, 0.4)	per PY	Calibration
Reduced HIV transmission and acquisition among people on OAT	rr_i^{oatHIV}	LGN(log(0.45), 0.19)	–	(MacArthur et al., 2012)
Reduced HIV transmission from PLHIV on ART	rr^{ART}	U(40, 90)	%	Calibration
Injecting behaviours				
Degree of assortative mixing by sex	ps^{assort}	U(0, 50)	%	Calibration
Degree of assortative mixing by HIV status	pv^{assort}	U(0,100)	%	Calibration
Degree of assortative mixing by OAT status	pi^{assort}	U(0,100)	%	Calibration
Injection cessation rate	δ_0	1/14	per PY	(Montain et al., 2016)
Interventions				
HCV testing rate	$\tau(t)$		per PY	(Leclerc et al., 2021)
2003		1/1.5		
2015		1/1.2		
HCV treatment rate	$\sigma(t)$		per PY	(*Canadian Coinfection Cohort, manuscript in preparation*)
<2015		U(0, 1/10)		
≥2015		U(1/10, 1/3.3)		
Relative increased HCV treatment rate among PLHIV[a] on ART[a]	rr^{σ}	U(1, 2)	–	Calibration
HCV treatment effectiveness	$\varepsilon_v(t)$		%	(Aspinall et al., 2013; Hajarizadeh et al., 2018; Rodriguez-Torres et al., 2012; Torriani
<2015				
Among HCV+/HIV-		Beta(207, 163)		
Among HCV+/HIV+		U(20, 40)		
≥2015		90		

Parameters	Symbols	Values or prior distributions	Units	Source
				et al., 2004); (*Canadian Coinfection Cohort, manuscript in preparation*)
HCV treatment duration	$DT(t)$		year	(Hull et al.,
<2015		U(1/2, 1)		2016)
≥2015		U(1/6, 1/4)		
HIV testing rate	$\kappa(t)$		per PY	(Leclerc et al.,
2003		1/0.98		2021)
2015		1/0.82		
HIV treatment rate (>350 CD4 cell count)	$\psi_1(t)$		per PY	(Richardson et al., 2014; Tseng et al., 2015) Calibration
<2014		0		
≥2014		U(1/0.5, 1/0.02)		
HIV treatment rate (200-350 CD4 cell count)	$\psi_2(t)$		per PY	(Richardson et al., 2014; Tseng et al., 2015) Calibration
<2007		0		
≥2007		U(1/0.5, 1/0.02)		
HIV treatment rate (<200 CD4 cell count)	ψ_3	U(1/0.5, 1/0.02)	per PY	Calibration
HIV treatment discontinuation rate	ν	U(0, 0.1)	per PY	Calibration
NSP[a] coverage	$cov(t)$		%	(Leclerc et al.,
2003		68%		2021)
2015		86%		
Effectiveness of NSP for preventing HCV	eff^{HCV}	Beta(3.2, 12.8)	%	(Platt et al., 2017)
Effectiveness of NSP for preventing HIV	eff^{HIV}	Beta(5.4, 10.6)	%	(Aspinall et al., 2014)
OAT engagement rate	δ_1	0.32	per PY	(Leclerc et al., 2021)

Parameters	Symbols	Values or prior distributions	Units	Source
OAT cessation rate	ω	U(0.44, 0.64)	per PY	(Bao et al., 2009)

[a] ART: antiretroviral treatment; HCV: hepatitis C virus; Beta: beta distribution where the first number is the alpha parameter and the second the beta parameter; LGN: log-normal distribution where the first number is the location parameter and the second the scale parameter; OAT: opioid agonist therapy; NSP: needle and syringe programs; PLHIV: people living with HIV; PWID: people who inject drugs; PY: person-years; U: uniform distribution where the first number is the minimum value and the second the maximum value.

[b] The subscripts s, v, and i refer to the sex, HIV status, and injection status, respectively.

[c] The recruitment parameter (θ_{svi}) is estimated from the yearly reduction in the population of active people who inject drugs and the yearly number of deaths. The male to female population ratio is maintained constant across time.

Model calibration

Parameters that best describe the past HCV and HIV epidemics were selected in a Bayesian framework using the sampling importance resampling method (Rubin, 1987). We first sampled 70,000 parameter sets using Latin hypercube sampling from our prior distributions (McKay & Conover, 1979). For each parameter set, the model was then run to reach equilibrium and epidemics were simulated starting in 2003, the year when data from the *SurvUDI* network first became available for HCV. Using the calibration targets, we estimated the likelihood associated with each parameter set, and resampled 350 sets with replacement from the prior distributions, using sampling weights proportional to the likelihood values (Menzies, Soeteman, Pandya, & Kim, 2017). We also cross-validated the total modelled population size by comparing it to the proportion of ever-injectors reported in population-based surveys (Camirand et al., 2016).

Primary analyses

Once calibrated, we optimised (Byrd, Lu, Nocedal, & Zhu, 1995) HCV testing and treatment rates from 2020 to reach the HCV elimination target of 80% incidence reduction

by 2030 (assuming a linear scale-up from 2020-2025). Concomitantly, OAT and NSP coverage were scaled-up to 40% and 95%, respectively, in line with current recommendations (Canadian Network on Hepatitis C, 2019).

From 2030 onward, we modelled four post-elimination scenarios: 1) pre-2020 levels of HCV testing (once per 14 months), HCV treatment (between 10% and 30% of diagnosed people per year), NSP coverage (82%), and OAT coverage (33%); 2) pre-2020 levels of testing and treatment, and harm reduction maintained at levels required for elimination (95% coverage of NSP; 40% coverage of OAT); 3) suspension of HCV testing and treatment (i.e., both rates set to 0) after reaching elimination and pre-2020 levels of harm reduction coverage; 4) suspension of testing and treatment and harm reduction maintained at levels required for elimination. The simulations suspending HCV testing and treatment allowed us to explore "worst-case scenarios" of post-elimination epidemic resurgence. We explored the impact of all scenarios on incidence of chronic HCV infection, HCV reinfection, HIV incidence, prevalence of HIV-HCV coinfection, and HCV-related mortality (among those who ever injected drugs).

Secondary analyses

We assessed the impact of variations in model parameter values on our results for the following parameters: the relative decline in the Montréal PWID population size over 2003-2010; the HCV spontaneous clearance rates among HIV-negative people and PLHIV; the HCV treatment rate pre-2015; the effectiveness of NSP for preventing HIV and HCV; the OAT cessation rate; the degrees of assortative mixing by sex, HIV status, and injecting behaviours; and the relative rate for increased HCV-related mortality among PLHIV who are not on ART. For each parameter, we examined the correlation between values of this parameter and trends in chronic HCV incidence, HCV-related mortality, and HIV-HCV coinfection prevalence for scenario 1. We also explored the potential impact of a 20% increase in stimulant use as the main drug of injection over the post-elimination period in scenario 2. The HCV and HIV transmission rates were increased 2.9- and 3.0-fold, respectively, to reflect the higher risks of HCV and HIV acquisition and transmission,

while OAT coverage was decreased (Butler, Rehm, & Fischer, 2017; Cepeda et al., 2020; Miller, Kerr, Fischer, Zhang, & Wood, 2009; Tavitian-Exley, Vickerman, Bastos, & Boily, 2015). All analyses were performed in the R statistical software using relevant libraries (Eddelbuettel & François, 2019; R Core Team, 2017). The compartmental model was coded using a C++ back-end and numerically solved with a Euler algorithm that used a time step of 0.1 year.

Ethics

The McGill University Health Centre Research Ethics Board approved this study (REB#: MP-37-2019-4700).

Results

Calibration

The calibrated model accurately reproduced past HCV and HIV transmission dynamics (Figure 6.2). An additional cross-validation of the total modelled population size with an empirical estimate, as well as prior and posterior parameter distributions are presented in the supplementary materials.

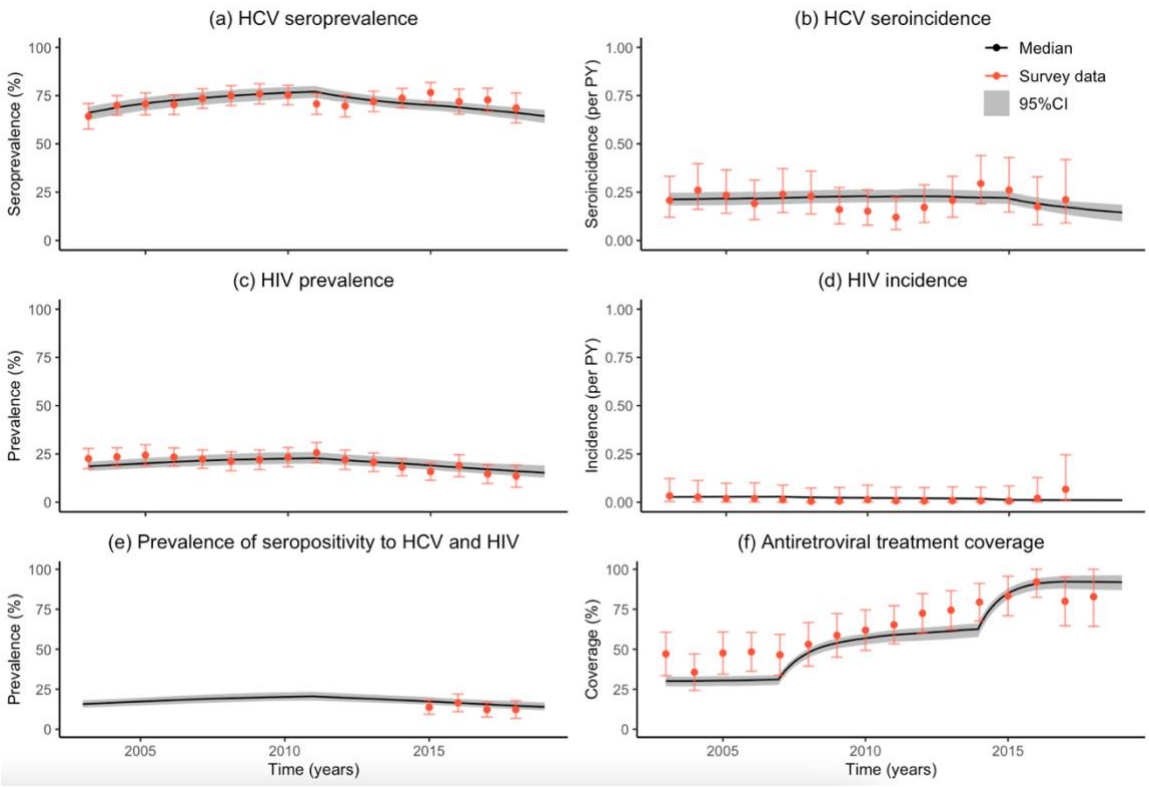


Figure 6.2. Model calibration to HCV and HIV survey estimates.

Figure legend: Model calibration to (a) annual hepatitis C (HCV) seroprevalence (2003-2018), (b) annual HCV seroincidence (i.e., anti-HCV seroconversions) (2003-2017), (c) annual HIV prevalence (2003-2018), (d) annual HIV incidence (2003-2017), (e) joint prevalence of anti-HCV antibodies and HIV infection (2015-2018), and (f) self-reported antiretroviral treatment coverage among people living with HIV (2003-2018). The empirical data points and confidence intervals were extracted from reports of the SurvUDI network surveys (a design effect of 2 is used to calculate standard errors) (Leclerc et al., 2021). Prevalence (a), (c), and (e) are estimated among participants at their first visit to the network. Incidence (b) and (d) are estimated among repeated testers. The calibration targets correspond to the confidence intervals of all estimates when a design effect of 10 is applied.

Elimination phase

Achieving HCV elimination by 2030 would require scaling-up HCV testing rates by a median factor of 1.2 (95% credible interval – CrI: 1.0-1.9) and treatment rates by a median factor of 1.9 (95%CrI: 1.0-3.5) over a five-year period if coverage of both OAT and NSP are scaled-up by 7%- and 13%-points, respectively. When HCV testing and treatment rates are assumed equal among current and former PWID (as modelled in our scenarios), optimising these rates to yield an 80% reduction in HCV incidence results in declines of HCV-related mortality that are greater than 65%.

Post-elimination transmission dynamics

Scenario 1

In scenario 1, all interventions were scaled down to their pre-2020 levels as of 2030 (i.e., HCV testing once per 14 months; 10% to 30% of diagnosed people treated every year; NSP coverage of 82%; OAT coverage of 33%). This led to a slight rebound in incidence of chronic HCV infection from a median of 2.4 per 100 person-years (PY) (95%CrI: 1.6-3.1 per 100 PY) in 2030 to 3.6 per 100 PY in 2050 (95%CrI: 0.8-7.2 per 100 PY), with substantial variability across simulations (Figure 6.3). The proportion of re-infections among incident chronic cases decreased from a median of 36% (95%CrI: 30-41%) in 2030 to 23% (95%CrI: 13-29%) in 2050. We observed a decline in the proportion of people diagnosed among those with chronic HCV infection over a one-year period following elimination and then a stabilisation over time at around 75%, five percentage-point lower than in 2020. The median HCV-related mortality rate rapidly declined from 2.5 per 1000 PY (95%CrI: 1.5-4.2 per 1000 PY) in 2020 to 0.5 per 1000 PY (95%CrI: 0.4-0.8 per 1000 PY) in 2030 and then increased slightly up to 0.7 per 1000 PY (95%CrI: 0.2-1.4 per 1000 PY) by 2050. Maintaining pre-2020 levels of ART coverage, HIV incidence slightly increased due to the harm reduction coverage scale-down in 2030, and then pursued its steady decline. Similarly, HIV-HCV coinfection followed a decreasing trend before and after 2030.

Scenario 2

When scaling-down HCV testing and treatment to pre-2020 levels but scaling-up harm reduction interventions to levels required for elimination (NSP = 95%; OAT = 40%), we observed a continued decrease in chronic HCV incidence until 2050 (2.1 per 100 PY; 95%CrI: 0.3-4.8 per 100 PY) (Figure 6.3). The proportion of reinfections declined slightly more than under scenario 1, from 36% (95%CrI: 30-41%) in 2030 to 19% (95%CrI: 11-25%) by the end of the post-elimination period. Without post-elimination changes in harm reduction coverage, and with stable levels of ART coverage, HIV incidence steadily declined. Other results were comparable across scenarios 1 and 2.

Scenario 3

Without any HCV testing and treatment in the post-elimination phase, and scaling-down harm reduction to pre-2020 levels, the incidence of chronic HCV rebounded to 11.4 per 100 PY (95%CrI: 7.4-15.5 per 100 PY; Figure 6.4). The proportion of reinfection decreased a bit faster than under scenarios 1 and 2 but reached similar levels by 2050 at 22% (95%CrI: 16-28%). In contrast to previous scenarios, we observed a rebound in mortality which climbed back to 3.2 per 1000 PY (95%CrI: 2.4-4.0 per 1000 PY) over the 2030-2050 period. All other outcomes were similar to what was found in scenarios 1 and 2**.**

Scenario 4

Maintaining harm reduction coverage at levels required for elimination while suspending HCV testing and treatment mitigated HCV resurgence as compared to scenario 3; chronic HCV incidence reached 9.2 per 100 PY (95%CrI: 5.8-13.1 per 100 PY) by 2050 (Figure 6.4) and HCV-related mortality 2.8 per 1000 PY (95%CrI: 2.0-3.5 per 1000 PY). As in scenario 3, there was little to no impact on HIV incidence, HIV-HCV coinfection, and on the proportion of individuals with reinfection among incident chronic HCV cases. Other outcomes were similar as in scenario 1, 2, and 3.

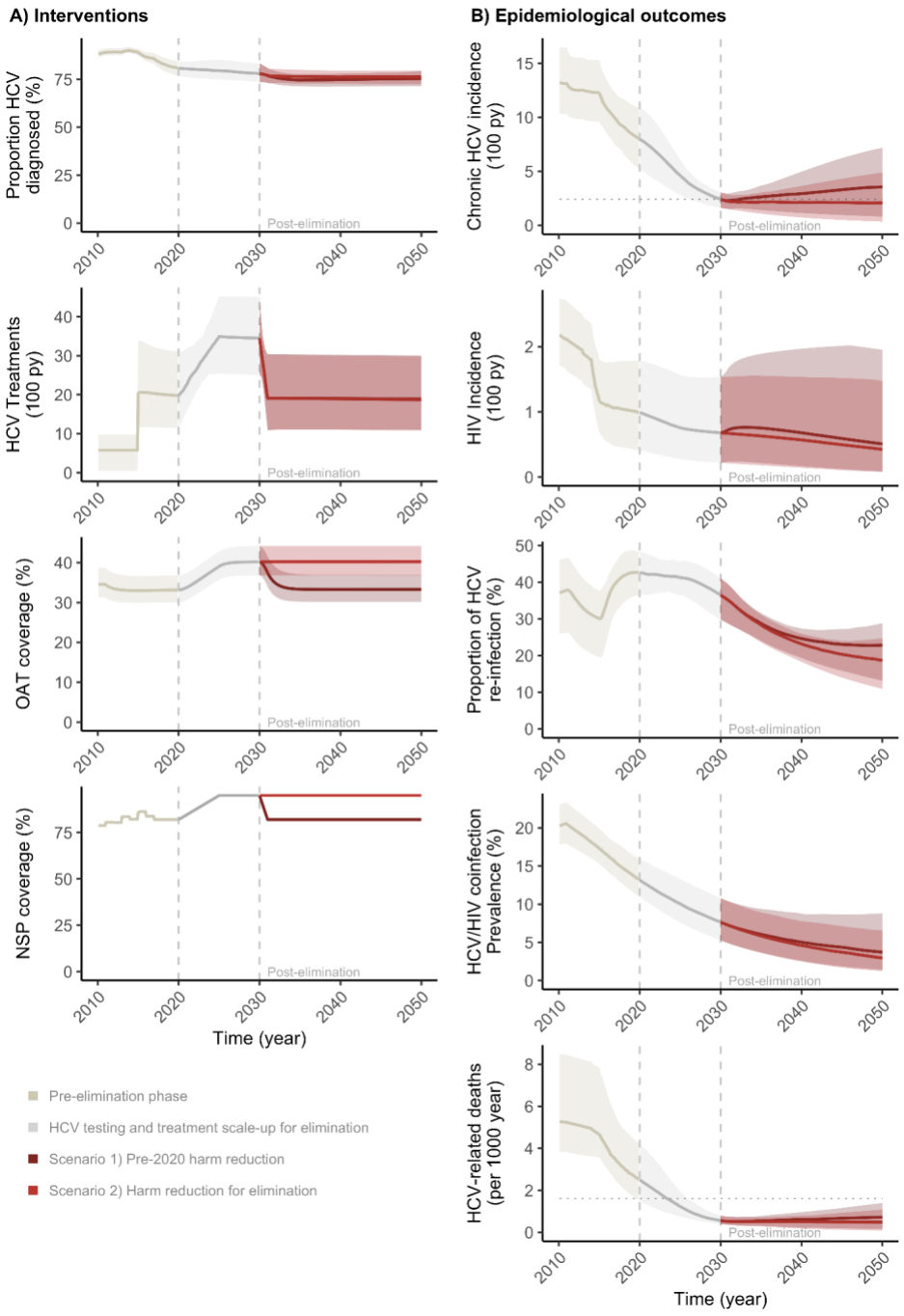


Figure 6.3. Interventions and HCV and HIV outcomes in the elimination and post-elimination periods (scenarios 1 and 2).

Figure legend: Hepatitis C virus (HCV) elimination and post-elimination interventions (A) and epidemiological outcomes (B) under scenarios 1 and 2. The solid lines represent the

median outcome, while the shaded areas represent 95% credible intervals. The dashed lines delimit the elimination phase, and the dotted lines represent World Health Organization targets for HCV elimination of 80% reduction in incidence and 65% reduction in HCV-related mortality, using 2015 as a baseline.

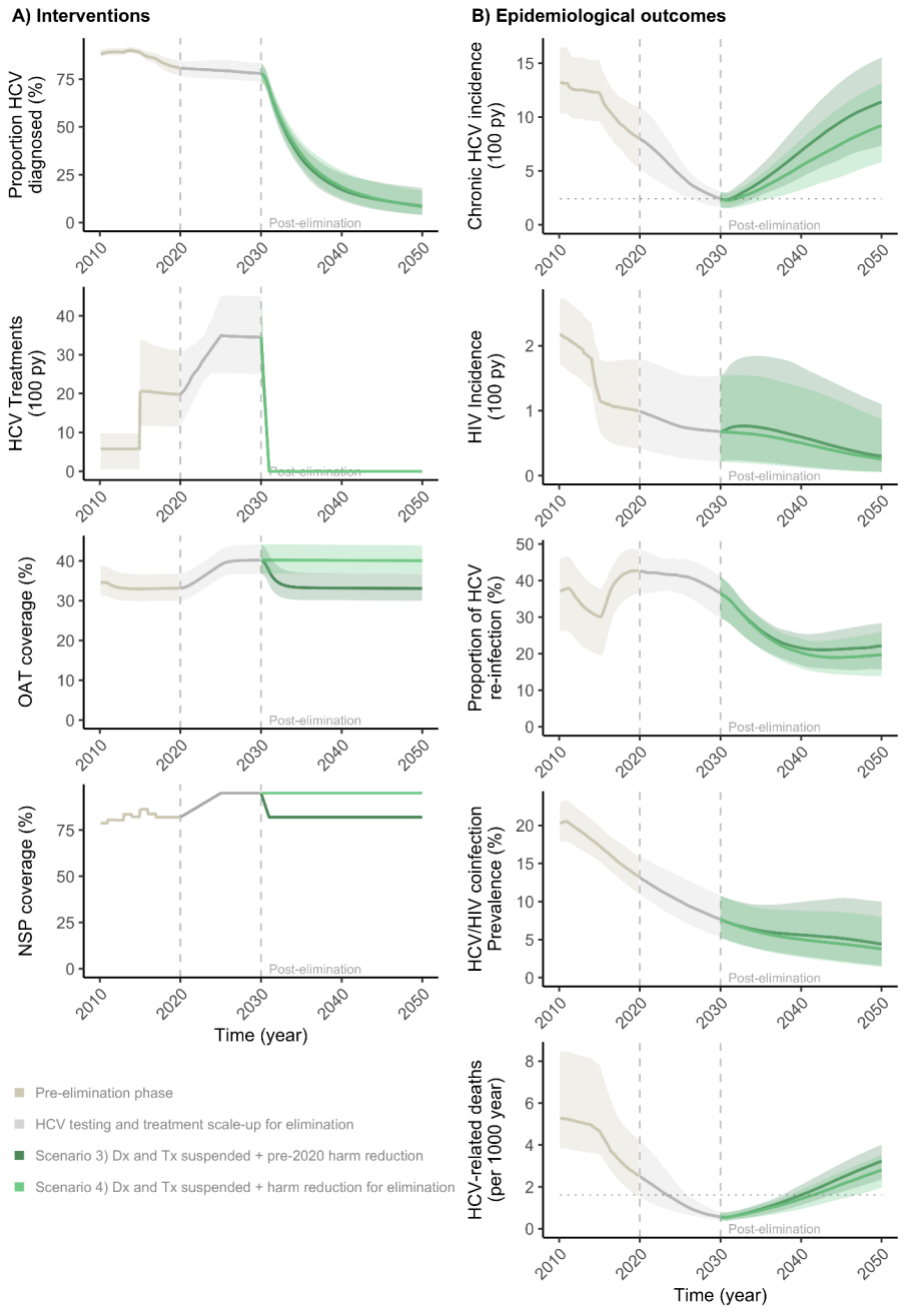


Figure 6.4. Interventions and HCV and HIV outcomes in the elimination and post-elimination periods (scenarios 3 and 4).

Figure legend: Hepatitis C virus (HCV) elimination and post-elimination interventions (A) and epidemiological outcomes (B) under scenarios 3 and 4. The solid lines represent the

median outcome, while the shaded areas represent 95% credible intervals. The dashed lines delimit the elimination phase, and the dotted lines represent World Health Organization targets for HCV elimination of 80% reduction in incidence and 65% reduction in HCV-related mortality, using 2015 as a baseline. Abbreviations: Dx = Diagnosis, Tx = Treatment.

Secondary analyses

We found that HCV incidence, mortality and co-infection prevalence were mostly insensitive to NSP efficacy for HCV and HIV; the degree of assortative mixing by injection status, HIV status and sex; spontaneous HCV clearance among PLHIV; OAT cessation; and the relative decline in the active PWID population size between 2003-2010. We also found that 2050 incidence, mortality and co-infection prevalence were higher in scenarios modelling higher pre-2015 treatment rates and in those using an increased mortality risk among PLHIV not on ART. Lower spontaneous clearance rates among individuals not living with HIV were associated with higher HCV incidence, mortality and co-infection prevalence in 2050 (Figures 6.10 to 6.12). Increasing stimulant injection by 20% over the 2030-2035 period led to higher rebounds in HCV incidence and HCV re-infection than those found in scenario 2. Trends in HIV incidence, HCV-HIV co-infection prevalence, and HCV-related mortality remained similar although at a slightly higher level (Figure 6.13).

Discussion

Little is known about the sustainability of reaching WHO's HCV elimination targets among populations with ongoing risk of HCV transmission. In this study, we demonstrate that HCV micro-elimination targets among PWID can be sustained in settings like Montréal. Our study provides timely evidence that, although reaching elimination may require substantial investments in HCV treatment, relatively low testing and treatment

levels could perpetuate these achievements after 2030. This is contingent, however, on maintaining high-coverage harm reduction programs among PWID.

These results are consistent with those of Gountas and colleagues (Gountas et al., 2018), who found that if HCV treatment was halted completely in 2030, high harm reduction coverage could prevent HCV incidence resurgence in settings or populations with low HCV incidence and prevalence, but not in high incidence and prevalence contexts (i.e., chronic HCV prevalence of 60%) such as Montréal. Indeed, in our study, scenarios suspending all HCV testing and treatment in 2030 led to rebounds in chronic HCV incidence and HCV-related mortality. Such epidemic resurgences were mitigated, but not entirely prevented, by high-coverage harm reduction programs, showing that moderate levels of testing and treatment must be maintained post-elimination. Adding to existing evidence, we showed that efforts to eliminate HCV as a public health threat could lead to long-term decreases in HIV-HCV co-infection prevalence and HIV incidence. Addressing the HIV-HCV syndemic among PWID could therefore yield prevention benefits for both viruses.

Our findings advocate for sustainably scaling-up NSP and OAT. Normatively, harm reduction programs should be strengthened regardless of HCV or HIV incidence as their multiple population- and individual-level benefits go beyond blood-borne disease prevention, and they are cost-effective (Platt et al., 2017; Wilson, Donald, Shattock, Wilson, & Fraser-Hurt, 2015). Enhancing access to harm reduction programs has context-specific implications. First, the highest achievable OAT coverage varies with time and across geographical settings, based on the proportion of PWID who inject opioids. For example, despite recent increases in the frequency of opioid injections (Bruneau, Arruda, Zang, Jutras-Aswad, & Roy, 2019), cocaine remains the most frequently injected drug in Montréal and polydrug use was reported among a majority of PWID participating in *SurvUDI* surveys (Leclerc et al., 2021). As such, the number of people who can benefit from OAT remains limited in our setting, which highlights the importance of developing effective treatments for stimulant use disorder to complement current harm reduction interventions (Ronsley et al., 2020). Our results notably highlight that increased stimulant

use would further limit OAT coverage while contributing to elevated HCV transmission and mortality, despite high treatment rates and NSP coverage. Second, although NSP could theoretically prevent blood-borne infections among all PWID, their effectiveness is multifactorial. PWID need a sufficient number of needles and syringes as well as other paraphernalia (e.g., cookers, spoons, filters) to perform all injections with sterile materials. Needs can vary with both injecting patterns and the drug used for injection (Bruneau et al., 2019). Finally, we simulated the HCV and HIV epidemics until 2050, and other harm reduction initiatives such as supervised injection sites, which were recently introduced in Montréal, could further contribute to preventing transmission in this time frame (Kerr, Mitra, Kennedy, & McNeil, 2017).

Our study has some limitations. First, we did not account for disruptions in HCV prevention and care programs due to the COVID-19 pandemic. Delays in accessing these services are likely to dent progress towards elimination (Blach et al., 2021). Nevertheless, our conclusions regarding post-elimination transmission dynamics are unlikely to be qualitatively affected by these interruptions if efforts are maintained over the next decade to reach elimination targets. Second, we did not explicitly model sexual transmission of HIV. Injecting drug use likely represents the predominant risk factor for both HIV and HCV acquisition among active PWID. Yet, we could have underestimated HIV incidence among individuals that have ceased to inject. Any underestimation should be small since ART coverage is high among PWID living with HIV. Third, PWID do not form a homogenous group and some of these individuals could face specific unmet HCV and HIV prevention and treatment needs that are not explicitly modelled. If heterogeneity is high, we could underestimate efforts to achieve elimination. Finally, people recruited in the *SurvUDI* network are in contact with organisations delivering various services to PWID (e.g., NSP, shelters, rehabilitation facilities) (Leclerc et al., 2021); these people could therefore be less representative of the underlying PWID population. Strengths of our study include that the model's predictions rely on two decades of longitudinal survey data, the inclusion of HIV-HCV co-infection, Bayesian model calibration to multiple

epidemiological outcomes, and robustness of our conclusions to a wide range of model parameters.

Conclusion

The WHO's HCV elimination targets can be sustained among PWID in high prevalence settings like Montréal. Maintaining access to proven harm reduction strategies is key to ensure that the financial investments to scale up DAA treatment by 2030 continue to provide long-term public health benefits.

Declaration of interest

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CReDiT author statement

Charlotte Lanièce Delaunay: conceptualization, methodology, software, formal analysis, data curation, visualization, writing. Arnaud Godin: conceptualization, methodology, software, formal analysis, validation, visualization, writing. Nadine Kronfli: validation, writing, supervision, resources, funding acquisition. Dimitra Panagiotoglou: validation, writing, supervision. Joseph Cox: validation, writing, supervision, resources, funding acquisition. Michel Alary: validation, writing, supervision, resources. Marina B. Klein: conceptualization, methodology, validation, writing, supervision, resources, funding acquisition. Mathieu Maheu-Giroux: conceptualization, methodology, software, writing, supervision, project administration.

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6.3. Manuscript 3 – Appendix

Table of contents

Methods

Model structure

We developed a dynamic, deterministic, sex-stratified compartmental model of HCV and HIV co-infection and transmission among people who inject drugs (PWID) living in Montréal (Canada), starting in 2003. The model structure was adapted from the work of Godin and colleagues (Godin, Kronfli, Cox, Alary, & Maheu-Giroux, 2020). Three concurrent dynamics were considered in a single model: 1) HCV transmission and care continuum, 2) HIV transmission and care continuum, and 3) injecting behaviours. The 294 compartments of the model result from the product of seven compartments for HCV status, two for sex, seven for HIV status, and three for injection status. People can therefore progress through different dynamics simultaneously.

People enter the model upon first drug injection ($PI(t)$, Figure 6.7), at which time everyone is assumed to be seronegative to HCV ($S^{hcv0}(t)$, Figure 6.5) and HIV ($S^{hiv}(t)$, Figure 6.6). People exit the model upon death, which can result from three causes: background mortality among PWID (μ), liver-related mortality among people chronically infected with HCV (μ_{1_v}), and AIDS-related mortality among people living with HIV (PLHIV) who are not on antiretroviral therapy (ART) and whose CD4 cell count is inferior to 200 cells/mm^3 (μ_2).

The recruitment rate $\theta_{svi}(t)$ was chosen to replicate the observed decline in the size of the active PWID population from 11,700 in 1996 (Remis et al., 1998) to 3,910 in 2010 (Leclerc et al., 2014). We assumed a constant population size after 2010 due to limited evidence on demographic trends among active PWID following that year. More specifically, $\theta_{svi}(t)$ was specified as the sum of two components. The first component ensures that the active PWID population remains stable over time by replacing those who died at time $t-1$ with new active PWID of the same sex (i.e., keeping the sex ratio constant). The second component allows the active PWID population to vary from 2003 to 2010, (Leclerc et al.,

2014; Remis et al., 1998), using the $dPWID(t)$ parameter to quantify the yearly reduction in the active PWID population size.

HCV transmission dynamics

HCV acquisition and transmission occurs through injection drug use. We modelled transmission per injecting partnership, by contaminated injection equipment. An effective injecting partnership was defined as one involving at least one contact, such as an episode of multiperson use of needles, syringes, or other paraphernalia between an individual susceptible to HCV and a person chronically infected with HCV. People acquire HCV at a time-varying force of infection $\lambda_{svi}(t)$ that changes according to chronic HCV prevalence among injecting contacts and the coverage of harm reduction programs (opioid agonist therapy –OAT– and needle and syringe programs –NSP). Following HCV infection, people experience an acute phase $A0(t)$ of duration DA (Westbrook & Dusheiko, 2014) during which they either spontaneously clear the infection at a probability α_{sv} or progress to chronic disease ($C(t)$). The spontaneous clearance rate was assumed lower among males and PLHIV (Grebely et al., 2014; D. J. Smith, Jordan, Frank, & Hagan, 2016). People with chronic HCV infection can ultimately die of HCV-related causes at a rate μ_{1_v} if left untreated. This mortality rate is higher among PLHIV who are not on ART (Hayashi et al., 2014; Trickey et al., 2019). PWID can be tested for HCV at a time-varying rate $\tau(t)$, and because PLHIV who are on ART are already engaged in HIV care, we assumed that they would get tested for HCV immediately. If diagnosed ($D(t)$), people can be linked to care and treated ($T(t)$) at a rate $\sigma(t)$. Before 2015, HCV treatment uptake was low among both HCV mono-infected and HIV-HCV co-infected PWID (Grebely et al., 2009; Saeed et al., 2017). In 2015, second-generation direct-acting antiviral (DAA) treatments became universally accessible in the province of Québec (Marshall et al., 2016). We estimated pre- and post-2015 HCV treatment uptake among HIV-HCV co-infected PWID using data from the *Canadian Co-infection Cohort* (manuscript in preparation; study details are provided in section on model parametrisation). Because co-infected PWID tend to be identified and engaged in HIV care (Sacks-Davis et al., 2018), we used the estimated rates as upper limits

in the prior distributions for the HCV treatment rate $\sigma(t)$. The introduction of second-generation DAAs considerably reduced treatment duration $DT(t)$ and improved HCV treatment effectiveness $\varepsilon_v(t)$ regardless of HIV-HCV coinfection, previously regarded as particularly difficult to address (Rodriguez-Torres et al., 2012; Saeed et al., 2017; Torriani et al., 2004) (Table 5.1). Due to their engagement in HIV care, we assumed that PLHIV on ART who are also chronically infected with HCV could be treated once to twice as fast as other PWID in the second-generation DAA era (rr^{σ}).

In the model, people are assumed to be non-infectious over the course of treatment (i.e., between six months and a year pre-2015, and between two and three months as of 2015) and cannot die of HCV-related mortality. Following successful treatment (i.e., sustained virologic response), people become HCV susceptible again but remain anti-HCV antibody positive ($S^{hcv1}(t)$). There is limited evidence supporting acquired immunity through past HCV exposures, as well as higher spontaneous clearance rate among those with anti-HCV antibodies. Therefore, we assumed that anti-HCV antibody positive, HCV RNA-negative people ($A1(t)$) could be re-infected at a rate equal to that of primary infection (Hajarizadeh et al., 2020), and that their rate of spontaneous clearance would be the same regardless of their past HCV exposures.

If treatment does not result in sustained virologic response, the natural disease progression follows its course, unless treatment is re-initiated. Re-treatment was assumed to occur at the same rate as a primary treatment, in line with current Canadian guidelines and the availability of pan-genotypic DAA therapies that minimise concerns for drug resistance (Feld & Foster, 2016; Shah et al., 2018).

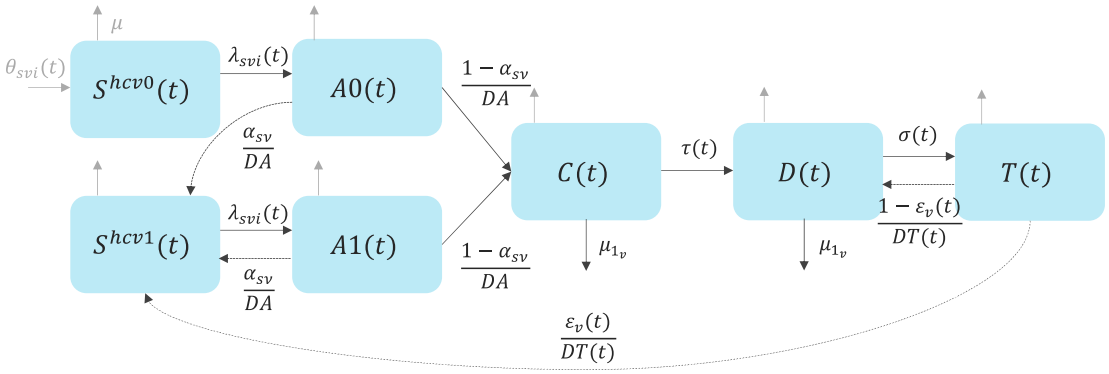

Figure 6.5. HCV natural history and continuum of care.

Figure legend: Hepatitis C (HCV) natural history and continuum of care. The model population is open, and people enter the model upon first injection (PI), as seronegative to HCV (S^{hcv0}) and HIV (S^{hiv}). They can become acutely infected with HCV at a time-dependent force of infection $\lambda(t)$, and either spontaneously clear the virus or progress to chronic infection (C). If diagnosed (D), chronically infected people can initiate HCV treatment (T). In the absence of treatment, the disease progresses, and liver-related mortality can occur. When treatment is successful, people remain anti-HCV antibody positive (S^{hcv1}) and can be reinfected.

The full system of ordinary differential equations for HCV transmission and continuum of care dynamics is presented below, for a person with sex s, HIV status v, and injection status i.

Susceptibles (antibody negative to HCV)

$$\frac{dS_{svi}^{hcv0}(t)}{dt} = \theta_{svi}(t) - (\mu + \lambda_{svi}(t))S_{svi}^{hcv0}(t)$$

Acute HCV phase (first exposure to HCV)

$$\frac{dA0_{svi}(t)}{dt} = \lambda_{svi}(t)S_{svi}^{hcv0}(t) - (\mu + \frac{1}{DA})A0_{svi}(t)$$

Susceptibles (antibody positive to HCV)

$$\frac{dS_{svi}^{hcv1}(t)}{dt} = \frac{\alpha_{sv}}{DA}\left(A0_{svi}(t) + A1_{svi}(t)\right) + \frac{\varepsilon_v(t)}{DT(t)}T_{svi}(t) - (\mu + \lambda_{svi}(t))S_{svi}^{hcv1}(t)$$

Acute HCV phase (prior exposure to HCV)

$$\frac{dA1_{svi}(t)}{dt} = \lambda_{svi}(t)S_{svi}^{hcv1}(t) - (\mu + \frac{1}{DA})A1_{svi}(t)$$

Chronic HCV infection (undiagnosed)

$$\frac{dC_{svi}(t)}{dt} = \frac{1-\alpha_{sv}}{DA}\left(A0_{svi}(t) + A1_{svi}(t)\right) - (\mu + \mu_{1_v} + \tau(t))C_{svi}(t)$$

Diagnosed chronic HCV infection

$$\frac{dD_{svi}(t)}{dt} = \tau(t)C_{svi}(t) + \frac{1-\varepsilon_v(t)}{DT(t)}T_{svi}(t) - \left(\mu + \mu_{1_v} + \sigma(t)\right)D_{svi}(t)$$

Chronic HCV infection on treatment

$$\frac{dT_{svi}(t)}{dt} = \sigma(t)D_{svi}(t) - (\mu + \frac{1}{DT(t)})\,T_{svi}(t)$$

Force of HCV infection and mixing patterns

Force of infection

The force of infection represents the per capita rate of HCV acquisition:

$$\lambda_{svi}(t) = \beta^{HCV}(1 - (cov(t) \times eff^{HCV}))(m_{svi} \times rr_i^{oatHCV} \times p_{svi}(t))$$

Where β^{HCV} is the baseline HCV transmission rate; $cov(t)$ is the time dependent NSP coverage estimated from *SurvUDI* surveys (Leclerc, Roy, Morissette, Alary, & Blouin, 2021); eff^{HCV} is the effectiveness of NSP for preventing HCV infection (Platt et al., 2017); m_{svi} is a vector of contact patterns based on sex, HIV status, and injection status (additional

information on mixing patterns below); rr_i^{oatHCV} is a vector of relative rate values for HCV transmission and acquisition among people on OAT (Platt et al., 2017); $p_{svi}(t)$ is a vector of time-varying HCV infectiousness prevalence among the different population subgroups. In brief, the prevalence is weighted by the relative rate vector to account for variations in the risk of acquiring and transmitting HCV).

Mixing patterns

The full HCV mixing matrix M contains information on the structure of injection contact patterns according to sex M_s, HIV status M_v, and injection status M_i. M was obtained by taking the Kronecker product of the three smaller matrices M_s, M_v, and M_i. s_{jk}, v_{jk}, and i_{jk} represent mixing probabilities, where s_{jk} is the proportion of contacts of an individual in group j that occurs with individuals in group k, in the mixing matrix by sex (s). These contact matrices and mixing probabilities were defined as follows:

$$M = M_s \otimes M_v \otimes M_i$$

$$= \begin{bmatrix} s_{11} & s_{12} \\ s_{21} & s_{22} \end{bmatrix} \otimes \begin{bmatrix} v_{11} & v_{12} & v_{13} & v_{14} & v_{15} & v_{16} & v_{17} \\ v_{21} & v_{22} & v_{23} & v_{24} & v_{25} & v_{26} & v_{27} \\ v_{31} & v_{32} & v_{33} & v_{34} & v_{35} & v_{36} & v_{37} \\ v_{41} & v_{42} & v_{43} & v_{44} & v_{45} & v_{46} & v_{47} \\ v_{51} & v_{52} & v_{53} & v_{54} & v_{55} & v_{56} & v_{57} \\ v_{61} & v_{62} & v_{63} & v_{64} & v_{65} & v_{66} & v_{67} \\ v_{71} & v_{72} & v_{73} & v_{74} & v_{75} & v_{76} & v_{77} \end{bmatrix} \otimes \begin{bmatrix} i_{11} & i_{12} & i_{13} \\ i_{21} & i_{22} & i_{23} \\ i_{31} & i_{32} & i_{33} \end{bmatrix}$$

$$= \begin{bmatrix} s_{11}v_{11}i_{11} & s_{11}v_{11}i_{12} & \cdots & s_{12}v_{17}i_{13} \\ s_{11}v_{11}i_{21} & s_{11}v_{11}i_{22} & \dots & s_{12}v_{17}i_{23} \\ \vdots & \vdots & \ddots & \vdots \\ s_{21}v_{71}i_{31} & s_{21}v_{71}i_{32} & \dots & s_{22}v_{77}i_{33} \end{bmatrix}$$

Sex

The contact matrix by sex M_s has dimensions 2 x 2, the first of which is the person's sex, and the second the sex of the contact. The first element of each dimension represents male, and the second female. Therefore, s_{12} corresponds to the mixing pattern of a male with a female. We assumed that mixing by sex is disassortative, i.e., that a male is more likely to inject with a female, and vice-versa (M. K. Smith, Graham, Latkin, Mehta, & Cummings,

2018). However, uncertainty in the degree of assortative mixing by sex was allowed by using parameter $ps^{assort} \in [0, 0.5]$, which represents the mixing pattern between two people of the same sex. The mixing matrix by sex was thereafter defined by:

$$M_s = \begin{bmatrix} ps^{assort} & 1 - ps^{assort} \\ 1 - ps^{assort} & ps^{assort} \end{bmatrix}$$

HIV status

The mixing matrix by HIV status M_v was of format 7 x 7, with the following elements on each dimension: 1) HIV-susceptible; 2) PLHIV, CD4 cell count >350, not on ART; 3) PLHIV, CD4 cell count 200-350, not on ART; 4) PLHIV, CD4 cell count <200, not on ART; 5) PLHIV, CD4 cell count >350, on ART; 6) PLHIV, CD4 cell count 200-350, on ART; 7) PLHIV, CD4 cell count <200, on ART. We assumed that preferential mixing could occur according to people's knowledge of their HIV status. We therefore considered two groups of HIV compartments: 1) those susceptible or living with HIV but not diagnosed (HIV compartments 1 to 4), and 2) those living with HIV, diagnosed, and on ART (HIV compartments 5 to 7). To account for uncertainty surrounding injection contacts by HIV status, we explored mixing patterns ranging from proportional to fully assortative between these two groups of compartments. In the first case, the rate at which two people from different groups come into contact was determined by the proportion of the total contacts generated by each group. In the second case, people only came into contact with members of their own population group (Vynnycky & White, 2010). The degree of assortative mixing was defined by the parameter $pv^{assort} \in [0, 1]$, and the final mixing matrix by HIV status was given by:

$$M_v = (1 - pv^{assort}) M_v^{prop} + pv^{assort} M_v^{assort}$$

Where M_v^{prop} was the proportionate matrix, and M_v^{assort} was the fully assortative one:

$$M_v^{prop} = \begin{bmatrix} v_{11} & v_{12} & v_{13} & v_{14} & v_{15} & v_{16} & v_{17} \\ v_{21} & v_{22} & v_{23} & v_{24} & v_{25} & v_{26} & v_{27} \\ v_{31} & v_{32} & v_{33} & v_{34} & v_{35} & v_{36} & v_{37} \\ v_{41} & v_{42} & v_{43} & v_{44} & v_{45} & v_{46} & v_{47} \\ v_{51} & v_{52} & v_{53} & v_{54} & v_{55} & v_{56} & v_{57} \\ v_{61} & v_{62} & v_{63} & v_{64} & v_{65} & v_{66} & v_{67} \\ v_{71} & v_{72} & v_{73} & v_{74} & v_{75} & v_{76} & v_{77} \end{bmatrix}$$

$$M_v^{assort} = \begin{bmatrix} 1/4 & 1/4 & 1/4 & 1/4 & 0 & 0 & 0 \\ 1/4 & 1/4 & 1/4 & 1/4 & 0 & 0 & 0 \\ 1/4 & 1/4 & 1/4 & 1/4 & 0 & 0 & 0 \\ 1/4 & 1/4 & 1/4 & 1/4 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1/3 & 1/3 & 1/3 \\ 0 & 0 & 0 & 0 & 1/3 & 1/3 & 1/3 \\ 0 & 0 & 0 & 0 & 1/3 & 1/3 & 1/3 \end{bmatrix}$$

Injection status

The mixing matrix by injection status M_i was of dimensions 3 x 3. On each dimension, the elements were: 1) active PWID not on OAT; 2) active PWID on OAT; 3) former PWID. The matrix obtained followed the same logic used for the HIV mixing matrix. The parameter $pi^{assort} \in [0, 1]$ quantified the degree of assortative mixing by injection status, and we explored patterns ranging from proportionate to fully assortative mixing. The full mixing matrix by injection status was given by:

$$M_i = (1 - pi^{assort})M_i^{prop} + pi^{assort}M_i^{assort}$$

Where M_i^{prop} was the proportionate mixing matrix by injection status, and M_i^{assort} the fully assortative one. In the model, it was assumed that former PWID no longer have injecting contacts, such that they cannot acquire or transmit HCV. This was reflected by null values in the mixing matrices:

$$M_i^{prop} = \begin{bmatrix} i_{11} & i_{12} & 0 \\ i_{21} & i_{22} & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$M_i^{assort} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

HIV transmission dynamics

Similarly to HCV, we modelled HIV transmission through injecting partnerships and the time-varying force of infection $\gamma_{sci}(t)$ varied according to HIV prevalence among injecting contacts, the coverage of harm reduction interventions, and the ART status of injecting partners. Although the risk of sexual transmission of HIV from PWID living with the virus to their sexual partners is not negligible –between 0.02% and 0.05% per heterosexual act, defined as vaginal or anal intercourse (Boily et al., 2009; Degenhardt et al., 2010; Marincovich et al., 2003; Pedraza et al., 1999)– the risk of transmission through multiperson use of contaminated needles or syringes is substantially higher –between 0.63% and 2.4% per injection (Baggaley, Boily, White, & Alary, 2006; Degenhardt et al., 2010). Given the small role of sexual HIV transmission among PWID to dynamics of HCV elimination, and the uncertainty in sexual mixing patterns among active PWID, former PWID, and those who never engaged in that behaviour, we did not model sexual HIV transmission.

People are assumed to be HIV seronegative at model entry ($S^{hiv}(t)$). Following HIV acquisition, they progress through three CD4 cell count stages: >350 cells/mm^3 ($I^{>350}(t)$); 200-350 cells/mm^3 ($I^{200-350}(t)$); <200 cells/mm^3 ($I^{<200}(t)$). If PLHIV are left untreated, they ultimately die of AIDS-related causes at a rate μ_2 (Cori et al., 2015). The continuum of care was simplified and only two statuses are allowed: PLHIV not on treatment and those being treated. PLHIV can initiate ART at a rate that is the sum of two processes: an HIV testing rate $\kappa(t)$ and a time-varying ART recruitment rate that depends on CD4 cell counts. In line with guidelines from the *World Health Organization* (WHO) and the *US Department of Health and Human Services*, the model allows treatment of people with <200 cells/mm^3 as of 2003, 200-350 cells/mm^3 as of 2007, and >350 cells/mm^3 as of 2014 (Richardson, Grant, & Zolopa, 2014; Tseng, Seet, & Phillips, 2015). While on treatment,

PLHIV can transmit HIV but the probability of transmission is greatly reduced (Lesko, Tong, Moore, & Lau, 2017; Westergaard, Hess, Astemborski, Mehta, & Kirk, 2013).

Although ART allows CD4 cell counts to increase (García et al., 2004), CD4 cell depletion tends to be faster among those previously on treatment than among ART-naïve patients, due to past damage to the immune system (Touloumi et al., 2006). Since we do not model individual trajectories but population averages, we assumed that when ART is discontinued people return to their pre-ART CD4 cell count category and disease can progress further.

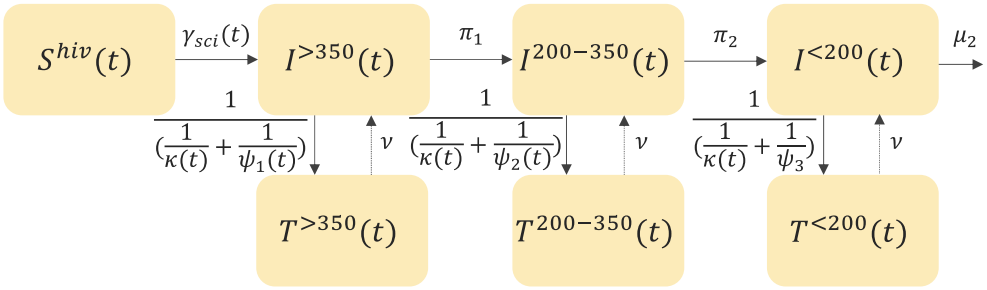

Figure 6.6. HIV natural history and continuum of care.

Figure legend: HIV natural history and continuum of care. HIV susceptible people can acquire HIV at a time-dependent force of infection $\gamma(t)$. Once infected, they progress through disease stages, represented by three decreasing CD4 cell count categories ($I^{>350}$, $I^{200-350}$, $I^{<200}$). AIDS-related death can occur when the CD4 cell count is inferior to 200 cells/mm^3. Antiretroviral therapy can be initiated among eligible individuals, and the model allows for treatment interruptions.

The ordinary differential equation system for HIV transmission and continuum of care dynamics is presented below, for a person with sex s, HCV status c, and injection status i.

Susceptible to HIV

$$\frac{dS_{sci}^{hiv}(t)}{dt} = -\gamma_{sci}(t)S_{sci}^{hiv}(t)$$

Untreated HIV infection (CD4 cell count >350)

$$\frac{dI_{sci}^{>350}(t)}{dt} = \gamma_{sci}(t)S_{sci}^{hiv}(t) + \nu\, T_{sci}^{>350}(t) - (\pi_1 + \frac{1}{(\frac{1}{\kappa(t)} + \frac{1}{\psi_1(t)})})I_{sci}^{>350}(t)$$

Untreated HIV infection (CD4 cell count 200-350)

$$\frac{dI_{sci}^{200-350}(t)}{dt} = \pi_1\, I_{sci}^{>350}(t) + \nu\, T_{sci}^{200-350}(t) - (\pi_2 + \frac{1}{(\frac{1}{\kappa(t)} + \frac{1}{\psi_2(t)})})I_{sci}^{200-350}(t)$$

Untreated HIV infection (CD4 cell count <200)

$$\frac{dI_{sci}^{<200}(t)}{dt} = \pi_2\, I_{sci}^{200-350}(t) + \nu\, T_{sci}^{<200}(t) - (\mu_2 + \frac{1}{(\frac{1}{\kappa(t)} + \frac{1}{\psi_3})})I_{sci}^{<200}(t)$$

Treated HIV infection (CD4 cell count >350)

$$\frac{dT_{sci}^{>350}(t)}{dt} = \frac{1}{(\frac{1}{\kappa(t)} + \frac{1}{\psi_1(t)})}\, I_{sci}^{>350}(t) - \nu\, T_{sci}^{>350}(t)$$

Treated HIV infection (CD4 cell count 200-350)

$$\frac{dT_{sci}^{200-350}(t)}{dt} = \frac{1}{(\frac{1}{\kappa(t)} + \frac{1}{\psi_2(t)})}\, I_{sci}^{200-350}(t) - \nu\, T_{sci}^{200-350}(t)$$

Treated HIV infection (CD4 cell count <200)

$$\frac{dT_{sci}^{<200}(t)}{dt} = \frac{1}{(\frac{1}{\kappa(t)} + \frac{1}{\psi_3})} I_{sci}^{<200}(t) - \nu\, T_{sci}^{<200}(t)$$

Force of HIV infection and mixing patterns

Force of infection

The force of infection represents the per capita rate of HIV acquisition:

$$\gamma_{sci}(t) = \beta^{HIV}(1 - (cov(t) \times eff^{HIV}))(m'_{sci} \times rr_i^{oatHIV} \times rr_v^{ART} \times p'_{sci}(t))$$

Where β^{HIV} is the baseline HIV transmission rate; $cov(t)$ is the time-dependent NSP coverage estimated from *SurvUDI* surveys (Leclerc et al., 2021); eff^{HIV} is the effectiveness of NSP for preventing HIV infection (Aspinall et al., 2014); m'_{sci} is a vector of contact patterns based on sex, HCV status, and injection status; rr_i^{oatHIV} is a vector of relative rate values for HIV transmission and acquisition among people on OAT (MacArthur et al., 2012); rr_v^{ART} is a vector of relative rate values for HIV transmission from PLHIV on ART; $p'_{sci}(t)$ is a vector of time-varying HIV prevalence among the different population subgroups. This prevalence is weighted by the relative rate vectors to account for variations in risk of acquiring and transmitting HIV.

Mixing patterns

The structure of the final HIV mixing matrix M' was similar to that of M. M' summarized information on contact patterns according to sex (M_s, previously described), HCV status (M_c), and injection status (M_i, described above). M' values were obtained by taking the Kronecker product of M_s, M_c, and M_i, as follows:

$$M' = M_s \otimes M_c \otimes M_i$$

$$= \begin{bmatrix} s_{11} & s_{12} \\ s_{21} & s_{22} \end{bmatrix} \otimes \begin{bmatrix} c_{11} & c_{12} & c_{13} & c_{14} & c_{15} & c_{16} & c_{17} \\ c_{21} & c_{22} & c_{23} & c_{24} & c_{25} & c_{26} & c_{27} \\ c_{31} & c_{32} & c_{33} & c_{34} & c_{35} & c_{36} & c_{37} \\ c_{41} & c_{42} & c_{43} & c_{44} & c_{45} & c_{46} & c_{47} \\ c_{51} & c_{52} & c_{53} & c_{54} & c_{55} & c_{56} & c_{57} \\ c_{61} & c_{62} & c_{63} & c_{64} & c_{65} & c_{66} & c_{67} \\ c_{71} & c_{72} & c_{73} & c_{74} & c_{75} & c_{76} & c_{77} \end{bmatrix} \otimes \begin{bmatrix} i_{11} & i_{12} & i_{13} \\ i_{21} & i_{22} & i_{23} \\ i_{31} & i_{32} & i_{33} \end{bmatrix}$$

$$= \begin{bmatrix} s_{11}c_{11}i_{11} & s_{11}c_{11}i_{12} & \cdots & s_{12}c_{17}i_{13} \\ s_{11}c_{11}i_{21} & s_{11}c_{11}i_{22} & \ldots & s_{12}c_{17}i_{23} \\ \vdots & \vdots & \ddots & \vdots \\ s_{21}c_{71}i_{31} & s_{21}c_{71}i_{32} & \ldots & s_{22}c_{77}i_{33} \end{bmatrix}$$

HCV status

The contact matrix by HCV status was of format 7 x 7 and each dimension included the following elements: 1) HCV susceptible, anti-HCV antibody negative; 2) acutely infected with HCV (primary infection); 3) HCV susceptible, anti-HCV antibody positive; 4) acutely infected with HCV (re-infection); 5) chronically infected, undiagnosed; 6) chronically infected, diagnosed; 7) chronically infected, on HCV treatment. We assumed proportional mixing by HCV status, due to the lack of evidence suggesting other types of patterns. The final mixing matrix by HCV status was the following:

$$M_c = \begin{bmatrix} c_{11} & c_{12} & c_{13} & c_{14} & c_{15} & c_{16} & c_{17} \\ c_{21} & c_{22} & c_{23} & c_{24} & c_{25} & c_{26} & c_{27} \\ c_{31} & c_{32} & c_{33} & c_{34} & c_{35} & c_{36} & c_{37} \\ c_{41} & c_{42} & c_{43} & c_{44} & c_{45} & c_{46} & c_{47} \\ c_{51} & c_{52} & c_{53} & c_{54} & c_{55} & c_{56} & c_{57} \\ c_{61} & c_{62} & c_{63} & c_{64} & c_{65} & c_{66} & c_{67} \\ c_{71} & c_{72} & c_{73} & c_{74} & c_{75} & c_{76} & c_{77} \end{bmatrix}$$

Injecting behaviour dynamics

When people who inject opioids engage in OAT, their injection frequency decreases, thereby reducing their risk of acquiring and/or transmitting blood-borne infections. We

used efficacies of 50% (Platt, 2017) and 54% (MacArthur et al., 2012) for the reduction of HCV and HIV transmission, respectively, among people on OAT. Regardless of OAT engagement, PWID cease to inject after an average of fourteen years (Montain et al., 2016). People who cease to inject are no longer at risk of acquiring or transmitting HIV and HCV, but still progress through the different HCV and HIV disease stages. NSP coverage was informed by surveillance data collected among PWID in Montréal (Leclerc et al., 2021), and was assumed to reduce HCV and HIV transmission by respectively 20% and 34% (Aspinall et al., 2014; Platt et al., 2017).

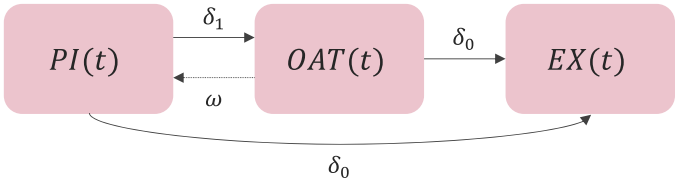

Figure 6.7. Injection behaviour dynamics.

Figure legend: Injection dynamics. A fraction of people who inject drugs can initiate opioid agonist therapy (OAT). They are then assumed to inject at lower frequencies and are therefore less likely to acquire and transmit HCV and HIV. Opioid agonist therapy can also be interrupted. After an average duration of 14 years, people who inject drugs cease to inject permanently (EX).

The system of ordinary differential equations injecting behaviour dynamics is presented below, for a person with sex s, HCV status c, and HIV status v.

People who inject drugs

$$\frac{dPI_{scv}(t)}{dt} = \omega\ OAT_{scv}(t) - (\delta_0 + \delta_1)PI_{scv}(t)$$

People who inject drugs on OAT

$$\frac{dOAT_{scv}(t)}{dt} = \delta_1 \, PI_{scv}(t) - (\omega + \delta_0) OAT_{scv}(t)$$

People who no longer inject drugs

$$\frac{dEX_{scv}(t)}{dt} = \delta_0 \, (PI_{scv}(t) + OAT_{scv}(t))$$

Model parametrisation

The model parameters were informed by data from the Montréal sites of the *SurvUDI* network (Blouin et al., 2016; Campeau et al., 2018; Leclerc et al., 2021; Roy et al., 2011). *SurvUDI* was established in 1995 for the epidemiological surveillance of HIV infections among PWID. In 2002, it became part of *I-Track,* the enhanced surveillance system among PWID in Canada, and HCV surveillance began in 2003. Continuous recruitment is conducted at NSP access centres, rehabilitations centres, and shelters. Eligible PWID (i.e., people who report injecting drugs in the past six months and provide informed consent) can only participate once within a six-month period. Individual identifiers allow the investigators to longitudinally track participation, which ultimately allows estimating annual HIV and HCV incidence among repeat testers. HCV-antibody and HIV prevalence rates are estimated among participants at their first lifetime visit to the network. Information on socio-demographic characteristics, substance use and injecting drug use, sexual behaviours, as well as HIV and HCV testing and management are collected through interviewer-administered questionnaires. Serological tests for HIV and HCV are performed. HCV and HIV testing rates, NSP coverage, and OAT engagement were estimated from this source.

This information was complemented by analyses of data from the *Canadian Co-infection Cohort*, a longitudinal cohort study launched in 2003, with ongoing recruitment and follow-up (Klein et al., 2010). As of January 2021, more than 2,000 participants had been recruited from 18 HIV treatment centres across six Canadian provinces. Recruitment has

been designed and conducted to reach marginalised populations who access diverse models of care and have various risk profiles (e.g., PWID, Indigenous people, men who have sex men). Participants must be 16 years of age or older, have a documented HIV infection, and chronic HCV infection or evidence of HCV exposure. Follow-up visits are scheduled every six months, and socio-demographic, medical, behavioural, and quality of life data are collected through a questionnaire and medical chart reviews. Blood tests are performed at each visit that include HIV- and HCV-RNA tests. The cohort was used to parametrise HCV treatment uptake and effectiveness among PLHIV (manuscript in preparation).

Other parameter values were drawn from the scientific literature, prioritising systematic reviews and meta-analyses when available.

Model calibration

Calibration refers to the statistical process of selecting model parameters so that model projections accurately reproduce epidemic trends measured from empirical data. The model was confronted to the following calibration targets: (1) annual HCV seroprevalence (2003-2018), (2) annual HCV seroincidence (2003-2017), (3) annual HIV prevalence (2003-2018), (4) annual HIV incidence (2003-2017), (5) joint prevalence of anti-HCV antibodies and HIV infection (2015-2018), and (6) self-reported antiretroviral treatment coverage among PLHIV (2003-2018). The empirical data points and confidence intervals were extracted from reports of the *SurvUDI* network surveys (Leclerc et al., 2021). Prevalence was estimated among participants at their first visit to the network, and incidence rates among repeated testers.

Parameters that best described the HCV and HIV epidemic trajectories were selected in a Bayesian framework using the sampling importance resampling method (Rubin, 1987). We first sampled 70,000 parameter sets using Latin hypercube sampling from our prior distributions (McKay & Conover, 1979). This sampling technique allows to efficiently explore the parameter space. For each parameter set, the model was first run for 100 years using baseline parameter values to reach endemic equilibrium. Using the empirical 2003

population size estimate (Leclerc et al., 2014) and the population distribution across compartments at equilibrium, epidemics were then simulated from 2003 to 2018, the years for which data from the *SurvUDI* network were available for both HCV and HIV infections. Model outcomes were then estimated for each parameter set. Using the calibration targets, we estimated the likelihood associated with each parameter set, and resampled 350 sets with replacement using sampling weights proportional to the likelihood values (Menzies, Soeteman, Pandya, & Kim, 2017). Because the *SurvUDI* recruitment was conducted using convenience sampling, and in order to allow for more flexibility in epidemic trajectories, we applied a design effect of 10 to the *SurvUDI* sample size when estimating the likelihood of each model simulation. With this approach, we could select the parameter sets that best reproduced the empirical data while propagating parameter uncertainty to the model's predictions.

Optimisation

We used numerical optimisation to estimate required rates of testing and treatment to reach elimination targets among PWID over the 2020-2030 period. Over this time frame, we simultaneously scaled-up OAT coverage to 40%, as recommended by the *Canadian Network on Hepatitis C* (Canadian Network on Hepatitis C, 2019) and NSP to 95%. For each simulation obtained from the calibration process, we estimated the scale-up factor for testing and treatment, which minimised the absolute distance between the modelled and WHO target (80%) relative HCV incidence reduction by 2030. To prevent discontinuities in the rates of the interventions, we simulated a progressive scale-up over a five-year period using linear interpolation (2020-2025). We also assumed that testing and treatment rates would remain at least as high as in 2020 during the elimination phase (2020-2030), which limited our optimisation problem to a scale-up or the status-quo. To account for this constraint, and reduce computer memory utilisation, we used a box constrained limited-memory Broyden-Fletcher-Goldfarb-Shanno algorithm (L-BFGS-B), a procedure commonly used for large-scale bounded optimisation problems (Byrd, Lu, Nocedal, & Zhu, 1995). The optimisation algorithm was performed in the *optimx* package from R (Nash, 2014; Nash & Varadhan, 2011).

Sensitivity analyses

We assessed the sensitivity of our model results to changes in various model parameter values. Specifically, we examined correlations between model outcomes and variations in the following parameters: the relative decline in the Montréal PWID population size from 2003 to 2010 ($dPWID$); the HCV spontaneous clearance rates among HIV-negative people ($\alpha_{HIV-HCV+}$) and PLHIV ($\alpha_{HIV+HCV+}$); the HCV treatment rate pre-2015 ($\sigma < 2015$); the effectiveness of NSP for preventing HIV (eff^{HIV}) and HCV (eff^{HCV}); the OAT cessation rate (ω); the degrees of assortative mixing by sex (ps^{assort}), HIV status (pi^{assort}), and injection status (pi^{assort}); and the relative rate for increased HCV-related mortality among PLHIV who are not on ART (rr^{μ_1}). For each parameter, we examined and plotted the correlation between all sampled values of this parameter and trends in chronic HCV incidence, HCV-related mortality, and HIV-HCV coinfection prevalence for post-elimination scenario 1 (i.e., pre-2020 levels of HCV testing, HCV treatment, NSP coverage, and OAT coverage).

<u>Increase in stimulants injection</u>

We additionally explored the impact of an augmentation in the proportion of individuals using stimulants as their main injecting drugs by increasing the HIV and HCV transmission rates and reducing OAT coverage. To model the increased HCV transmission rate, we first assumed the baseline overall transmission rate (β_{hcv}) to be a weighted average of stimulant- and opioid-specific transmission rates.

$$\beta_{hcv} = \nu\, \beta_{stim} + (1 - \nu)\beta_{opi}$$

Where ν is the proportion of people who use stimulants as their main drugs of injection extracted from *SurvUDI*. We then assumed the following relationship: $\beta_{stim} = rr_{stim}\beta_{opi}$ such that we were able to estimate the underlying β_{opi} as

$$\beta_{opi} = \frac{\beta_{hcv}}{\left(1 - \nu\,(1 - rr_{stim})\right)}$$

Where $rr_{stim} = 2.9$ is the elevated risk of HCV acquisition and transmission among people who inject stimulant as extracted from Butler and colleagues (Butler, Rehm, & Fischer, 2017). We then increased the proportion of people who inject stimulant such that $\nu' = 1.2\nu$ and estimated the new overall HCV transmission (β'_{hcv}) rate such that

$$\beta'_{hcv} = \beta_{opi}\left(1 - \nu'\ (1 - \ rr_{stim})\right)$$

We followed the same approach to estimate the new overall HIV transmission rate, using a factor $rr_{stimHIV} = 3.0$ to model the increased risk of HIV acquisition and transmission among people who inject stimulants (Tavitian-Exley, Vickerman, Bastos, & Boily, 2015).

We concomitantly adjusted the rate of engagement on OAT to reflect the change in the proportion of people who inject stimulants. The change in the transmission parameter and the rate of engagement on OAT was linearly interpolated over a 5-year period (2030-2035) to replicate slow changes in injecting drug use patterns. This scenario is otherwise identical to scenario 2 from the main analyses, to which it was compared, where testing and treatment rates are scaled down to pre-2020 levels and NSP coverage is maintained at 95%.

Additional results

Prior versus posterior distributions

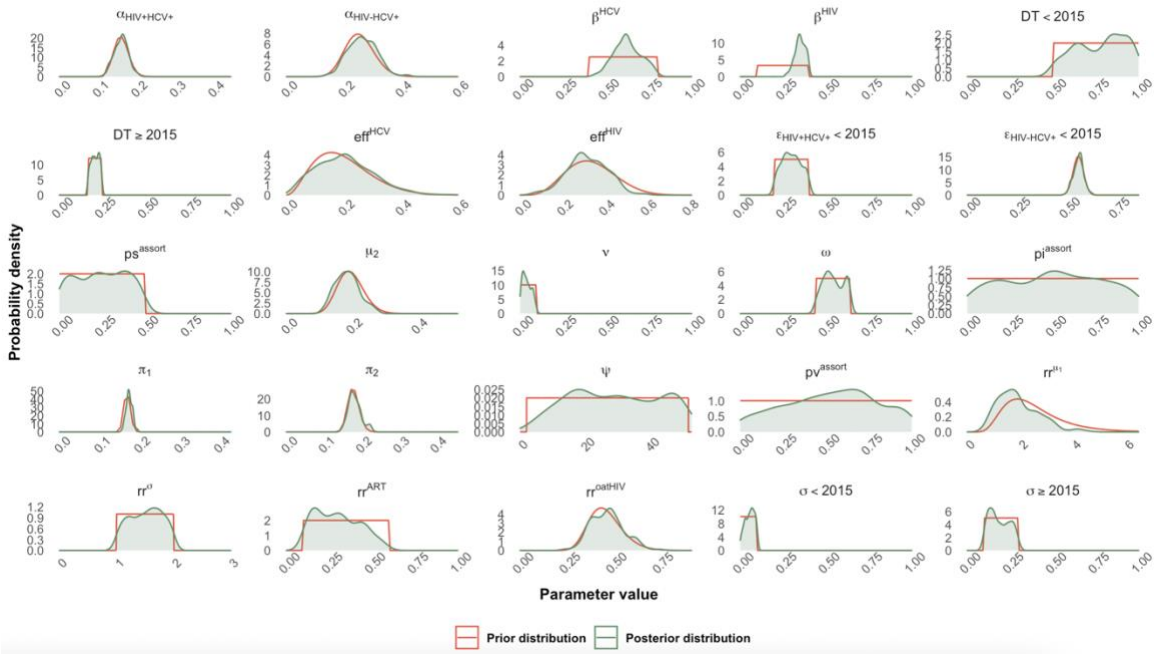

Figure 6.8. Prior versus posterior distributions of model parameters.

Figure legend: Prior versus posterior parameter distributions. Out of 70,000 parameter sets sampled using Latin hypercube sampling, we resampled (with replacement) 350 parameter sets using the sampling importance resampling method (Menzies et al., 2017; Rubin, 1987). Only parameters that were sampled (as opposed to parameters with fixed values) are represented. $\alpha_{HIV+HCV+}$ *and* $\alpha_{HIV-HCV+}$ *are the hepatitis C virus (HCV) spontaneous clearance rates among HIV-HCV co-infected and HCV mono-infected people, respectively;* β^{HCV} *and* β^{HIV} *are the baseline transmission rates of HCV and HIV, respectively;* $DT < 2015$ *and* $DT \geq 2015$ *represent the HCV treatment durations pre- and post-2015, respectively;* eff^{HCV} *and* eff^{HIV} *refer to the effectiveness of NSP for preventing HCV and HIV acquisition, respectively;* $\varepsilon_{HIV+HCV+} < 2015$ *and* $\varepsilon_{HIV-HCV+} <$

2015 *refer to pre-2015 HCV treatment effectiveness among HIV-HCV coinfected and HCV mono-infected people, respectively;* ps^{assort} *is the degree of assortative mixing by sex;* μ_2 *is the AIDS-related mortality rate;* ν *represents the HIV treatment discontinuation rate;* ω *is the OAT cessation rate;* pi^{assort} *is the degree of assortative mixing by opioid agonist therapy status;* π_1 *and* π_2 *correspond to the progression rates from >350 to <200-350 CD4 cell count category, and from 200-350 CD4 cell count to <200 CD4 cell count category, respectively;* ψ *is the HIV treatment rate among eligible people (i.e., people with a CD4 cell count <200 from 2003 to 2006, people with a CD4 cell count <350 from 2007 to 2013, and all people living with HIV as of 2014);* pv^{assort} *refers to the degree of assortative mixing by HIV status;* rr^{μ_1} *is the increased liver-related mortality rate among people living with HIV who are not on antiretroviral treatment;* rr^{σ} *is the post-2015 increase in HCV treatment rate among people living with HIV who are on antiretroviral treatment;* rr^{ART} *is the percentage reduction in HIV transmission from people living with HIV who are on antiretroviral treatment;* rr^{oatHIV} *is the relative rate of HIV transmission and acquisition among people on opioid agonist therapy;* $\sigma < 2015$ *and* $\sigma \geq 2015$ *refer to the HCV treatment rate pre- and post-2015, respectively.*

Cross-validation of the population size

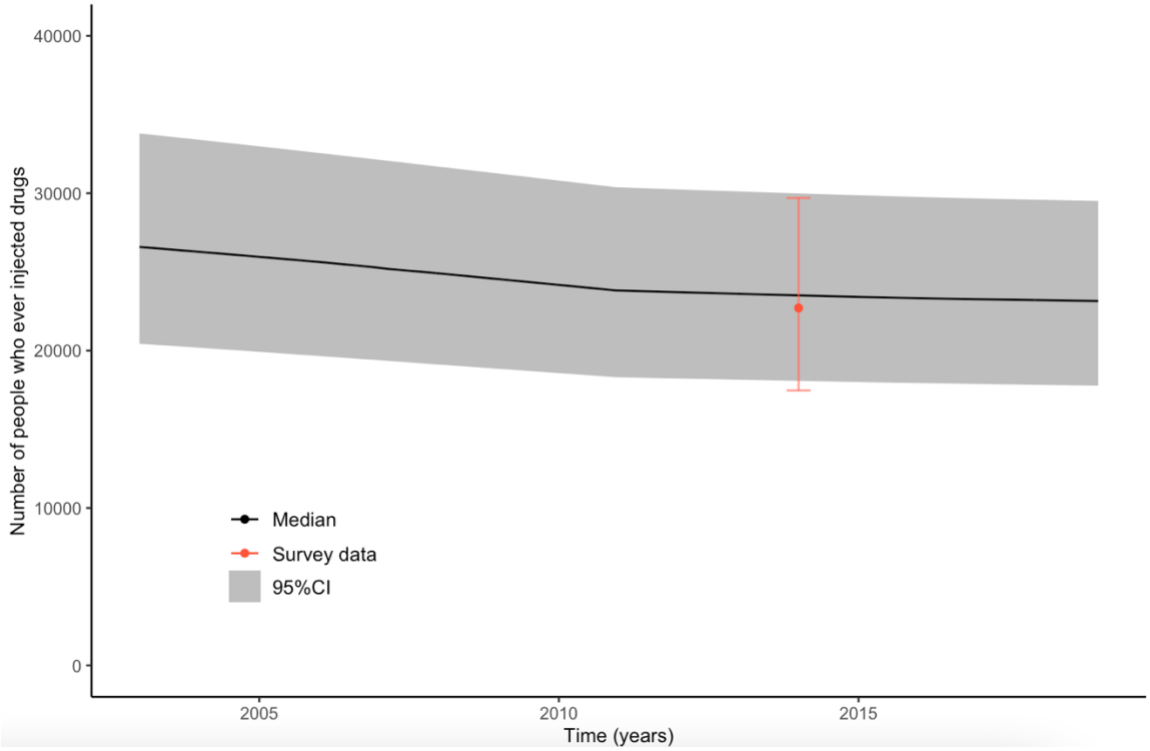

Figure 6.9. Cross-validation of the model population size.

Figure legend: Comparison of trends in total modelled population size to population-based survey estimate of the number of people who ever injected drugs in Montréal (Canada) in 2014. The empirical estimate of the population of self-reported ever injectors was obtained from a report published by Camirand and colleagues in 2016 (Camirand, Traoré, Baulne, & Courtemanche, 2016).

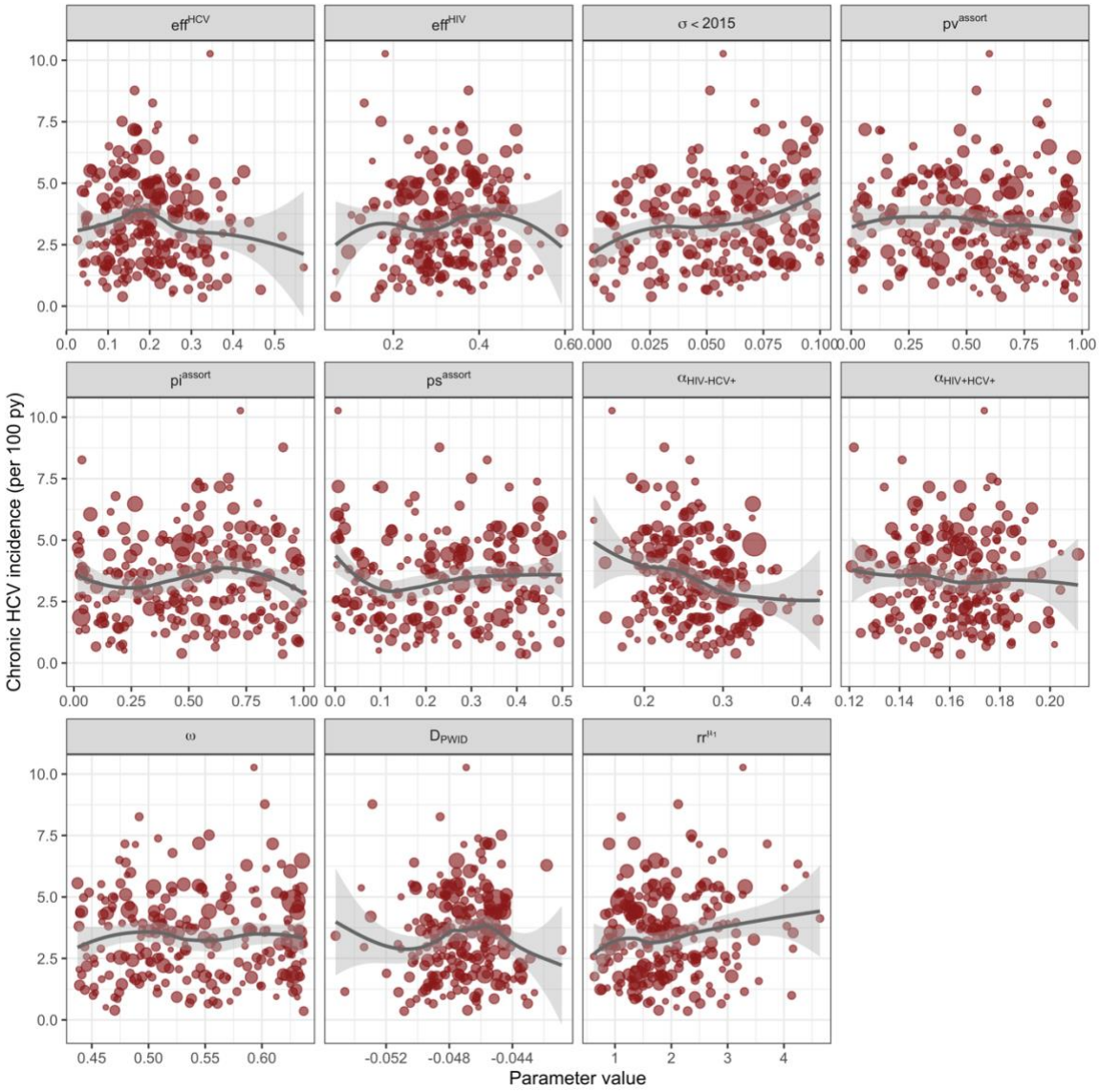

Figure 6.10. Sensitivity analyses for chronic HCV incidence.

Figure legend: Sensitivity analyses for incidence of chronic infections (including re-infections) in 2050 as a function of needle and syringe program effectiveness to reduce HCV (eff^{hcv}) and HIV infection (eff^{hiv}); the HCV treatment rate for people who inject

drugs (PWID) pre-2015 ($\sigma_{<2015}$); mixing by sex (p_s^{assort}), OAT status (p_i^{assort}), and HIV status (p_v^{assort}), where a degree of 1 means only assortative mixing (like-with-like); the rate of HCV spontaneous clearance among people living with HIV (PLHIV, $\alpha_{HIV+HCV+}$) and HIV-negative individuals ($\alpha_{HIV-HCV+}$); the rate of cessation of OAT (ω); the relative decline in the PWID population over the 2003-2010 period (D_{PWID}); and the increased risk of HCV-related mortality among PLHIV not on ART (rr^{μ_1}). The points represent parameter sets and their sizes are relative to their likelihood weight. The line and shaded area represent a LOESS smoothing curve and its 95% confidence interval.

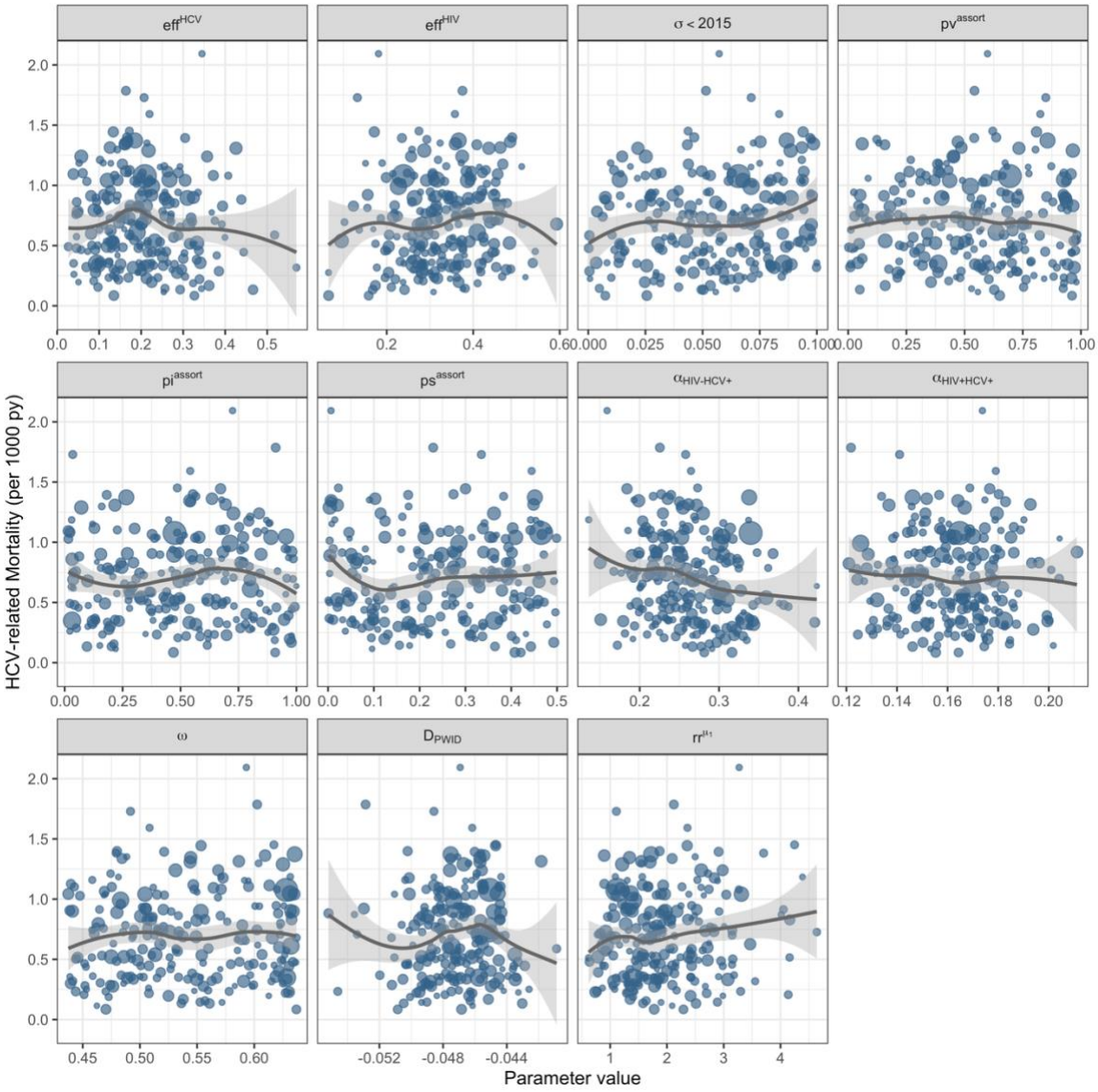

Figure 6.11. Sensitivity analyses for HCV-related mortality.

Figure legend: Sensitivity analyses for HCV-related mortality in 2050 as a function of needle and syringe program effectiveness to reduce HCV (eff^{hcv}) and HIV infection (eff^{hiv}); the HCV treatment rate for people who inject drugs (PWID) pre-2015 ($\sigma_{<2015}$); mixing by sex (p_s^{assort}), OAT status (p_i^{assort}), and HIV status (p_v^{assort}), where a degree of 1 means only assortative mixing (like-with-like); the rate of HCV spontaneous clearance among people living with HIV (PLHIV, $\alpha_{HIV+HCV+}$) and HIV-negative individuals

($\alpha_{HIV-HCV+}$); the rate of cessation of OAT (ω); the relative decline in the PWID population over the 2003-2010 period (D_{PWID}); and the increased risk of HCV-related mortality among PLHIV not on ART (rr^{μ_1}). The points represent parameter sets and their sizes are relative to their likelihood weight. The line and shaded area represent a LOESS smoothing curve and its 95% confidence interval.

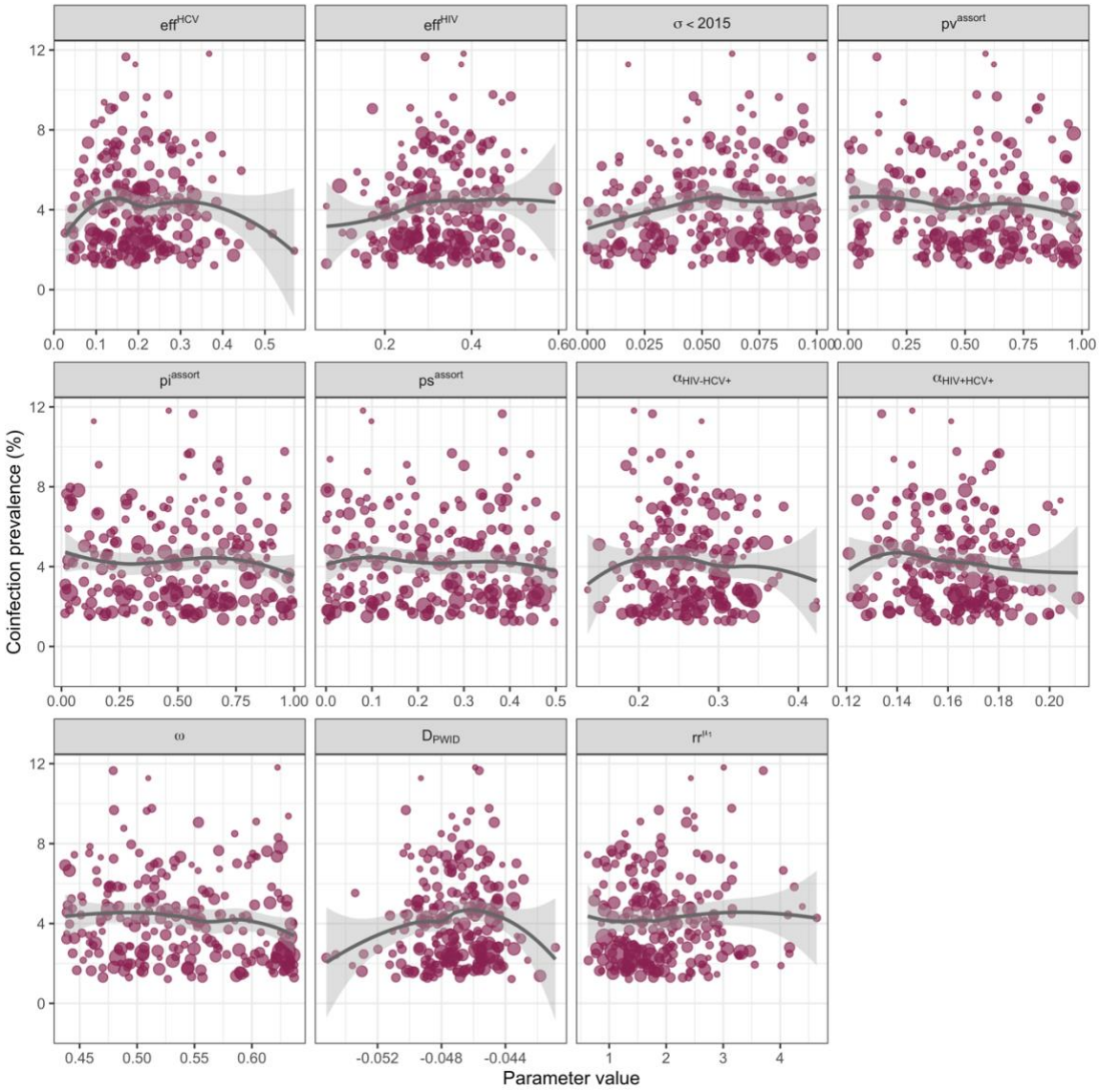

Figure 6.12. Sensitivity analyses for HIV-HCV coinfection prevalence.

Figure legend: Sensitivity analyses for co-infection prevalence in 2050 as a function of needle and syringe program effectiveness to reduce HCV (eff^{hcv}) and HIV infection (eff^{hiv}); the HCV treatment rate for people who inject drugs (PWID) pre-2015 ($\sigma_{<2015}$); mixing by sex (p_s^{assort}), OAT status (p_i^{assort}), and HIV status (p_v^{assort}), where a degree of 1 means only assortative mixing (like-with-like); the rate of HCV spontaneous clearance among people living with HIV (PLHIV, $\alpha_{HIV+HCV+}$) and HIV-negative individuals

($\alpha_{HIV-HCV+}$); the rate of cessation of OAT (ω); the relative decline in the PWID population over the 2003-2010 period (D_{PWID}); and the increased risk of HCV-related mortality among PLHIV not on ART (rr^{μ_1}). The points represent parameter sets and their sizes are relative to their likelihood weight. The line and shaded area represent a LOESS smoothing curve and its 95% confidence interval.

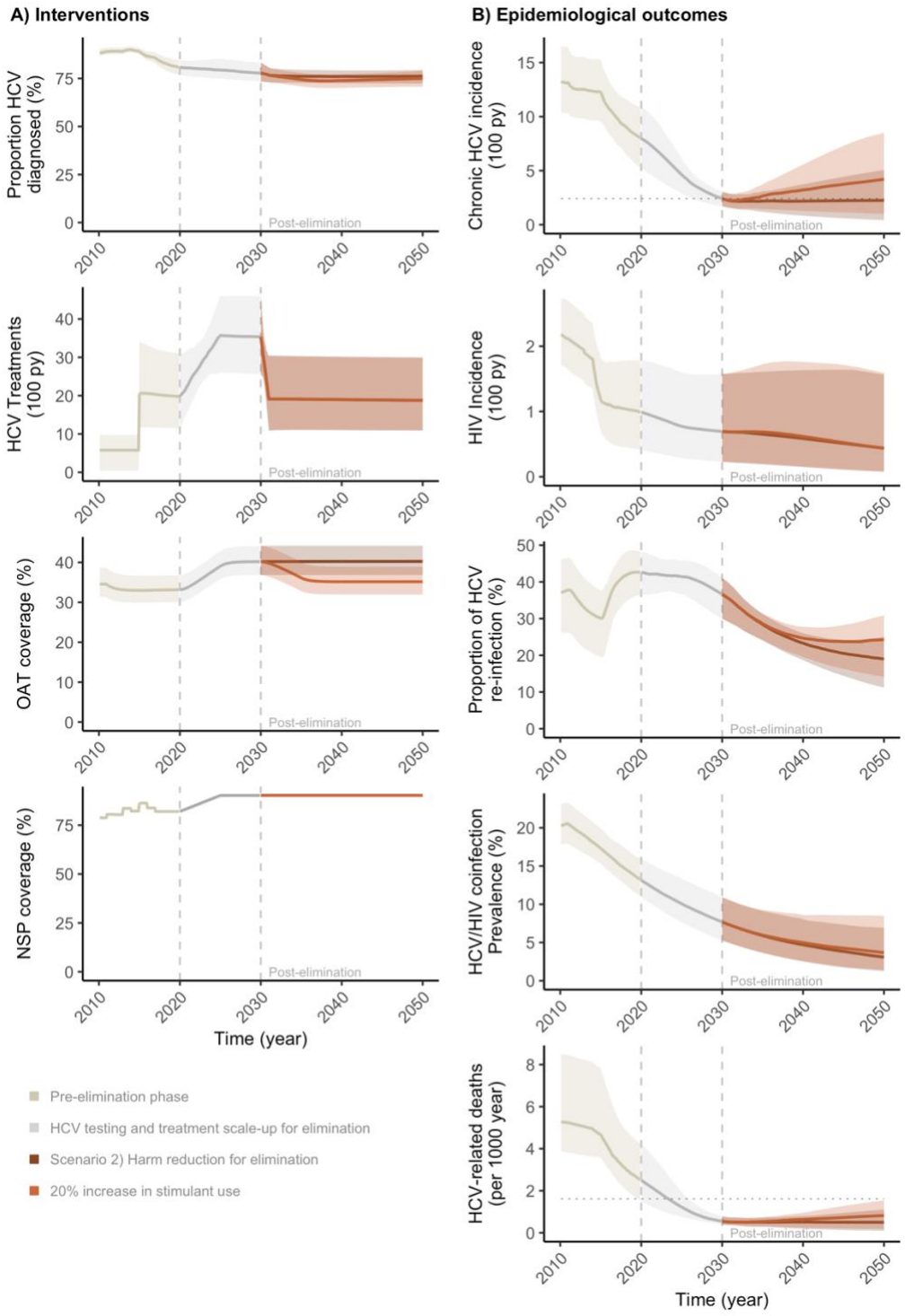

Figure 6.13. Interventions and HCV and HIV outcomes in the elimination and post-elimination periods with increased stimulant use.

Figure legend: Hepatitis C virus (HCV) elimination and post-elimination interventions (A) and epidemiological outcomes (B) under scenario 2 and a 20% increase in stimulant use over the 2030-2035 period. The solid lines represent the median outcome, while the shaded areas represent 95% credible intervals. The dashed lines delimit the elimination phase, and the dotted lines represent World Health Organization targets for HCV elimination of 80% reduction in incidence and 65% reduction in HCV-related mortality, using 2015 as a baseline.

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7. Chapter 7: Discussion and conclusions

7.1. Summary of findings

The overarching aim of my doctoral research was to identify interventions that can achieve and sustain HCV elimination as a public health threat by 2030 among MSM and PWID in Montreal, with specific attention to members of these groups LWH. In Manuscript 1, I generated comparable, representative estimates of HCV seroprevalence among MSM living in Montreal at different points in time. Standardised HCV seroprevalence remained stable around 8% from 2005 to 2018. Past HCV exposure was more frequent among MSM with a history of IDU, MSM LWH, and MSM older than 45 years old. While HCV seropositivity was strongly associated with past IDU, I observed no association with recent sexual behaviours.

I then developed and calibrated a model of HCV and HIV transmission via IDU in Montreal. In Manuscript 2, I used this model to simulate HCV prevention and care strategies from 2022 to 2030, for different subgroups of interest among PWID (PWID LWH, active injectors). Importantly, these analyses accounted for disruptions in HCV care and prevention services due to the COVID-19 pandemic. Pre-pandemic intervention levels were unlikely to achieve the WHO HCV incidence target by 2030, neither among PWID nor among PWID LWH. Engagement in HCV testing and harm reduction programs is already relatively high among PWID in Montreal, and therefore a greater coverage of these interventions had little impact on HCV prevalence, incidence, or mortality. In contrast, scaling-up DAA uptake among PWID LWH only, reduced HCV-related mortality among all PWID by over 65% –achieving the WHO mortality target. This strategy also reduced overall chronic HCV incidence substantially but failed to achieve the WHO incidence target. For this target, increasing treatment rates for all PWID was necessary. COVID-19 disruptions did not prevent these targets from being reached provided intervention-levels were rapidly restored to pre-pandemic levels. Interestingly, treatment increase had the same impact on HCV incidence when implemented among active injectors only (regardless of

HIV status). Yet, including ex-injectors in HCV treatment efforts was crucial to prevent high numbers of HCV-related deaths.

In Manuscript 3, I evaluated four post-HCV-elimination scenarios among PWID from 2030 to 2050. Scaling down all interventions to pre-2020 levels led to a slight rebound in HCV incidence, later followed by an increase in mortality. This resurgence could be avoided by maintaining high-coverage NSP and OAT. When completely interrupting HCV testing and treatment, chronic HCV incidence rebounded. The scale of this rebound was inversely proportional to the coverage of harm reduction programs. In a nutshell, these results suggest that moderate levels of testing and treatment could be sufficient to sustain HCV elimination targets among PWID if high access to NSP and OAT is ensured. Regardless of post-elimination intervention levels, HIV incidence and HIV-HCV coinfection prevalence continued to decrease after 2030. Investments targeting HCV micro-elimination among priority populations could therefore yield indirect benefits for HIV prevention.

7.2. Strengths and limitations in context

Some aspects of my approach to this thesis' aim merit special attention. First, in Manuscript 1, I used the *Engage* data sample, which was collected via RDS, as a reference for data standardisation. There is no guarantee that estimates from RDS are representative of the underlying population of interest. Nevertheless, the *Engage* study protocol and my analyses are in line with current recruitment and analysis guidelines (101, 102). Besides, RDS is one of the most robust methods to study hard-to-reach and/or hidden populations. Second, in Manuscripts 2 and 3, MSM who inject drugs were not modelled separately from other PWID. Yet, they may engage in sexualised IDU, inject specific substances such as methamphetamine, have separate injecting networks, and be less familiar with traditional harm reduction services, all factors that can affect HCV transmission (103). Missing important sources of heterogeneity in HCV risk could lead to underestimating efforts required to reach and sustain micro-elimination (74). However, robust empirical data is scarce to adequately model HCV risk heterogeneity among MSM who inject drugs in Montreal. Besides, there is little evidence to suggest that incident HCV and HIV infections

occurred among MSM who engage in sexualised IDU in recent years in Montreal (104, 105). As such, it seems unlikely that my decision to model MSM who inject drugs as an integral part of PWID would qualitatively affect the scenarios modelled. Finally, I modelled an increase in HCV treatment rate to 100 per 100 PY. This represents a tripling of rates empirically observed among HIV-HCV coinfected PWID in Montreal (42). Concerted efforts will be needed to reach this level of engagement in treatment, especially because as the number of cured PWID increases, those left to treat will likely be the ones facing the greatest barriers to care (23).

In this dissertation, I evaluated strategies that could sustainably alleviate the HCV burden among disproportionately affected groups in Montreal. I based this evaluation on targets defined by the WHO Assembly in 2016 (3). The commitment to these targets has raised awareness about the burden of viral hepatitis while generating momentum to reduce this burden in a clear timeframe. However, criticism of these targets has emerged. Choosing to measure countries' progress relatively to a 2015 baseline can penalise countries who started HCV prevention and care programs prior to 2015, countries with a young population, and countries with low HCV prevalence (15). For these latter, it may be unrealistic to expect large investments into reducing incidence and prevalence of an infection that may not be a public health priority. Members of the *Polaris Observatory* (15) have suggested revising relative targets into absolute ones, aiming for a reduction of HCV incidence and mortality rates to less than 5 per 100,000 PY by 2030. Their approach presents several advantages: baseline incidence and mortality estimates, which were unavailable for many countries/populations, are not required; absolute targets recognise past and current elimination efforts; they measure progress towards a standard definition of HCV elimination; and they may generate momentum to meet these goals even in countries with low incidence and mortality (15). Nevertheless, achieving these absolute targets may be a daunting task among priority populations with high HCV incidence and mortality. For instance, scaling-up HCV treatment to 100 per 100 PY among all PWID in Montreal (Manuscript 2) achieved the WHO relative targets. Yet, the 2030 median estimates for

HCV incidence (800 per 100,000 PY) and mortality (10 per 100,000 PY) were far above the suggested absolute targets.

Beyond the HCV elimination agenda, this thesis aimed to contribute to improve the overall health of PWID, with a specific attention to those LWH. Yet this population faces multiple drug-related harms beyond HCV and HIV. Fatal overdose is the leading cause of mortality among PWID (106). Between 2008 and 2018, one in five PWID globally experienced a non-fatal overdose episode every year (107). Since then, annual numbers of non-fatal and fatal overdoses have continued to rise in Canada, especially during the COVID-19 pandemic. Factors that can explain this rise include increases in high-risk IDU behaviours due to pandemic-induced stress, increased social isolation, and aggravation of mental health issues; a more volatile drug supply due to border and travel restrictions; and restricted access to essential services such as addiction, mental health, and harm reductions programs (108). Drug-related harms have been described as a syndemic (i.e., synergistically interacting epidemics) where health needs come into competition with other essential needs such as housing and food security (99). PWID face numerous barriers to fulfilling these needs, including stigma, a strong determinant of health behaviours that leads to poor health outcomes. As long as these barriers are not addressed, they will continue to impede HCV elimination as a public health threat (99).

7.3. Implications

First, my thesis work has implications for the surveillance of HCV and other STBBIs among PWID and MSM in Montreal. We could capitalise on a well-established STBBI surveillance network among PWID (7) to add HCV RNA tests (e.g., dried blood spot tests) to routinely performed tests. This would allow us to estimate and monitor trends in chronic HCV incidence and prevalence among PWID. I initiated important work on HCV seroprevalence among MSM. With the continuation of the *Engage* cohort, this work can be extended and we can fill knowledge gaps on chronic HCV incidence, prevalence, and routes of transmission among MSM. Indeed, HCV RNA tests are conducted at each study visit, and comprehensive information is collected on drug-use and sexual behaviours that

could be associated with HCV acquisition and transmission (9). This wealth of surveillance data for PWID and MSM should be regularly analysed to inform effective policies, monitor progress towards HCV micro-elimination goals, and alert on potential rebounds post-elimination (5). In that respect, the COVID-19 pandemic has interfered with STBBI surveillance and research. Data collection and analysis should resume for us to assess the impact of this pandemic on key HCV epidemiological indicators.

Second, my doctoral research has implications for HCV care delivered to PWID and MSM in Montreal. DAA uptake should be scaled-up among all people with a history of IDU. This may be challenging, first because scarce public health resources have been diverted to the COVID-19 pandemic response, and second due to the ongoing overdose crisis in Canada (95). The multi-faceted, interrelated health and social challenges affecting PWID call for an integrated response. Empirical evidence from various settings suggests that HCV treatment should be offered as part of interventions that are less "disease-focused" and more "person-centric" (99). These include interventions enhancing patient engagement with care, such as patient navigation programs involving peers, patient reminders for appointments, and patient education (109). Also promising are interventions improving provider engagement, such as medical chart reminders, provider education, and provider care coordination (109). MSM who engage in sexualised IDU may benefit from services that address drug-use-related and sex-related risks conjointly. Recommendations for such programs include starting a discussion within the MSM community, providing culturally informed and context-specific counselling and support, talking to MSM who engage in sexualised drug use about consent, and choosing sex-positive approaches to harm reduction (110). Strategies should also be developed for diagnosing and treating people who have ceased to inject. Because these people may no longer be in contact with drug-related services, campaigns targeting the general population may be warranted (5).

Simulations of increased DAA uptake among PWID LWH were promising, hence my thesis' results are being used to design pilot interventions to increase DAA uptake among CCC participants. The effectiveness and reach of these interventions will be measured and will determine their potential roll-out. This empirical evidence will also be fed back to my

mathematical model to continue improving our understanding of potential levers of action for the micro-elimination of HCV among PWID and MSM in Canada.

7.4. Conclusions

In Canada, PWID, MSM, and PLWH are priority populations for the elimination of HCV as a public health threat by 2030. This dissertation focused on HCV micro-elimination among these groups in the city of Montreal. I showed that previous exposure to HCV is common among MSM in Montreal, and associated with a history of IDU and HIV infection. I also demonstrated that wide uptake of DAA treatment is the key to HCV micro-elimination among all people who a history of IDU in this city. Finally, I demonstrated that post-elimination HCV resurgence could be avoided by maintaining modest levels of HCV testing and treatment, and high-coverage harm reduction programs.

The COVID-19 pandemic has further exposed PWID to drug-related harms, including hepatitis C infection and its consequences. As a society, we have a responsibility to restore access to essential social and health services for this population. We will not eliminate HCV globally without addressing the health needs of PWID. In Montreal, HCV micro-elimination is within reach, achievable, and sustainable.

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Appendix: Doctoral training publication list

1. Mathieu Maheu-Giroux, Kimberly Marsh, Carla M Doyle, Arnaud Godin, Charlotte Lanièce Delaunay, Leigh F Johnson, Andreas Jahn, Kouamé Abo, Francisco Mbofana, Marie-Claude Boily, David L Buckeridge, Catherine A Hankins, Jeffrey W Eaton. National HIV testing and diagnosis coverage in sub-Saharan Africa: a new modeling tool for estimating the 'first 90' from program and survey data. *AIDS*. 2019; 33:S255-S269.

2. Charlotte Lanièce Delaunay, Joseph Cox, Marina B Klein, Gilles Lambert, Daniel Grace, Nathan J Lachowsky, Mathieu Maheu-Giroux. Trends in hepatitis C virus seroprevalence and associated risk factors among men who have sex with men in Montreal: results from three cross-sectional studies (2005, 2009, 2018). *Sexually Transmitted Infections*. 2020; 97:209-296.

3. Charlotte Lanièce Delaunay, Sahar Saeed, Quoc Nguyen. Evaluation of testing frequency and sampling for Severe Acute Respiratory Syndrome Coronavirus 2 surveillance strategies in long-term care facilities. *Journal of the American Medical Directors Association*. 2020; 21(11):1574-1576.

4. Charlotte Lanièce Delaunay, Zoë R Greenwald, Nanor Minoyan, Andreea Adelina Artenie, Dahn Jeong, Gayatri Marathe, Yasmin A Saeed, Gillian Kolla, Rasika D Kunden, Chisom Ifeoma Adaeze Okwor, Hannah L Wallace, Andrew Mendlowitz, Ching-Hsuan Liu, Sabrina Mazouz, Simmone D'souza, Catia Taniela Perciani, Marylin Rheault, Michael A Palmer, Adam Palayew, Mohamed N Abdelnabi, Evan B Cunningham on behalf of the 2020-2021 trainees of the *Canadian Network on Hepatitis C*. Striving towards hepatitis C elimination in the era of COVID-19. *Canadian Liver Journal*. 2020; 4(1):4-7.

5. Charlotte Lanièce Delaunay, Arnaud Godin, Nadine Kronfli, Dimitra Panagiotoglou, Joseph Cox, Michel Alary, Marina B Klein, Mathieu Maheu-Giroux. Can Hepatitis C elimination targets be sustained among people who inject drugs post-2030? *International Journal of Drug Policy*. 2021; 96:103343.

6. Charlotte Lanièce Delaunay, Mathieu Maheu-Giroux, Gayatri Marathe, Sahar Saeed, Valérie Martel-Laferrière, Curtis L Cooper, Sharon Walmsley, Joseph Cox, Alexander Wong, Marina B Klein, Canadian Co-infection Cohort. Gaps in hepatitis C virus prevention and care for HIV-hepatitis C virus co-infected people who inject drugs in Canada. *International Journal of Drug Policy.* 2022; 103:103627.

7. Gayatri Marathe, Erica E M Moodie, Marie-Josée Brouillette, Joseph Cox, Charlotte Lanièce Delaunay, Curtis L Cooper, Mark Hull, John Gill, Sharon Walmsley, Neora Pick, Marina B Klein, Canadian Co-infection Cohort. Depressive symptoms are no longer a barrier to HCV treatment initiation in the HIV-HCV coinfected population in Canada. *Antiviral Therapy*. 2022; 27(1):13596535211067610.

8. Gayatri Marathe, Erica E M Moodie, Marie-Josée Brouillette, Charlotte Lanièce Delaunay, Joseph Cox, Valérie Martel-Laferrière, John Gill, Curtis L Cooper, Neora Pick, Marie-Louise Vachon, Sharon Walmsley, Marina B Klein, Canadian Co-infection Cohort. Impact of HCV cure on depressive symptoms in the HIV-HCV co-infected population in Canada. *Clinical Infectious Diseases*. 2022; ciac540.

9. Carla M Doyle, Joseph Cox, Rachael Milwid, Raphaël Bitera, Charlotte Lanièce Delaunay, Michel Alary, Gilles Lambert, Cécile Tremblay, Sharmistha Mishra, Mathieu Maheu-Giroux. Measuring progress towards reaching zero new HIV infections among key populations in Quebec (Canada) using routine surveillance data: a mathematical modeling study. *Manuscript accepted for publication in the Journal of the International AIDS Society*.

10. Gayatri Marathe, Erica E M Moodie, Marie-Josée Brouillette, Joseph Cox, Curtis L Cooper, Charlotte Lanièce Delaunay, Brian Conway, Mark Hull, Valérie Martel-Laferrière, Marie-Louise Vachon, Sharon Walmsley, Alexander Wong, Marina B Klein, Canadian Co-infection Cohort. Predicting the presence of depressive symptoms in the HIV-HCV co-infected population in Canada using supervised machine learning. *Manuscript accepted for publication in BMC Medical Research Methodology*.

11. Gayatri Marathe, Erica E M Moodie, Marie-Josée Brouillette, Charlotte Lanièce Delaunay, Curtis L Cooper, Mark Hull, Valérie Martel-Laferrière, Sharon Walmsley, Joseph Cox, Marina B Klein, Canadian Co-infection Cohort. Effect of depressive symptoms on health services utilization in the HIV and hepatitis C co-infected population in Canada. *Manuscript submitted for publication*.

12. Charlotte Lanièce Delaunay, Marina B Klein, Arnaud Godin, Joseph Cox, Nadine Kronfli, Carla M Doyle, Bertrand Lebouché, Mathieu Maheu-Giroux. Public health interventions, priority populations, and the impact of COVID-19 disruptions on hepatitis C micro-elimination among people who inject drugs in Montreal (Canada): a modeling study. *Manuscript submitted for publication.*