The Hepatitis C Treatment Revolution:
Are Key HIV-Hepatitis C Co-Infected Populations Being Left Behind?

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ABSTRACT

Deaths due to viral hepatitis will soon surpass HIV, tuberculosis and malaria worldwide. The emergence of direct-acting antivirals (DAAs), for the treatment of hepatitis C virus (HCV) marked one of the most significant advances in modern therapeutics. Unlike previous generations of therapies, DAAs are well-tolerated and cure >90% of chronically infected individuals. Given the advent of DAAs and the significant clinical and economic cost of doing nothing, the World Health Organization (WHO) has defined targets to scale up screening, access to treatment and harm reduction in order to eliminate HCV as a public health threat by 2030. Nonetheless increasing HCV treatment initiation rates, particularly among marginalized populations, remains a significant public health challenge.

The overall goals of this dissertation were to evaluate access to DAA treatments and treatment outcomes among people co-infected with HIV and HCV in Canada. To this end, I used data from the Canadian HIV-HCV Co-Infection Cohort (CCC), one of the largest prospective cohorts in the world. Since 2003, adults living with HIV with evidence of HCV infection (antibody positive) have been eligible to participate. Data on socio-demographic, behavioural, and clinical characteristics are collected bi-annually. As of 2018, 1917 participants had been recruited, an estimated 23% of the total co-infected population in care in Canada including active people who inject drugs (PWID), women, people of Indigenous ethnicity and men who have sex with men (MSM).

The first objective of this thesis was to examine the generalizability of the clinical trials used to license DAAs. Here we found only a minority of CCC participants (6-43%) would have been eligible for enrolment into these trials. The most restrictive eligibility criteria across all trials were concomitant HIV antiretroviral therapies and evidence of illicit drug use. The majority of the exclusions appeared to be related to improving treatment outcomes by not including those at higher risk of poor adherence. The results from this study highlighted the need to evaluate the real-world impact of DAAs on access to treatment and health outcomes.

I then evaluated DAA treatment uptake by key populations and their subsequent treatment response in a real-world setting as the second objective of this thesis. Treatment rates increased significantly from 8 initiations per 100-person years before the DAA era to 28 per 100-person years, after the introduction of DAAs starting in 2013. I used multivariate Cox proportional hazards models to estimate the rate of HCV treatment initiation among key populations (PWID, MSM, Indigenous populations and women). After adjustment, PWID and more generally people with lower income (<$18,000 CAD/year) were less likely to initiate treatment. Reflective of reimbursement restrictions, people with significant liver fibrosis were more likely to initiate treatment. Treatment response rates were high (>82%) across the key populations.

As the price of DAAs were reduced and reimbursement restrictions were broadened, the third objective of this thesis was to evaluate the impact of removing fibrosis stage restrictions on HCV treatment initiation. This was done by leveraging a natural experiment occurring across Canada. I applied a difference-in-differences approach using a negative binomial regression with generalized estimating equations to account for repeated outcomes to evaluate the impact of the

policy change. I then used a modified Poisson regression model to identify characteristics of people left to be treated. Removing fibrosis stage restrictions, increased treatment uptake by 1.8 times (95% CI, 1.4, 2.5) accounting for temporal trends and the time-invariant difference between provinces. Among PWID the impact appeared even stronger; adjusted incidence rate ratio (aIRR), 3.6 (95% CI 1.8, 7.4). Four years after the advent of DAAs, marginalized participants (PWID and those of Indigenous ethnicity) and those disengaged from care, remained more likely to require treatment. While removal of fibrosis restrictions increased treatment initiations, in the short term, these rates may not be sustainable. To reach elimination, an emphasis on finding innovative ways to address persistent disparities in treatment uptake among vulnerable populations is needed.

The final objective of this thesis was to investigate the real-world impact of successful DAA treatment on health-related quality of life (HR-QoL). HR-QoL was measured using the EuroQoL Group-5 Dimensional, 3-Level Version (EQ-5D-3L) instrument and a segmented multivariate linear mixed model was used to evaluate its change over time. In contrast to clinical trial results, we observed only modest improvements in HR-QoL following a sustained virologic response (SVR) with DAA therapy. The results from this study demonstrate curing HCV may only have temporary effects on health-related quality of life.

In addition to these substantive objectives, this dissertation also contributes to the advancement of epidemiological methods by including two published tutorials detailing the methods used to answer the research questions for the third and fourth objectives, the difference-in-differences approach and segmented mixed effect models, respectively.

This is an unprecedented time in clinical medicine. DAAs have transformed clinical practise by curing a chronic infection in the vast majority of patients in less than 12 weeks, but challenges remain. This work describes and quantifies barriers to HCV treatment uptake that can inform HCV elimination efforts currently underway worldwide.

RESUME

Les décès causés par l'hépatite virale, à travers le monde, dépasseront bientôt ceux causés par le VIH, la tuberculose et le paludisme. Le traitement de l'hépatite C a été révolutionné par les antiviraux à action directe (AAD). Contrairement aux traitements antérieurs, les AAD sont bien tolérés et permettent de guérir plus de 90% des personnes infectées. À la lumière des AAD et du coût clinique et économique de l'inaction, l'Organisation mondiale de la santé (OMS) a défini des objectifs pour renforcer le dépistage, l'accès au traitement et la réduction des risques de transmission afin d'éliminer l'hépatite C en tant que menace pour la santé publique d'ici 2030. Cependant, à ce jour, l'augmentation des taux d'initiation du traitement contre l'hépatite C, en particulier chez les populations marginalisées, reste un défi majeur pour la santé publique.

Les objectifs principaux de cette thèse étaient d'évaluer l'accès aux traitements par AAD et aux résultats de ces traitements chez les personnes co-infectées par le VIH et l'hépatite C au Canada. À cette fin, les données de la cohorte canadienne de co-infection VIH- hépatite C (CCC) ont été utilisées. Cette cohorte de personnes co-infectées est l'une des plus importantes au monde. Depuis 2003, les adultes vivant avec le VIH et présentant des signes d'infection par l'hépatite C (anticorps positifs) sont éligibles. Les données sur les caractéristiques sociodémographiques, comportementales et cliniques sont collectées deux fois par an. En 2018, 1917 participants avaient été recrutés, soit environ 23% de la population co-infectée prise en charge au Canada. La cohorte comprend des personnes qui s'injectent des drogues, des femmes, des autochtones et des hommes ayant des relations sexuelles avec d'autres hommes.

Le premier objectif de cette thèse était d'examiner la possibilité de généraliser à la population

Canadienne les résultats des essais cliniques utilisés pour obtenir l'approbation des AAD. Nous avons constaté que seulement une minorité de participants CCC (6-43% selon les essais) aurait été éligible pour participer à ces essais. Les critères d'éligibilité les plus restrictifs de ces essais étaient les traitements antirétroviraux anti-VIH concomitants et les preuves de consommation de drogues illicites. Ces critères d'exclusion pourraient avoir surévalué l'effet du traitement en excluant les patients présentant un risque d'élevé inobservance thérapeutique. Les résultats de cette étude ont mis en évidence la nécessité d'évaluer l'impact réel de l'introduction des AAD sur l'initiation d'un traitement de l'hépatite C et sur le système de la santé.

Le deuxième objectif de cette thèse était d'évaluer, dans des populations clés, le taux de traitement par les AAD et leur réponse au traitement dans un contexte réel.
Le taux de traitement a considérablement augmenté passant de 8 initiations par 100 personnes-année avant l'ère AAD à 28 initiations par 100 personnes-année, après l'introduction des AAD en 2013. Des modèles multivariés de Cox ont été utilisés pour estimer le taux de traitement par les personnes qui s'injectent des drogues, les femmes, les autochtones et les hommes ayant des rapports sexuels avec d'autres hommes. Après ajustement, les personnes qui s'injectent des drogues et plus généralement les personnes à faible revenu (<18 000 $ CAD / an) étaient moins susceptibles de commencer un traitement. Reflétant les restrictions de remboursement, les personnes atteintes d'une fibrose hépatique significative étaient plus susceptibles de commencer un traitement. Le taux de réponse au traitement était élevé (> 82%) dans toutes ces « key populations ».

Considérant, que le prix des AAD a été réduit et que les restrictions de remboursement ont été assouplies, le troisième objectif de cette thèse était d'évaluer l'impact sur l'initiation du traitement de l'hépatite C de l'élimination des restrictions de remboursement en fonction du stade de la fibrose. Cela a été fait en tirant parti d'une expérience naturelle menée dans tout le Canada. Une analyse de « Différence dans les Différences » a été utilisée avec une régression binomiale négative et des équations d'estimation généralisées pour prendre en compte les mesures répétés afin d'évaluer l'impact du changement de politique. Un modèle de régression de Poisson modifié a ensuite été utilisé pour identifier les caractéristiques des personnes non- traitées. L'élimination des restrictions d'indication thérapeutique / ou de remboursement au stade de la fibrose et l'augmentation de l'initiation du traitement de 1,8 fois (IC à 95%, 1,4, 2,5), expliquent les tendances temporelles et la différence invariante dans le temps entre les provinces. Parmi les utilisateurs de drogues injectables, l'impact était encore plus fort de 3,6 fois (IC à 95%, 1,8, 7,4). Quatre ans après l'avènement des AAD, les participants marginalisés (les personnes qui s'injectent des drogues, et les autochtones) et ceux qui étaient désengagés des soins restent plus susceptibles de ne pas avoir accès au traitement. Bien que l'élimination des restrictions liées à la fibrose ait augmenté le nombre de traitements de base amorcés, ces taux pourraient être temporaires à court terme. Pour parvenir à l'élimination, il est nécessaire de rechercher des moyens novateurs de remédier aux disparités persistantes en matière d'initiation du traitement chez les populations vulnérables.

L'objectif final de cette thèse était d'étudier l'impact réel d'un traitement par AAD sur la qualité de vie liée à la santé (HR-QoL). La qualité de vie a été mesurée à l'aide de l'instrument EQ-5D-3 (EuroQoL Group-5 Dimensional) version à 3 niveaux. Un modèle mixte multivarié linéaire

segmenté a été utilisé pour évaluer son évolution dans le temps. Contrairement aux résultats des essais cliniques, nous n'avons observé que de modestes améliorations de la HR-QoL après la réponse virologique soutenue (RVS) avec le traitement au AAD. Les résultats de cette étude démontrent que la guérison du l'hépatite C peut avoir des effets seulement temporaires sur la qualité de vie liée à la santé.

En plus de ces objectifs de fond, cette thèse contribue également à l'avancement des méthodes épidémiologiques en incluant deux tutoriels publiés détaillant les méthodes utilisées pour répondre aux questions de recherche des troisième et quatrième objectifs, l'analyse de « Différence dans les Différences » et les modèles à effets mixtes segmentés respectivement.

Nous sommes témoins d'une période sans précédent en médecine clinique. Les AAD ont transformé la pratique clinique en guérissant une infection chronique chez la grande majorité des patients en moins de 12 semaines. Toutefois, des problèmes subsistent. Ce travail décrit et quantifie les obstacles à l'utilisation du traitement du VHC qui peuvent informer et aider les efforts d'élimination du VHC dans le monde entier.

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I dedicate this thesis to Dominique Marion, my husband of eleven years (*and despite this PhD still counting*), who unknowingly partnered with me through this four-year rollercoaster and never failed to make me feel supported and loved. None of this would have been possible without you! And to our two beautiful children Sarah and Noah who were only 3 and 2 years old respectively, when I decided to stratify my time between being a mother and student. I hope my addiction to my laptop hasn't scared you from pursuing your own dreams.

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CONTRIBUTIONS OF AUTHORS

Manuscript 1: Sahar Saeed, Erin C Strumpf, Sharon Walmsley, Kathleen Rollet-Kurhajec, Neora Pick, Valerie Martel-Laferriere, Mark Hull, M. John Gill, Joseph Cox, Curtis Cooper, Marina B Klein for the Canadian Co-Infection Cohort Study. How Generalizable are the Results from Trials of Direct Antiviral Agents to People Co-infected with HIV/Hepatitis C Virus in the Real World? *Clinical Infectious Disease*. 2016 Apr; 62(7): 919-926

Manuscript 2: Sahar Saeed, Erin C Strumpf, Erica EM Moodie, Jim Young, Roy Nitulescu, Joseph Cox, Alexander Wong, Sharon Walmsely, Curtis Cooper, Marie-Lousie Vachon, Valerie Martel-Laferriere, Mark Hull, Brian Conway, Marina B Klein for the Canadian Co-Infection Cohort Study. Disparities in Direct Acting Antivirals Uptake in HIV-Hepatitis C Co-Infected Populations in Canada. *Journal of the International AIDS Society*. 2017 Nov;20(3)

Manuscript 3: Sahar Saeed, Erin Strumpf, Erica EM Moodie, Leo Wong, Joseph Cox, Sharon Walmsley, Mark Tyndall, Curtis Cooper, Brian Conway, Mark Hull, Lisa Barrett, Valerie Martel-Laferriere, John Gill, Marina B Klein for the Canadian Co-Infection Cohort Study Investigators. Eliminating a Structural Barrier: Impact of Removing Fibrosis Stage Restrictions on HCV Treatment Uptake among People Living with HIV *(Resubmitted to Clinical Infectious Disease-July 16 2019)*

Manuscript 4: Sahar Saeed, Erica EM Moodie, Erin Strumpf, John Gill, Alexander Wong, Curtis Cooper, Sharon Walmsley, Mark Hull MD, Valerie Martel-Laferriere, Marina B Klein for the Canadian Co-Infection Cohort Study Investigators. Real-World Impact of Direct Acting

Antiviral Therapy on Health-Related Quality of Life in HIV/Hepatitis C Co-Infected Individuals. *Journal of Viral Hepatitis.* 2018 Dec;25(12):1507-1514

Tutorial 1: Sahar Saeed, Erica EM Moodie, Erin C Strumpf and Marina B Klein Evaluating the Impact of Health Policies: Using a Difference-in-Differences Approach. *International Journal of Public Health*. 2019 May; 64(4):637-642

Tutorial 2: Sahar Saeed, Erica EM Moodie, Erin C Strumpf and Marina B Klein Segmented Generalized Mixed Effect Models to Evaluate Health Outcomes. *International Journal of Public Health*. 2018 May;63(4):547-555

As the first author of the six thesis manuscripts, I was responsible for conceiving the research questions, designing and executing each study. This included all data management, statistical analysis, interpreting the results and writing the manuscripts. This work was conducted with guidance from my co-authors.

In addition, I also assisted in collecting the data required for the thesis. This involved developing case report forms to collect detailed information on DAA treatment initiations and other clinical information. Once the majority of the initiations (n=544) had been collected, I created and entered the data into a new database (a database that has since been used by multiple students and members of the CCC research team).

Dr. Marina Klein (co-supervisor), Dr. Erin Strumpf (co-supervisor) and Dr. Erica Moodie (committee member) provided me guidance in: the study design, the interpretation of results and with substantive and methodological aspects of the studies. Dr. Marina Klein is an Infectious Disease Specialist, Epidemiologist and Professor in the Department of Medicine at McGill University. She is also the principal investigator of the CCC. Dr. Erin Stumpf is a Health Economist and an Associate Professor jointly appointed in the Department of Epidemiology, Biostatistics and Occupational Health and the Department of Economics at McGill University. Dr. Erica Moodie is a Biostatistician and Associate Professor in the Department of Epidemiology, Biostatistics and Occupational Health at McGill University.

Kathleen Rollet-Kurhajec, Roy Nitulescu, Leo Wong managed the CCC database at the various time the studies were conducted and assisted with verifying data. Dr. Jim Young is a biostatistician and provided input on methodology and interpretation of the results for the second manuscript.

Dr.'s Alexander Wong, Sharon Walmsely, Marie-Lousie Vachon, Mark Tyndall, Neora Pick, Valerie Martel-Laferriere, Mark Hull, M. John Gill, Joseph Cox, Curtis Cooper, Brian Conway, are coinvestigators of CCC (and site principal investigators). Co-investigators provided substantive support, recruited and followed participants of the CCC, and critically reviewed the manuscripts they are listed as coauthors.

STATEMENT OF ORIGINALITY

The work presented in this thesis constitutes original scholarship that contributes to advancing knowledge of barriers to Hepatitis C treatments and changes in health outcomes following treatment among people living with HIV and HCV, in addition to contributing to advancing epidemiological methodology.

Specifically, Manuscript 1 is the first study to evaluate the generalizability of clinical trials used to license DAA therapies. Manuscript 2 was the first study to evaluate DAA treatment uptake and subsequent treatment responses by four key populations in Canada. Manuscript 3 is the first study in the world to evaluate and quantify the impact of treatment initiation rates after the removal of fibrosis stage restrictions. Manuscript 4 is the first real world evaluation of the impact of curing HCV (known as a sustained virologic response) on health-related quality of life.

In addition to the four main chapters of this thesis, two tutorials were published to provide researchers with guidance on how to utilize the methods in Manuscripts' 3 and 4 (Chapter 4).

While I received guidance from my supervisors, committee member and co-authors on the substantive, methodological, and statistical aspects of this thesis, I declare that the conception, execution, and drafting of the work in this thesis are my own.

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ACRONYMS AND ABBREVIATIONS

3D	ombitasvir, paritaprevir/ritonavir and dasabuvir
aHR	adjusted Hazard Ratio
AIDS	Acquired Immune Deficiency Syndrome
aIRR	adjusted Incidence Rate Ratio
ALT	Alanine aminotransferase
APRI	AST to Platelet Ratio Index
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AZT	zidovudine
BC	British Columbia
BMI	Body Mass Index
BOC	Boceprevir
CAD	Canadian Dollars
CanHepC	Canadian Network for Hepatitis C Network
cART	Combination antiretroviral therapy
CCC	Canadian HIV-HCV Co-Infection Cohort
CD4+ T cells	CD4+ T lymphocytes
CI	Confidence Intervals
CIHR	Canadian Institutes of Health Research
CLDQ	Chronic Liver Disease Questionnaire
CROI	Conference on Retroviruses and Opportunistic Infections
CTN	Canadian HIV Trials Network
CVIS	Chronic Viral Infectious Service
DAAs	Direct Acting Antivirals
DHS	Demographic and Health Surveys
DiD or DD	Difference-in-Differences
EIAs	Enzyme Immunoassays
ELISA	Enzyme-Linked Immunosorbent Assay
EOT	End of Treatment
EQ-5D-3L	EuroQoL Group-5 Dimensional, 3-Level Version
ESLD	End-stage liver disease
F0-F4	Fibrosis Stage 0-4
FIB-4	Fibrosis-4 Score
FRQ-S	Fonds de recherche du Québec-Santé
GT	Genotype
HbsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Viruses

HR-QoL	Health-Related Quality of Life
IDU	Injection drug use
INR	International normalized ratio
IQR	Interquartile range
kPa	kiloPascal's
LED	Ledipasvir
MCID	Minimal clinical important difference
MOS	Medical Outcomes Study
MSM	Men who have sex with men
NIHB	First Nations and Inuit Health Branch
NNRTI	Non-nucleoside reverse-transcriptase inhibitors
NR	Non-response
NRTI	Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
NSP	Needle and syringe programs
ON	Ontario
OST	Opioid substitution therapy
pCPA	pan-Canadian Pharmaceutical Alliance
Peg-IFN	Pegylated-interferon
PI	Protease Inhibitors
PRO	Patient-reported outcomes
PWID	People who inject drugs
QC	Quebec
RBV	Ribavirin
RCT	Randomized Clinical Trials
RIBA II	Recombinant immunoblot assay
RNA	Ribonucleic acid
RR	Risk ratio
SF-36	36-Item Short Form Health Survey
SIM	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virologic response
TEL	Telaprevir
U=U	Undetectable=Untransmissible
ULN	Upper limit of normal
UNAIDS	Joint United Nations Programme on HIV and AIDS
USD	United States Dollars
VAS	Visual analogue scale
WHO	World Health Organization

CHAPTER 1: GENERAL INTRODUCTION

1.1 Introduction and Significance

Tremendous progress has been made to improve the lives of people living with HIV. In 1996, the clinical landscape of HIV was forever changed with the introduction of combination antiretroviral therapy (cART), which led to dramatic reductions of Acquired Immune Deficiency Syndrome (AIDS)-related morbidity and mortality in industrial countries with broad access to treatment [1,2]. Despite these advances, non-AIDS related mortality continues to increase. Liver disease is now one of the leading causes of death among people living with HIV, largely due to hepatitis c virus (HCV) co-infection [3,4]. Approximately 2.3 million people globally are co-infected with HIV and HCV[5]. Due to similar modes of transmission, principally people who, or previously have, injected drugs (PWID) are at the highest risk of being co-infected.

While an estimated, 20% of people infected with HCV can spontaneously clear the virus, 80% develop chronic infections. HCV predominantly affects the liver, comprising the structural integrity of hepatic cells leading to scaring known as fibrosis. This damage can accumulate over 20 years without any clinical symptoms but over time HCV infections increase the risk of cirrhosis, end-stage liver disease (ESLD)[1] and ultimately death. The natural progression of HCV is accelerated considerably among individuals co-infected with HIV-HCV compared to those HCV mono-infected [6,7]. The burden of disease is not only felt by the individual but on society in general. Given the aging population, progression to end-stage liver disease is expected to

[1] ESLD defined as a clinical event of ascites, variceal hemorrhage, hepatic encephalopathy, or renal impairment

increase by 89% by 2035. Health care costs (excluding treatments) are expected to increase by 60% from 2013 until 2032 in Canada [8]

While there are no cures for HIV, HCV can be treated and cured. Curing HCV after treatment is known as a sustained virologic response (SVR). Achieving an SVR has been shown to stop liver disease progression, thus reducing morbidity, mortality and costs over time [9-11]. To reduce the clinical and healthcare burden of advanced liver disease, HCV treatment is recommended [9-11]. But until only recently, the only option for HCV treatments were interferon-based regimens. These regimens were only marginally efficacious (20-50% of patients were cured) while the vast majority of patients endured debilitating adverse events, lasting the duration of the treatment (24-48 weeks)[10,12-14]. Given the combination of low efficacy and many side effects this created a reluctance to initiate treatment by both providers and patients.

The development of direct acting antivirals (DAAs) for the treatment of HCV has been rightfully described as revolutionary [15]. Since 2010, based on compelling clinical trial results (91-97% cure rates), multiple DAAs were approved by licensing authorities globally [16-22] [23-25]. While the improved efficacy and tolerability of DAAs helped eliminate many clinical barriers, financial barriers emerged. Most of the media attention surrounding these revolutionary treatments has been focused on their cost. When DAAs were first approved, the list price of a 12-week course of treatment was $84,000; translating to $1000/pill [26]. The costs of these medications were compared to the unit cost of diamonds, where gram for gram, DAA treatments were more expensive (Figure 1.1) [27]. While the costs have been

Figure 1.1 Medicines shouldn't be luxury (Médecins sans frontieres)

reduced, they remain expensive. Furthermore, pharmaceutical companies priced treatments as cures, but curing HCV provides no immunity for future infections. Therefore, without concurrent harm reduction strategies for people who continue to engage in behaviors exposing themselves to the HCV, reinfections may be an inevitable occurrence. As a result of the exorbitant cost of DAAs and the fears of reinfections both public and private insurers enacted policies limiting access to HCV treatments worldwide [28-30].

HCV is the first chronic viral disease that can be cured, with organizations such as the World Health Organization (WHO) expressing enthusiasm that HCV can be eventually eliminated. However, significant challenges exist. DAAs are some of the most expensive antivirals ever developed, while HCV disproportionately affects the poorest and most disenfranchised populations globally. Moreover, while clinical trials have demonstrated very high efficacy in ideal trial settings, the participants in these trials may not adequately represent target populations. Despite breakthroughs in HCV treatments, many psychosocial disadvantages still require interventions to increase treatment uptake and obtain successful and sustained clinical outcomes. This thesis addresses fundamental issues regarding the identification and quantification of barriers to DAA treatment initiation, in addition to assessing the real-world impact of treatment on individuals in Canada who are co-infected with HIV-HCV.

1.2 Research Objectives

The overall goal of this dissertation was to further understand barriers to DAA therapies and the impact of these treatments on patient-reported outcomes among people in Canada who are co-infected with HIV and HCV. More specifically, my research:

1. Examined the generalizability of DAA clinical trials in HIV-HCV co-infected individuals.
2. Described HCV treatment initiation rates among key HIV-HCV co-infected populations and identified predictors of second-generation DAA initiations in Canada.
3. Evaluated the impact of removing advance fibrosis stage restrictions for DAA treatments on HCV treatment initiation rates among HIV-HCV co-infected populations.
4. Investigated the real-world impact of successful DAA treatment on health-related quality of life.

1.3 Organization of Thesis

The format of this thesis is manuscript-based. It includes four original research manuscripts, each corresponding to a thesis objective and each presented as its own chapter. Each manuscript chapter begins with a preface explaining its rationale, the relation to the corresponding thesis objective, the research question(s) it answers, and the citation of the corresponding publication. To support the objectives of this thesis, Chapter 2 consists of a focused literature review.

Chapter 3 describes the data source used for this dissertation and provides a detailed description of the methods used in manuscripts 1 - 4. Chapter 4 provides two tutorials to describe the methodology for manuscripts 3 and 4 in greater detail.

Chapter 5 includes manuscript 1, which examined the generalizability of the clinical trials used to license DAAs among people co-infected with HIV and HCV. Chapter 6 contains manuscript 2, which evaluated DAA treatment uptake and efficacy in key HIV-HCV co-infected populations in Canada. Chapter 7 contains manuscript 3, which investigated the impact of removing significant liver fibrosis restrictions on treatment initiation rates. Chapter 8 contains manuscript 4, which evaluated the impact of successfully treating HCV infections in the DAA era on health-related quality of life.

Chapter 9 discusses the overall findings of this thesis, the implications of the work, future directions, and makes concluding remarks. All references to the articles, book chapters, and other documents cited in this work are provided in the References section at the end.

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology of HIV

The Human Immunodeficiency Virus (HIV) remains a significant global public health threat. In 2017, the World Health Organization (WHO) estimated that worldwide, 37 million people were living with HIV and 1.8 million people became newly infected[31]. The WHO and the Joint United Nations Programme on HIV and AIDS (UNAIDS) consider gay men and other men who have sex with men (MSM), sex workers, transgender people, people who inject drugs (PWID) and incarcerated people as the five key population groups that are vulnerable to HIV[31]. These key populations often face legal[32], social[33] and economic[34,35] adversities related to their lifestyle that increase susceptibility to HIV infection and reduce access and linkage to care.

Tremendous progress has been made to improve the lives of people living with HIV. In 1996, the clinical landscape of HIV was forever changed by the introduction of combination antiretroviral therapy (cART), which led to dramatic reductions of Acquired Immune Deficiency Syndrome (AIDS)-related morbidity and mortality in industrial countries[1,2]. cART suppresses HIV replication to undetectable levels, thereby controlling HIV infection and preserving the immune system (as measured by the number of CD4+ T lymphocytes (CD4+ T cells))[36,37]. Initially, clinical guidelines recommended cART only to immunocompromised patients (i.e. those with low CD4+ T cells counts). However, based on recent high-grade evidence, cART is currently recommended to be initiated immediately regardless of CD4+ T cells count [37]. As the result of broad access to cART, the number of AIDS-related deaths has continued to decline from 1.5 million to 940,000 between 2010 and 2017. Furthermore, we are in the era of "Treatment as Prevention", recently advocated by the Undetectable=Untransmissible (U=U) campaign. U=U is

based on results from large international studies concluding that HIV is not transmitted between serodiscordant partners when the partner living with HIV has an undetectable viral load[38-40]. Taken together, these findings support the individual and population-level benefits of early diagnosis and treatment. But despite the benefits of cART, liver disease has emerged as a leading cause of death among HIV-positive individuals, largely due to co-infection with Hepatitis C virus (HCV)[3,4,41].

In 2016, the Public Health Agency of Canada estimated that 63,000 Canadians were living with HIV, 14% of whom were unaware of their infection status[42]. The overall HIV incidence rate is 6.0 per 100,000 Canadians. Similar to the global epidemic, the Canadian epidemic is heterogeneous. The prevalence of HIV is concentrated in specific populations defined by transmission risk factors. MSM represent 52% (32,762 people) of all people living with HIV in Canada; PWID represent 17% (10,986 people); migrants from endemic countries represent 15% (9438 people); <1% contracted HIV by contaminated blood products, injuries, or mother to child transmission; and the remaining 15% are assumed to have contracted HIV through heterosexual sex. The diversity of the HIV epidemic in Canada also varies by region and ethnicity. While Indigenous people make up 4.9% of the total Canadian population they represent 11.3% of new infections[43]. Incident HIV infections in Indigenous populations are concentrated in Saskatchewan[44], where 76% of infections have been found to be transmitted by injection drug use.

2.2 Epidemiology of HCV

Hepatitis C is also a major global public health concern, with approximately 130-150 million prevalent cases, 3 - 4 million people newly infected each year and 400 000 deaths annually [45-47].

In 2011, it was estimated that more than 268,000 Canadians were infected with HCV, disproportionately affecting marginalized populations including PWID, incarcerated individuals, and people of Indigenous ethnicity [48,49,50,51]. In Canada, approximately 80% of incident HCV infections are due to injection drug use [52]. PWID are not a negligible proportion of the Canadian population: a 2014 national surveillance survey (I-Track) estimated that 90,000 people injected drugs; this number is likely an underestimate[53]. Indeed, in a recent study, Jacka *et al* estimate the population of PWID in Canada to be as high as 171,000 people[54].

Comprehensive harm reduction interventions for PWID have been shown to reduce HCV incidence. These include needle and syringe programs (NSP) and opioid substitution therapy (OST). A meta-analysis of 28 studies (n = 6279) found that OST was associated with a 50% reduction in HCV acquisition risk [risk ratio (RR) 0.50, 95% CI, 0.40–0.63][45]. After stratifying by region, high NSP coverage in Europe was associated with a 56% (95% CI, 20%- 76%) reduction in HCV acquisition risk [45]. The synergistic effect of combined OST/NSP was associated with a 74% (95% CI 11%- 93%) reduction in HCV acquisition risk [45].

In Canada, HCV incidence has decreased over the last 15 years largely due to broad access to harm reduction interventions in major metropolitan cities. Based on data from a 2015 national surveillance study, 10,890 HCV diagnoses (30 per 100,000 Canadians) were reported to the Public Health Agency of Canada. This number represents a 25% reduction compared to what was reported in 2005 (40 per 100,000 Canadians). One exception is a growing epidemic in Saskatchewan. In 2012, the HCV incidence rate in Saskatchewan First Nations living on-reserve was 140 per 100,000 individuals, i.e. four times the national rate[55]. The epidemiology of HCV

infection in Saskatchewan is distinguished from that in the rest of Canada in that three-quarters of new infections are among PWIDs[43,55]. This phenomenon is not unique: Australia has reported similar statistics, with incident cases of HCV among Indigenous populations increasing 38% from 2010 to 2014. In contrast, during the same time period, notification rates in Australia among non-Indigenous people decreased by 15% [56]. Limited harm reduction programs to address this growing population have been blamed for this spike in incidence[44].

2.2.1 Epidemiology of HIV-HCV co-infection

Because of shared modes of transmission, it is estimated that 2.3 million people globally are co-infected with HIV and HCV[5]. It is further estimated that 20-30% of all Canadians living with HIV are co-infected with HCV, translating to between 12,620 to 18,930 people [57]. The rate of co-infection in Canada also varies by risk factors and geographic location [48].

Currently, injection drug use (IDU) remains the main mode of HCV transmission, responsible for about 80% of infections and is an important risk factor for HIV infection, accounting for an estimated 14% of new HIV infections [42,57]. HCV incidence by IDU has declined in recent years due to harm reduction[2]. HCV infection from sexual transmission is now a growing concern among HIV-positive MSM in many European countries, Australia and the United States [58-60]. A meta-analysis published in 2015 reported that the incidence of HCV in MSM had increased from 4.2/1000 person-years in 1991 to 10.9/1000 person-years in 2010, and again to 13.4/1000 person-years in 2012[60]. A more recent meta-analysis reported the

[2] With the exception of Saskatchewan, where close to 90% of people newly infected with HIV are co-infected with HCV.

pooled incidence of HCV among MSM in high income countries at 6.3/1000 person-years (95% CI 5.0-7.5). Moreover, the overall incidence of HIV-positive MSM is estimated to be 19-fold higher compared to that of HIV negative MSM[61].

2.3 Natural history of HCV

HCV is a ribonucleic acid (RNA) virus of the Flaviviridae family with six viral genotypes (1-6). Before HCV was discovered in 1989 by a team of scientists led by Canadian virologist Dr. Michael Houghton; it was known as non-A non-B viral hepatitis[62]. Unlike Hepatitis A and B, there are no preventative vaccines available for HCV. An HCV antibody test is used to diagnosis HCV. A reactive or positive antibody test means that at some point in time, the individual was infected with HCV. Approximately 20% of people who become HCV-infected spontaneously clear the infection [63]. These "spontaneous clearers" have a positive antibody test but a negative or undetectable qualitative or quantitative test for replicating HCV RNA. For the remaining 80% who develop chronic infection, natural progression is slow, but fatal. HCV primarily attacks the liver; over many years the virus silently compromises the structure of liver cells, causing liver fibrosis and leading to increased risk of irreversible end stage liver disease and cancer[7]. This relatively slow disease progression is accelerated considerably when individuals are co-infected with HIV (Figure 2.1) [6,7,41]. This liver disease acceleration has been hypothesized to arise from toxicities due to long-term use of older HIV regimens, alcohol consumption, and compromised immune function from infection with HIV[6,7,41].

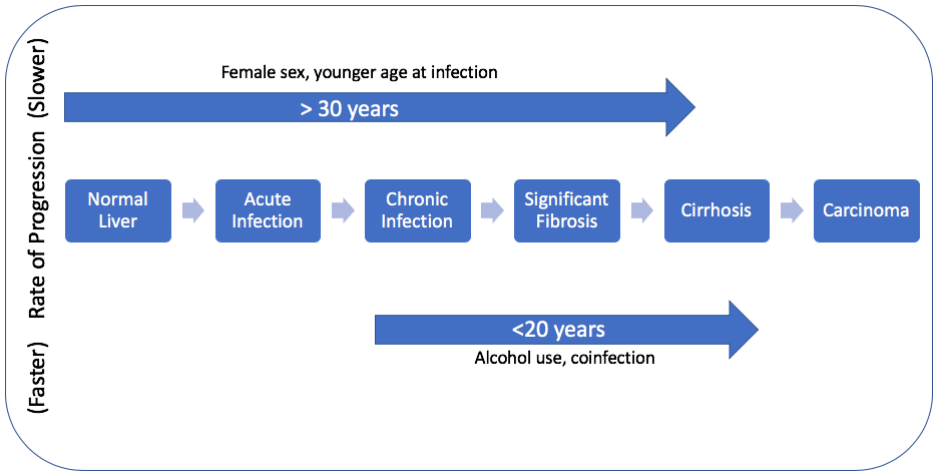


Figure 2.1 The Natural History of HCV Infection and Its Variability from Person to Person
Adapted from Lauer GM et al. NEJM, 2001 345:1

Liver fibrosis is dichotomized as mild fibrosis (Fibrosis Stage 0 to 1 (F0-F1)) and significant or advanced fibrosis (Fibrosis stage 2 (>F2)). Over time, significant fibrosis leads to cirrhosis (Fibrosis stage 4 (F4)), which results in a greater risk of end stage liver disease and hepatocellular carcinoma[41]. Once the liver is decompensated, treatment options are limited to liver transplant.

Liver fibrosis is diagnosed by invasive methods such as liver biopsy (an imperfect gold standard)[64]; non-invasive methods such as imaging (ultrasound, MRI, CT scans); and most recently by transient elastography (known as Fibroscan®), a technique used to assess liver stiffness measured. Clinical markers such as the AST to Platelet Ratio Index (APRI) and fibrosis-4 (FIB-4) have also been validated and are commonly used in clinical practice to monitor liver fibrosis[65]. APRI Score greater than 1.5 has been validated to predict significant liver fibrosis for people co-infected with HIV and HCV[66]. Fibroscan score greater than 7.2 (kiloPascal's) kPa has been validated to predict significant liver fibrosis for people co-infected with HIV and HCV[67].

2.4 The burden of HCV infection

HCV causes more years of life lost than any infectious disease in Canada[68]. This is primarily driven by progressive liver damage leading to end-stage liver disease. Currently the only cancer with increasing mortality rates in Canada is hepatocellular carcinoma (liver cancer). Which is predominately attributable to untreated chronic HCV infection[69]. Modelling studies have shown that without interventions by 2035, rates of HCV-related liver failure and liver cancer are expected to increase by 89% and 205%, respectively[8]**.** Extrahepatic manifestations of HCV are also a major concern. HCV is associated with increased prevalence of type 2 diabetes, heart disease, cryoglobulinemia, chronic kidney disease, B-cell lymphoma, lichen planus, Sjögren's syndrome, porphyria cutanea tarda, and rheumatoid-like arthritis [70,71]. Psychiatric diagnoses such as depression are also widespread among people living with HCV infections. A third of patients with HCV are depressed, a prevalence 1.5 to 4.0 times higher than people with chronic hepatitis B virus infection or the general population[72]. Finally, as liver disease progresses, quality of life is also impacted[73]. However, it is difficult to disentangle the causal relationship between HCV infection and extra-hepatic conditions especially in the presence of other co-morbidities such as alcohol, illicit drug use and more generally low socioeconomic status.

The burden of disease is borne by the infected individual and also by society at large. For instance, the lifetime cost of a single HCV infection (excluding the cost of treatment) in Canada is estimated between $52,000 to $320,000 (if a liver transplant is required)[8]. The health care costs associated with HCV–mostly due to cirrhosis and its complications, are to increase 60% in the coming years, from $161.4 million in 2013 to $258.4 million in 2032 [8]. Similarly, in the United States where an estimated 2.4 million people are living with HCV; HCV infection is associated with substantial health care utilization[74], with an estimated direct cost of $6.5 billion

USD annually[75,76]. And these costs may well be an underestimation as they do not include extra-hepatic manifestations of HCV and indirect costs of productivity[75].

2.5 HCV Treatment Evolution

Unlike HIV, treatments that cure HCV exist. A virologic cure following treatment is defined as a sustained virologic response (SVR). The clinical definition of SVR is an undetectable HCV RNA result (either by an RNA quantitative or qualitative test), 12 weeks following the termination of HCV treatment. Unsuccessful treatment response is defined as a non-response. Non-response can occur if: 1) HCV RNA replication does not cease after treatment (known as a null response); and 2) if after cessation of treatment the virus rebounds (known as relapse). As HCV treatment does not provide immunity against future infection, regardless of cure status, reinfections remain a possibility.

2.5.1 The Interferon Era (2002-2010)

Until recently, pegylated-interferon in combination with ribavirin (Peg-IFN/RBV) was the standard of care. Although IFN's exact mechanism of action against HCV remains unknown, it is thought to induce a non-specific antiviral response[77]. Studies using cell culture and animal models have shown that infection with HCV blocks IFN-α induction, impairing the host's innate immune response[77]. Ribavirin is a nucleoside inhibitor that disrupts viral RNA metabolism required for replication, thereby stopping RNA synthesis and viral mRNA capping [78].

The non-specific nature of IFN/RBV made this treatment suboptimal. Overall, studies found that only 20-50% of HCV infected individuals responded favorably to treatment[10,13,14]. Treatment success depended in part on (1) patient-related characteristics, including liver disease severity, age, sex, host genetics and other co-morbidities (co-infection with HIV, insulin resistance); and

(2) viral characteristics, primarily HCV genotype. This regimen consisted of weekly injections of pegylated interferon alfa-2a or pegylated interferon alfa2b in combination with daily oral ribavirin. Typical duration of therapy was 48 weeks for patients with HCV genotypes 1 and 4, or 24 weeks for genotypes 2 and 3. Since people co-infected with HIV responded slower, 48 weeks of treatment was recommended regardless of genotype[79]. "Difficult-to-treat" patient populations, included people of African descent, individuals with advanced fibrosis or cirrhosis, and people with HIV-HCV coinfection because of their lower likelihood of achieving SVR[80].

In addition to the intensive treatment schedule, Interferon-based regimens caused many side effects[79]. These consisted of flu-like symptoms including: fever, fatigue, malaise, headache, loss of appetite, muscle and joint aches, and depression. Of particular concern to people co-infected with HIV these treatments could also cause neutropenia (low white blood cell count), which increased the risk of bacterial infections. Ribavirin caused hemolytic anemia (low red blood cell count or low hemoglobin level)[79]. Because of the intolerability to these treatments, it was common to reduce their drug doses. And up to 40% of people discontinued therapy prematurely due to adverse events[81]. To manage side effects, many patients would take additional medications, including antidepressants, erythropoietin for anemia, and granulocyte colony-stimulating factor for neutropenia. It was also found that certain side effects were more frequent or more severe among HIV-HCV co-infected individuals compared to people with HCV alone. Drug-drug interactions between (Peg-IFN and ribavirin) and certain cART regimens were known to produce toxicities. For example, anemia was common side effect of zidovudine (AZT). Ribavirin contributed to mitochondrial toxicity, and therefore was not recommended for people taking didanosine or stavudine.

Due to the slow progression of HCV infection, poor response rates and high toxicity, during the interferon era it was not deemed urgent to start treatment immediately unless advanced liver disease was present. As such, HCV treatments were prioritized for patients at greatest risk of poor health outcomes in the short term. Co-morbid clinical, social and behavioral factors (e.g. mental instability, illicit drug/alcohol abuse, food/shelter insecurities), created reluctance to initiate treatment by both providers [82] and patients [83]. Thus, during the interferon era, treatment rates among co-infected patients were very low (<10% ever treated), particularly among PWIDs[84-86].

2.5.2 The Direct Acting Antiviral Era (2011-current)

Beginning in 2011, HCV therapy rapidly evolved. Regimens were transformed with the advent of DAAs. Unlike previous therapies, these medications directly targeted the enzymes that were necessary for the virus to replicate. Because of their targeted effects, the efficacy of the treatments improved considerably. Figure 2.2 summarizes the HCV treatment evolution from interferon-based regimens with low efficacy and low tolerability, until a fictional all-oral regimen coined "perfectovir" that would ideally have

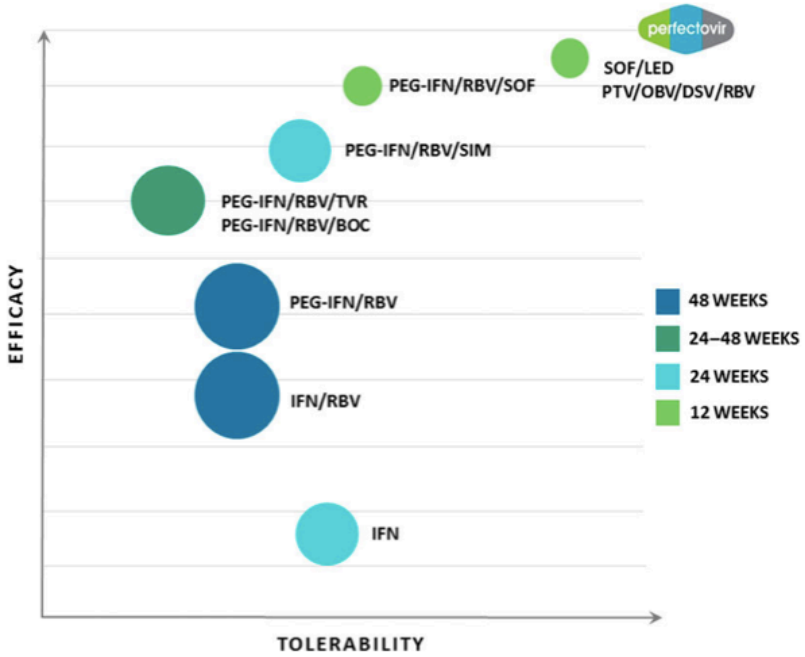


Figure 2.2 HCV Treatment Evolution
(Dore GJ, Feld JJ. Hepatitis C Virus Therapeutic Development: In Pursuit of "Perfectovir". *Clinical Infectious Diseases.* 2015;60(12):1829-1836)

perfect efficacy across all genotypes, well tolerated and be short in duration (<12 weeks of treatment)[87].

First-generation DAAs included boceprevir (BOC) and telaprevir (TVR). These drugs inhibit the activity of HCV *NS3/4A protease* (essential enzyme for HCV replication). In May 2011, Health Canada approved TEL and BOC in combination with Peg-IFN/RBV for people with genotype 1 HCV infections. These agents significantly improved response rates in co-infected patients from 20-50% to 63-74% [88,89]. However, these drugs still needed to be co-administered with Peg-IFN/RBV. This meant in addition to the side effects associated with interferon-based regimens, these DAAs had additional side effects including dermatological symptoms. Furthermore, patients were required to take an additional two pills daily with food; and treatments still lasted 48 weeks; therefore, tolerability worsened.

In late 2013, second-generation DAAs simeprevir (SIM) (*NS3/4A inhibitor*) and sofosbuvir (SOF) (*nucleotide analog inhibitor of NS5B, the RNA polymerase*) were approved in Canada. Clinical trial results showed even higher efficacy, fewer side effects, fewer drug interactions with HIV medications, and a reduced pill burden [90,91]. This eventually resulted in the voluntarily removal of BOC and TEL from the market. Although the combination of SIM and SOF was better tolerated than first generation DAAs, they still required co-administration of Peg-IFN/RBV and therefore had many of the same drawbacks as their predecessors. In late 2014, a "game-changing" treatment was marketed, consisting of ledipasvir (LED) (*NS5A inhibitor*) co-formulated with sofosbuvir in a single tablet administered once per day. Ledipasvir/sofosbuvir was approved after clinical trial results showed >95% cure rates [24] without Peg-IFN/RBV and

with only 12 weeks of treatment. This marked the first approval of a highly efficacious, well-tolerated, all-oral treatment. In addition, from what was known in the HIV literature, combining multiple antivirals, reduced the possibility of viral resistance. Furthermore, there were very few drug-drug interactions between ledipasvir/sofosbuvir and HIV medication (exception was tenofovir, where limited data is available) nor with psychiatric medications or OST which made this DAA suitable for a population of co-infected individuals[67].

Since the approval of ledipasvir/sofosbuvir, many other IFN-free combination regimens have been approved, including daclatasvir/sofosbuvir; ombitasvir/paritaprevir/ritonavir/dasabuvir; elbasvir/grazoprevir, and sofosbuvir/velpatasvir. While "perfectovir" was dreamt of in 2015, only four years later the fantasy has turned into a reality with drugs like glecaprevir/pibrentasvir/sofosbuvir being approved by health authorities around the world. The newest DAAs approved are now effective for treating multiple genotypes of HCV (pan-genotypic), well tolerated, highly efficacious and only involve 8-12 weeks of treatment. While efficacy has been maximized for patients without cirrhosis, pharmaceutical companies continue to try to make treatments shorter and many trials are underway to cure HCV in as little as 4-6 weeks[92].

A recent meta-analysis showed similar overall efficacy of DAAs between mono-infected and co-infected individuals, with SVR >93%[93]. Moreover, many studies have confirmed that co-infected individuals should no longer be considered "hard to treat"[94]. However, these high SVR rates are based on clinical trials results. Specifically, for co-infected people DAA trials included relatively small numbers of participants (sub-groups ranging from 6-160 people) and very strict eligibility

criteria were applied. Real world data on the effectiveness of DAAs in HCV mono-infected populations have been on average 5-15% lower than what was reported in phase 3 trials [95,96]. It is unclear what proportion of these lower SVR rates are explained by patients not adhering to their medications or being lost to follow-up as opposed to poorer efficacy. Fundamentally, trial participants are different, they include highly motivated people who may receive compensation, extensive support from trial staff, including for adherence. Such extensive programs may not be feasible in most real-world healthcare settings.

2.6 Benefits of curing HCV

When SVR is achieved it has been associated with reductions in liver disease progression, thus reducing mortality, morbidity and long-term costs [9-11,97]. A meta-analysis including 31 studies of 33,360 participants found achieving an SVR reduced mortality by 50% (adjusted hazard ratio (aHR) 0.50 (95% CI, 0.37, 0.67) in a general population. Among people with advanced liver disease (those with cirrhosis) and people co-infected with HIV, results were even more beneficial, reducing all-cause mortality by 73% (aHR 0.26 (95% CI, 0.18, 0.74) and 79% (aHR 0.21 (95% CI, 0.10, 0.45) respectively[98]. Results from 1600 participants of the Spanish GESIDA HCV-HIV co-infection cohort found people who achieved SVR compared to non-responders during the IFN era, were associated with a seven-fold reduction in all-cause mortality rates (2.6 vs. 18.2 per 1,000 person-years) and a nine-fold reduction in incident ESLD rates (3.2 vs. 28.7 per 1,000 person-years), over a median of five years of follow-up[99]. Similar results were observed in the large collaborative European COHERE HIV cohort study (n = 2,670), which reported that failure to achieve SVR was associated with a 53% greater risk of mortality (aHR 1.53, 95% CI, 1.06, 2.22) and a more than three-fold greater risk of liver-related death (aHR 3.39, 95% CI, 1.32, 8.75), relative to those who achieved SVR. Non-responders compared to

responders also had increased risk of: AIDS-defining conditions [0.84 per 100 person years (95% CI, 0.59-1.10) vs. 0.29 per 100 person years (95% CI, 0.10-0.48)]; non-liver-related deaths [0.65 per 100 person years (95% CI, 0.42-0.87) vs. 0.16 per 100 person years (95% CI, 0.02-.30)], and non-liver-related, non-AIDS-related deaths [0.55 (95% CI, 0.34-0.75) vs. 0.16 (95% CI, 0.02-0.30)][100].

Similar to the "treatment as prevention" approach to reduce the incidence of HIV infections, there is evidence to support that as more HCV-infected individuals are treated, this will also decrease incidence over time. This is particularly important among people who continue to engage in activities placing them at high risk of HCV transmission and reinfection, specifically active PWID. Modeling studies have suggested treating active PWID to be cost-effective[101]. One study estimated that in Vancouver, a city where the prevalence of HCV among PWID is high (65%), two new cases of HCV could be averted for every case treated if treatments are scaled up significantly, to 98 treatments per 1,000 PWID annually. This could reduce prevalence of HCV by 75% within 15 years[102]. Most recently, an empirical study from the Netherlands found evidence to support modelling studies– that treatment can reduce incidence[103]. In a setting with rapid DAA treatment uptake, Boerekamps et al., found the incidence of acute HCV infection decreased from 93 infections during 8290 person-years in 2014 (rate 11.2/1000 person-years; 95% CI, 9.1-13.7) to 49 during 8961 person-years in 2016 (rate 5.5/1000 person-years; 95% CI, 4.1-7.2) among HIV positive MSM. This resulted in a 51% reduction in incidence (incidence rate ratio (IRR), 0.49 (95% CI, 0.35-0.69)) 2016 compared with 2014)[103].

In addition to SVR being associated with improvements in mortality, decreased liver related complication and reduction in transmission, patient-reported outcomes (PROs) are also of great

interest. PROs are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response" [104]. They include multidimensional constructs, such as Health-Related Quality of Life (HR-QoL), that assess the well-being (including physical, emotional, and social functioning) of individuals. HR-QoL has gained worldwide recognition as a patient-centered outcome of healthcare interventions and has become an increasingly important metric for examining the relationship between treatment cost and value [104].

During the Interferon-era, significant improvements in HR-QoL were observed following SVR[105]. Currently the only studies that have assessed improvements in PRO in the DAA era are from the clinical trial that were designed to evaluate efficacy. Trial results demonstrated significant improvements for people mono-infected with HCV[106-124]. For example, the ION-4 trial which evaluated the efficacy of sofosbuvir/ledipasvir found general health, as measured using the 36-Item Short Form Health Survey (SF-36) survey, improved by 5%, from baseline to 4 weeks post treatment [124]. The same investigators evaluated the sofosbuvir/velpatasvir regimen from the ASTRAL-5 clinical trial and found that SVR was associated with significant improvements in 19/26 PRO domains, resulting in improvements ranging from 3.2% to 13.3% [122]. However, it remains unknown if similar benefits will be observed in real-world settings.

While SVR has been associated with substantial health benefits, second generation DAAs were first approved for market with a shocking price tag (between $84,000 and $150,000 per treatment). Multiple modeling studies justified the costs of DAAs by demonstrating these drugs were not only cost-effective at either willingness-to-treat threshold of $50,000 or $100,000 per quality-adjusted life year (QALY) but were also cost-saving[125]. Based on a meta-analysis of 31

cost-effectiveness analyses, the median threshold prices at which second-generation DAAs became cost-effective was estimated at $227,200 (interquartile range, $142,800–$355,800). Authors concluded that at a discounted price of $60,000, 71% of the analyses would find second-generation DAAs to be cost-saving[126]. While the price of DAAs have decreased over time, these drugs remain expensive. Given the considerable proportion of the population that is in need of these treatments, the expenditure required to treat all affected remains substantial.

2.7 Global Health Sector Strategy on Viral Hepatitis

In light of the tremendous health and societal benefits of curing HCV and the availability of DAAs to do so, the WHO adopted the Global Health Sector Strategy on Viral Hepatitis in 2016[127]. The strategy defines targets for eliminating HCV as a public health threat by 2030. These targets included identifying 90% of existing infections, increasing harm reduction, and treating 80% of people with HCV. By meeting these targets, HCV incidence would decline by 90% and HCV related-mortality by 65%[47,127]. Based on the Polaris Observatory, as of 2018, 12 countries were on track to achieve these targets: Iceland, Egypt, France, Japan, Netherlands, Georgia, Australia, Italy, Spain, Switzerland, the United Kingdom and Mongolia[128]. Each of these countries continues to treat at least 7% of their infected population each year, and have unrestricted access to DAAs[129]. Canada is one of the 194 countries who has agreed to the WHO targets; however, a systematic plan to meet these goals is not yet in place.

Given the scale of identifying and treating very large numbers of people chronically infected with HCV, a pragmatic approach is to focus on elimination targets for "micro"-populations[130]. This approach has worked successfully with other infectious diseases such as polio (with micro-

populations based on geographic regions) and HIV (with micro-populations based on specific transmission risks, such as mother-to-child transmission). Micro-populations that have been identified as targets for elimination of HCV are patients with advanced liver disease, patients with hemophilia, patients who are co-infected with HIV, incarcerated individuals, children, migrant communities, PWID, MSM, generational cohorts and geographically defined areas[130].

2.8 Continuum of care

A continuum of care (also known as a cascade of care) is a concept that guides and tracks patients over time through a comprehensive array of health services. Originally used to describe the identification and linkage to care for people living with HIV[131,132], this concept has now been expanded to include other chronic and infectious diseases. The HCV care continuum tracks the steps required from diagnosis with HCV to successful treatment, using a denominator-numerator linkage within each step. The first step in the continuum is identify or estimate the number of people with HCV infection; the second step quantifies the number of individuals diagnosed with HCV infection (i.e. testing antibody-positive); (3) the number of individuals with chronic HCV infection (i.e. testing RNA-positive); (4) the number of individuals who have been linked to the appropriate treatment provider (i.e. evidence by having had an HCV genotype test performed, liver fibrosis staged); (5) the number of individuals who have initiated treatment; and (6) the number of individuals who have been successfully treated (cured). Figure 2.3 is an example of the HCV care continuum for the province of British Columbia in 2012[133].

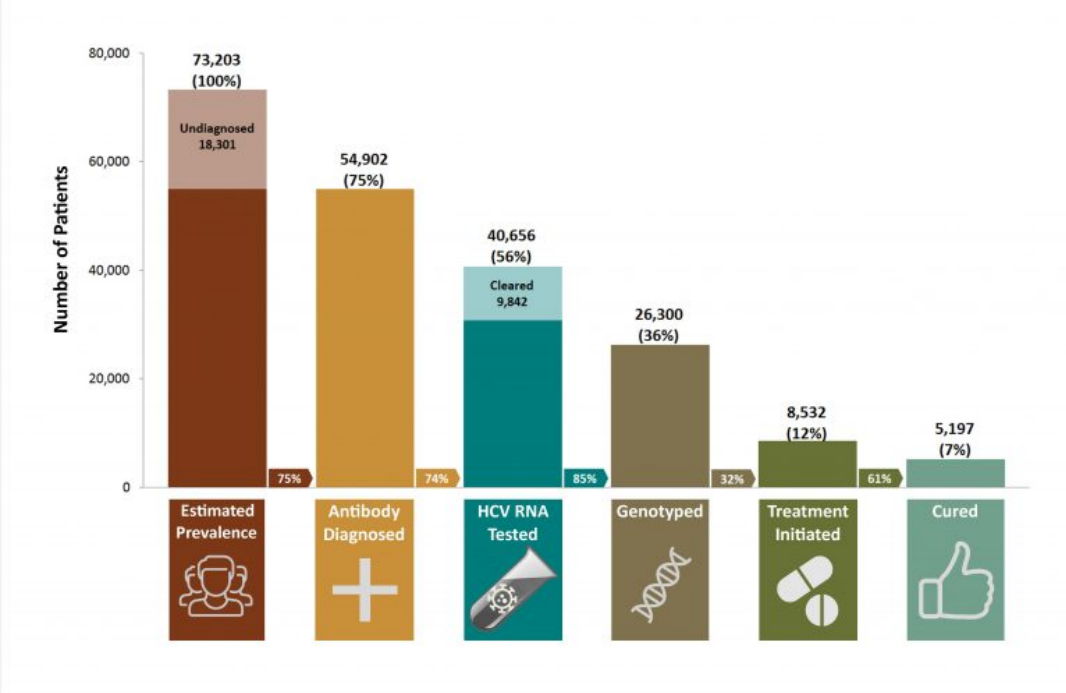


Figure 2.3 The Population Level Cascade of Care for Hepatitis C in British Columbia, Canada (Janjua NZ, Kuo M, Yu A, et al. The Population Level Cascade of Care for Hepatitis C in British Columbia, Canada: The BC Hepatitis Testers Cohort (BC-HTC). *EBioMedicine.* 2016;12:189-195)

Overall, the HCV care continuum among HCV mono-infected individuals has highlighted the need for better identification of HCV-infected individuals (diagnosis and linkage to care) to ultimately cure HCV[133-135]. In contrast, HIV-HCV co-infected populations (in high income countries), are generally already well identified since >80% have already engaged in HIV care[136]. More recently, a prospective study evaluating the HCV cascade of care among PWIDs in Vancouver, Canada, found 80% of PWID had been linked to care and undergone the workup necessary to initiate treatment[137]. Despite the vast majority of PWID linked to care, only a fraction (10%) had started treatment[137]. These results were consistent with other HCV cascades of care in Canada, the United States, and Australia showing low rates of treatment initiation, particularly among PWID[85,133,138-143].

2.9 Barriers to accessing HCV treatment

Barriers to accessing HCV treatment emerge at each step of the HCV care continuum[135] and are frequently categorized at the patient-, provider- or system-level[83]. Although the improved efficacy and tolerability of DAAs have enabled many clinical barriers to treatment initiation to be overcome, financial barriers have now emerged[87].

2.9.1 Patient-Level

Globally, lower socioeconomic status, substance abuse and mental illness have all been associated with barriers to accessing healthcare[82,83,85, 144,145]. Individual-level factors identified as reasons why HCV treatment is deferred include: limited awareness, economic pressures, treatment fears, psychiatric disease, and injection drug use[80]. Among PWID living with HIV and HCV, a review found the following social factors: stigma, housing, criminalization, past experiences with health care systems/providers, and gender were all associated with poor treatment access[146]. Key facilitating factors to treatment access included: combination intervention approaches encompassing social as well as biomedical interventions, low threshold access to OST, and integrated delivery of multidisciplinary care[146]. Despite the clinical improvements associated with DAAs, similar barriers to treatment access continue to be identified among PWID. Key opinion leaders have suggested reforms to include: decriminalization of drug use, possession of drugs and drug injecting equipment; removal of exclusionary criteria to access treatment; improve communication and education to strengthen links between health providers and increase participation of PWID in treatment implementation protocols[147]. Generally, women are considered a vulnerable population and face unique barriers to linkage to care and treatment access. Women who inject drugs face additional potential

barriers to accessing healthcare and treatment, including ongoing sex work, higher rates of mental health issues, and lower access to harm-reduction programs [148].

2.9.2 Provider-Level

PWID face stigmatization and discrimination from health professionals, which in turn leads to poor access to healthcare[149]. During the interferon era, provider-level barriers included preconceived fears of poor adherence and risk of reinfection [80, 42,82,150,151]. A study of the Canadian HIV-HCV Co-Infection Cohort reported that the most important criteria reported by providers for determining eligibility for HCV treatment during the interferon era were fibrosis stage, psychiatric comorbidities, alcohol intake, past HCV treatment and if the patient had a history of reinfection with HCV[82]. Wide variation in treatment uptake was observed by centres, and providers expressed diverse opinions about the importance of treatment eligibility criteria, suggesting that provider-related barriers are equally as important as patient-related barriers[82]. Yet, in a more recent survey of infectious disease specialists in Canada, all prescribers and 79% of non-prescribers agreed that PWID should be offered DAA therapy[152]. Respondents of the survey did attribute low treatment initiation rates to patients' competing priorities, mental health comorbidities, poor access to harm reduction services, and insufficient physician training.

2.9.3 System-Level

The extraordinary cost of DAAs has led many insurers to restrict access to DAAs based on a variety of factors. In many countries, financial barriers are the principal reasons for reduced access to HCV therapy. The first review of DAA coverage for Medicare recipients in the United States was conducted in 2014[30]. The study found that the majority of states restricted access to DAAs for a variety of reasons, including both clinical criteria (74% limited sofosbuvir access to persons with advanced fibrosis and 25% required co-infected persons to have suppressed HIV

RNA levels) and behavioural criteria (50% required a period of abstinence of drug or alcohol use). Four years later, despite advocacy efforts and threats of legal action, both public and private health insurers in the United States continue to deny coverage for HCV medications at increasingly high rates. Gowda and colleagues reported that the overall incidence of absolute denial in the United States was 35.5% – substantially higher than the incidences found in two prior analyses conducted shortly after the release of all-oral DAA regimens (absolute denial range, 8.2%–16.2%)[10, 16, 153]. While the reasons for the increase in absolute denial remain unclear, constrained budgets of payers continue to contribute to treatment prioritization by insurers.

Similar reviews of coverage have been conducted in Canada and in Europe, where restrictions were found to be more homogeneous than in the United States [28,154-157]. As of June 2016, Marshall and colleagues reviewed the reimbursement criteria of the four DAAs that had been approved by Health Canada (simeprevir, sofosbuvir, ledipasvir/sofosbuvir and paritaprevir/ritonavir/ombitasvir/dasabuvir) in the 10 provinces and 3 territories in Canada. They found that overall, 85%-92% of provinces/territories limited access to patients with significant fibrosis (fibrosis stage F2 or greater). While they did not report the use of absolute drug and alcohol use restrictions, whether such criteria (e.g., active injection drug use) were actually used for restriction was left to the discretion of the physician.

Restricting treatments to those with significant fibrosis was a way for people at an increased risk of short-term health outcomes to be prioritized for treatment while reducing the overall health costs. But since PWID tend to be younger and have less advance liver disease these policies

differentially created additional barriers to accessing treatments for this population. While these medications have been deemed cost-effective, they remain expensive. Given the approximate 250,000 Canadians infected with HCV, and DAAs costing between $45 000 to more than $100 000 per treatment, it would cost a considerable proportion of the health care budget to treat everyone[3]. Thanks to a combination of market forces (multiple DAAs approved by multiple pharmaceutical companies) and price negotiations between the pan-Canadian Pharmaceutical Alliance, drug prices have decreased, but it is unknown to the public by how much. The World Hepatitis Alliance estimates Australia pays an estimated $16 000 per patient, and therefore similar costs are estimated in Canada.

Although all Canadian citizens and permanent residents have insurance coverage for in-hospital and physician services, medication coverage varies across the 10 provinces and 3 territories, consisting of a mix of public and private insurance sources. For example, people on social assistance receive public coverage for medications with no or minimal co-payments and Indigenous people receive medication coverage from the First Nations and Inuit Health Branch (NIHB). The decision as to what medications are covered and under what circumstances is made independently by health authorities of each province for Canadian residents and by the NIHB.

As with most countries, second-generation DAAs were approved for the market in late 2013 by Health Canada and most provinces limited access to treatment to people with significant liver fibrosis[28]. In Quebec, health authorities took a different approach. When simeprevir and

[3] In 2018, total health expenditure in Canada is expected to reach $253.5 billion, or $ 6,839 per person https://www.cihi.ca/en/health-spending

sofosbuvir were first approved, these treatments were not restricted to those with significant fibrosis. When the next set of DAAs (ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir/dasabuvir) became available, health authorities proposed a five-year plan to provide access to treatment to everyone in the province progressively. As of March 2016, people co-infected with HIV and HCV had unrestricted access to DAAs, regardless of their fibrosis stage. In 2017, after the pan-Canadian Pharmaceutical Alliance used collective bargaining power to reduce drug prices across Canada, all other provinces progressively removed fibrosis stage restrictions as a criterion for treatment reimbursement. As of 2018, across Canada, DAA therapy were reimbursed for all infected patients (no/few restrictions), with little or no extra cost to the patients.

CHAPTER 3: METHODS

3.1 Canadian HIV-HCV Co-Infection Cohort (CCC)

The Canadian HIV-HCV Co-infection Cohort (CCC) Study is a publicly funded prospective cohort of HIV-HCV co-infected individuals from five provinces across Canada. With the goal of capturing diverse risk profiles (e.g. active and former-PWID, MSM, women, Indigenous peoples), a variety of HIV centres – including major urban tertiary care hospitals and smaller community-based clinics and outreach programs – were included[158]. In Quebec, HIV-positive adults with evidence of HCV infection (antibody-positive) have been eligible to participate since 2003. In 2006, the cohort expanded nationally and continues to actively recruit from the following 18 centres, from : (1) Montreal (4 centres): Immunodeficiency Services at the Montreal Chest Institute[4], Hopital Notre-Dame, La Clinique Médicale du Quartier Latin and Montreal General Hospital[2]; (2) Quebec City (1 centre): Le Centre Hospitalier Universitaire de Québec; (3) Vancouver (4 centres): Pender Community Health Centre, British Columbia Centre for Excellence in HIV/AIDS, Oak Tree Clinic, the Native Health Centre; (4) Calgary (1 centre): Southern Alberta HIV Clinic; (5) Toronto (2 centres): Sunnybrook Hospital and Toronto General Hospital; (6) Windsor (1 centre): Windsor Regional Hospital; (7) Hamilton (1 centre): McMaster University Medical Centre; (8) Ottawa (1 centre): Ottawa General Hospital; (9) Sudbury (1 centre): Sudbury Regional Hospital; and (10) Halifax (1 centre): Queen Elizabeth Halifax Health Centre. In light of the emerging epidemic in Saskatchewan, in 2013 centres were added to the CCC in Saskatoon (1 centre, SHARE clinic at the University of Saskatchewan) and Regina (1 centre, Regina Qu'Appelle Health Region Hospital).

[4] As of 2014, collectively known as the Chronic Viral Infectious Service (CVIS)

As of December 2018, 1917 HIV-HCV co-infected participants had enrolled in the study.

After informed consent is obtained, data on socio-demographic, behavioural, clinical characteristics and treatments are collected bi-annually using a detailed self-administered questionnaire (details below). Clinical data are extracted from medical records using standardized case report forms. Linkage to vital statistic are made every two years to confirm deaths and evaluate if people who had been lost-to-follow-up had indeed died.

3.1.1 Inclusion Criteria

The main cohort eligibility criteria are:

1. Age >16 years old (i.e. adults, may vary according to provincial criteria) and able to provide informed consent;
2. HIV-seropositive (by enzyme-linked immunosorbent assay (ELISA) with confirmation by western blot);
3. HCV-infected (antibody-positive) or evidence of exposure (HCV-seropositive by ELISA with recombinant immunoblot assay (RIBA II) or enzyme immunoassays (EIAs) confirmation, or if serologically false negative, HCV RNA-positive.

3.1.2 Data collection

Data are collected via a combination of self-reporting and extraction by chart review at participant's baseline visit and every 6 months thereafter. The following data elements were used for this thesis:

1. Patient-reported data: socio-demographics, drug and alcohol use, injection behaviour and

quality of life measure, using the Euro-Quality of Life 5-Dimensional Questionnaire (EQ-5D);

2. Medical history: hepatic and HIV-related diagnoses, HIV and HCV treatments, HCV genotype
3. Laboratory tests: CD4 + T-cells, HIV viral load and HCV RNA, liver enzymes

3.1.3 HCV treatment data

Since the original CCC questionnaires were created before DAAs were approved, in 2012 a new case report form was created to include details of DAA treatments, including DAA class, dose, duration and response. Other information (e.g. whether the patient had failed previous courses of HCV treatment, HCV genotype, fibrosis stage and adherence to DAA treatments was also collected. These forms were filled out by study coordinators or nurses after each participant completed a DAA treatment. Since 2015, the "DAA database" has included all treatment initiations that have been verified by each of the study sites.

3.1.4 HCV chronic infections

HCV treatment initiation was the outcome of interest for objectives 2 and 3, therefore it was important to distinguish who would be "at risk" of initiating treatment (persons included in the denominator). Such participants were defined as individuals with chronic HCV infection, defined as being HCV-RNA positive. HCV RNA was measured at each site's local laboratory using either a qualitative assay (COBAS® Ampliprep/TaqMan® HCV Test, v2.0, Roche Molecular Systems, or other local lab assay) or quantitative assay (Abbot RealTime PCR; Abbott Molecular Inc, or other local lab assay). The lower limit of detection varied by assay and year.

3.1.5 Cohort Description

Figure 3.1 illustrates the demographic diversity of the cohort in terms of the acquisition of HIV and HCV risk factors and geographic region. Based on the characteristics given at each participant's first visit, 81% of the CCC participants had a history of injection drug use, 28% were female, 21% were of Indigenous descent, 23% were MSM and 30% were active PWID. This cohort has been estimated to represent 23% of the total co-infected population in care in Canada; it is also one of the largest prospective co-infection cohort in the world[158].

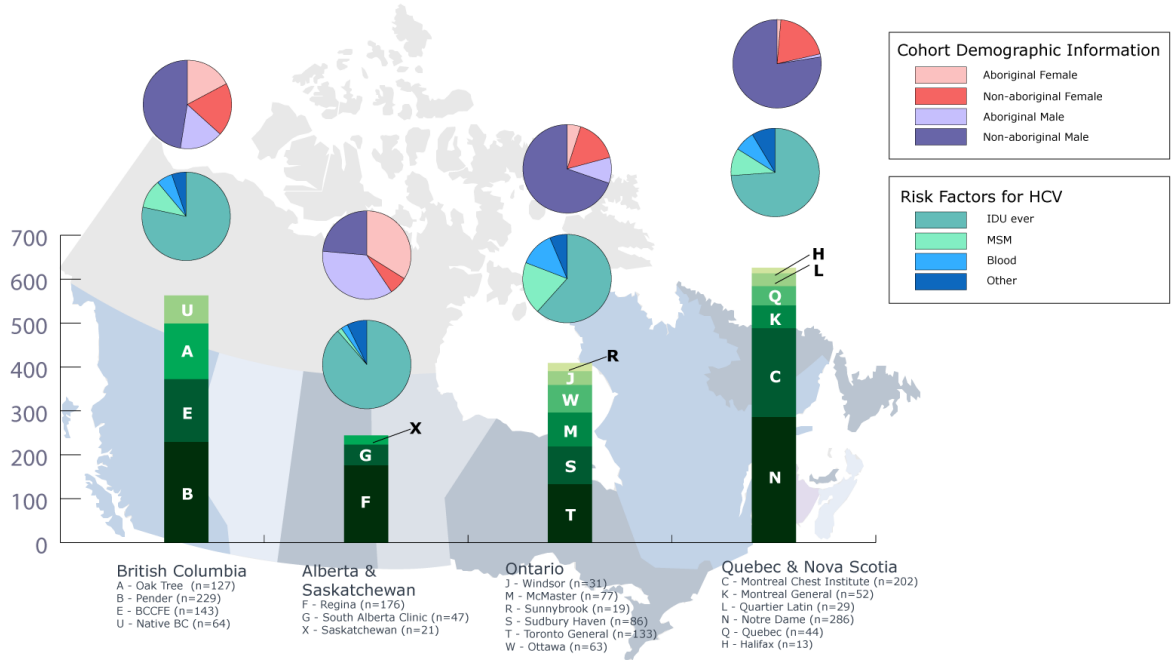


Figure 3.1 CCC diversity by demographic, HCV risk factors and geographic region

3.2 Ethical Approval and Confidentiality

The CCC cohort has been approved by the Community Advisory Committee of the Canadian Institutes of Health Research (CIHR)- Canadian HIV Trials Network (CTN) and by the relevant institutional ethics boards of all participating centres**,** including approval from the McGill University Health Center Ethics Board (REB#2006-1875). All CCC participants signed the required informed consent forms. All participant data were entered de-identified and the database is managed by the CCC Data Management Team at the McGill University Health Centre.

3.3 Manuscript 1: How generalizable are the results from trials of Direct Antiviral Agents?

3.3.1 Analytical sample

To address the first objective of this thesis "evaluate the generalizability of the results of trials of DAAs to people co-infected with HIV-HCV in the real world", I designed a cross sectional study of participants actively engaged in the study and chronically infected with HCV. As of April 1, 2015, the CCC had enrolled 1423 HIV-HCV co-infected participants. Of the 1423 cohort participants ever enrolled, I excluded those who died (n=184), withdrew from the study (n=107) or were lost to follow-up (n=258), defined as not completing a questionnaire within 18 months of April 1st, 2015. Since I was interested in creating a representative sample of co-infected patients who could potentially initiate treatment, I restricted the analytical sample to HCV-viremic patients. Of the 874 remaining participants, 615 (70%) had evidence of chronic HCV infection (HCV RNA positive). I further stratified the analytical sample based on HCV genotype that reflected the genotypes that had been studied in clinical trials. Participants with missing genotypes (n=74) were excluded from the analysis, since these people were not being considered for treatment. The final analytical sample included 410 co-infected individuals with HCV

genotype 1, 26 with genotype 2, 94 with genotype 3 and 11 with genotype 4.

3.3.2 Analysis

I first performed a review of all phase three trials evaluating second generation DAAs in individuals with HIV-HCV co-infection. I retrieved the relevant papers by searching PubMed and clinical trial registries (clinicaltrials.gov); the search included all papers published as of November 2015. I identified papers studying the following DAAs: sofosbuvir, ledipasvir, grazoprevir/elbasvir, ombitasvir, paritaprevir/ritonavir/dasabuvir, faldaprevir, and daclatasvir. I restricted trials to those where protocols were available (either published as supplemental material (4 out 5 trials) or available after requesting the protocol from the corresponding author (1 out of 5 trials). The following trials met the inclusion criteria and were included in the analysis: NCT01479868 (evaluating simeprevir), the PHOTON-1 trial (NCT01667731, evaluating sofosbuvir), the TURQUOISE-I trial (NCT01939197, evaluating ombitasvir, paritaprevir/ritonavir and dasabuvir (3D)), the ION-4 trial (NCT02073656, evaluating sofosbuvir/ledipasvir) and the ALLY-2 trial (NCT02032888, evaluating daclatasvir/sofosbuvir)[23-25,90,91]. The specific exclusion criteria for each of the five trials used to assess the generalizability are listed in **Table 3.1**.

Table 3.1 Exclusion criteria for the five included clinical trials of second-generation DAAs in HIV-HCV co-infected individuals

Categories	Exclusion criterion	Trial-Specific Thresholds
Sociodemographic	Age (years)	<18[2, 4, 5] <18 & >70[1,3]
	BMI (kg/m^2)	<18[2,4]; ≤18 &>38[3] ≤18 &>35[5]
	Active illicit drug use (excluding marijuana)	Supplemental Table 2 (Chapter 5)
Clinical	Specific cART regimen[1,2,3,4,5]	Supplemental Table 1 (Chapter 5)
	CD4+ T-cell count (cells/mm^3)	<300[1]; <200[2, 3, 5]; <100[4]
	HIV RNA (copies/mL)	>50[1,2,4,5]; >40[3]
	Neutrophils (cells/mm^3)	<1.5[1]; <1.2[3]; <0.75[5]
	Albumin (g/dL)	<3.3[1]; <3.0[2,4,5]; <2.8[3]
	Hemoglobin (g/dL)	<110 (female) or <120 (male)[1,2,3,4] <100[5]
	Platelets (cells/mm^3)	<90,000[1];<60,000[2,3];<50,000[4,5]
	Bilirubin	>3 mg/dL[1,2,3,4]; > 2 mg/dL[5]
	International normalized ratio (INR)	>1.5
	Alpha-fetoprotein	<50 ng/mL[1]; <100 ng/mL[3,5]
	Aspartate aminotransferase (U/L)	<10x ULN[1,2,4]; <7x ULN[3]
	Alanine aminotransferase (U/L)	<10x ULN[1,2,4,5]; <7x ULN[3]
Diagnosis	Serum creatinine (mg/dL) or Cockcroft-Gault equation	<1.5[1]; <60 mL/min[2,3,4]; <50 mL/min[5]
	Decompensated liver disease[b]	present
	AIDS illness[§]	present
	Co-Infection with Hepatitis B	HbsAg positive

cART-combined antiretroviral therapy; ULN-upper limit of normal; BMI-body mass index; INR-international normalized ratio

[1] Simeprevir trial allowed: raltegravir, efavirenz and ripilvirine;
[2] PHOTON-1 trial (sofosbuvir) allowed: tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, efavirenz, raltegravir or ripilvirine;
[3] TURQUOISE-I trial (ombitasvir, paritaprevir/ritonavir and dasabuvir) allowed: tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, raltegravir
[4] ION-4 trial (ledipasvir/sofosbuvir) allowed: tenofovir/emtricitabine with efavirenz, raltegravir or ripilvirine
[5] ALLY-2 trial (daclatasvir/sofosbuvir) only excluded unboosted protease inhibitors and cobicistat
¶ Active psychiatric disorders including but not limited to, schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder, and mania.
[b]Including but not limited to radiologic criteria, history or presence of ascites, bleeding varices, or hepatic encephalopathy.
[§]Presence of AIDS-defining opportunistic infections.

Supplemental Tables 5.1 and 5.2 (appendix of Chapter 5) summarize the permitted cART regimens by trial and provide the trial-specific definitions of active drug use, respectively. I then applied the exclusion criteria to the analytic sample of the CCC to evaluate the proportion of CCC participants who would be eligible to participate in each of these trials separately. Finally, I summarized the results graphically as the proportions of eligible CCC participants based on modifiable (e.g. cART regimens) and non-modifiable clinical factors.

3.4 Manuscript 2: Disparities in Direct Acting Antiviral Uptake

3.4.1 Analytical samples

For Manuscript 2, I answered three research questions with two distinct analytical samples.

(1) Temporal trends in HCV treatment initiation rates: This analytical sample included all CCC participants at risk of initiating any HCV treatment between 2007-2015. Participants were considered "at risk" if they were alive, chronically infected with HCV and actively participating in the CCC (defined as having a CCC study visit within 18 months of each calendar year) as of January 2007.

(2) Predictors of DAA initiation and efficacy of DAAs: This analytical sample included all CCC participants at risk of initiating second generation DAAs who were HCV RNA-positive as of November 21, 2013 (time zero). This date was chosen as time zero as it was the date Health Canada approved the first second generation DAA, simeprevir. Participants who initiated DAA through a clinical trial were excluded from this sample as the purpose of this objective was to estimate treatment uptake in a real-world setting. Participants were followed until DAA initiation or until the participant was lost to follow-up (no study visit for at least one year), death, study withdrawal or December 31st, 2015 (administrative censoring date).

3.4.2 Analysis

Exposures: The four key populations, identified *a priori* based on WHO guidelines[159]. CCC participants were characterized as belonging to a key population based on self-reported data collected by questionnaires. The four key populations were: active PWID, defined as injection drug use within the last 6 months; Indigenous people of Canada, defined as people of First Nations, Inuit or Metis origins; women, defined by biological sex-at-birth; and MSM, defined as men who self-identify their sexual orientation as homosexual or bisexual.

Outcomes:

(1) Initiating HCV treatment between 2007-2015

(2) Initiating DAA treatment between 2013-2015

(3) Efficacy: I determined the real-world efficacy of second-generation DAAs. Efficacy was defined as a sustained virologic response (SVR), i.e. achieving a negative HCV RNA result at least 12 weeks after completing HCV treatment. Participants who initiated treatment but did not achieve SVR were considered non-responders.

Statistical Analysis:

Temporal trends: I first described temporal trends in HCV treatment initiation rates, both overall and stratified by key population. HCV treatment initiation rates were reported from January 1, 2007 (the date on which the CCC first had national representation from the recruiting centres) until December 31, 2015 (administrative end date). All approved HCV treatments, including interferon-based regimens and DAA therapies, were used to calculate HCV treatment initiation rates. Rates were reported per 100 person-years, by calendar year. Standard errors were

calculated using Greenwood's formula.

Predictors of DAA initiation: To estimate time to second-generation DAA initiation, I used Cox proportional hazards models to fit unadjusted and adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). The multivariate model was adjusted for other predictors (facilitators and barriers) of treatment initiation selected *a priori* based on consultation with providers and reviewing the literature. Covariates included: (1) socio-demographic [age (centered at the mean), low income (<$18,000 CAD)]; (2) behavioural [past (but not current) injection drug use and current alcohol use (within 6 months)]; (3) clinical [HCV genotype (1, 2, 3 or 4), significant fibrosis (defined as an AST to Platelet Ratio Index (APRI) score > 1.5) and undetectable HIV RNA (<50 copies/mL)] and (4) health care system [Canadian province of residence (British Columbia, Saskatchewan, Alberta/Ontario and Quebec; grouped to reflect DAA policy restrictions at the time of the study [28])]. Robust standard errors were used to adjust for possible clustering by centres. Using the adjusted Cox model, the baseline survival function at 2 years was estimated using post-estimation commands (predict) to calculate the probabilities of second-generation DAA initiation and their corresponding 95% CIs [160]. The two-year probability of second-generation DAA initiation was summarized graphically for the key groups of interest who were less likely to initiate treatment (combination of being Indigenous, a woman and reporting active injection drug use). As a sensitivity analysis, stratified Cox models were evaluated independently for each of the key populations. Graphical methods were used to check the proportional hazards assumption of the Cox models.

Approximately 10% of HCV genotypes were missing from the database. To account for these

missing values, I employed multiple imputation by chained equation (MICE) in multivariate models [161]. The imputation model included all covariates in the multivariable model, an indicator for DAA initiation, and a measure of the cumulative baseline hazard using the Nelson-Aalen estimator. Twenty imputed data sets were created and combined based on Rubin's rules [162]. We compared results from models with and without the use of MICE.

3.5 Manuscript 3: Impact of Removing Fibrosis Stage Restrictions on HCV Treatment Uptake

3.5.1 Analytical sample

For the primary analysis, CCC participants who were chronically infected with HCV (HCV RNA positive) as of March 24, 2010 and residing in (British Columbia (BC), Ontario (ON) and Quebec (QC)) were included. This analysis was restricted to three of the six provinces because either the sites had not joined the cohort as of time zero (Saskatchewan) or there were less than 50 eligible participants recruited (Alberta and Nova Scotia). HCV RNA was measured in local laboratories using either a qualitative assay (COBAS® Ampliprep/TaqMan® HCV Test, v2.0, Roche Molecular Systems, or other local lab assays) or quantitative assay (Abbot RealTime PCR; Abbott Molecular Inc, or other local lab assays); lower limit of detection varied by assay and year. Time zero was defined as March 24, 2010, as first generation DAAs began to be approved by health authorities worldwide and in Canada[163].

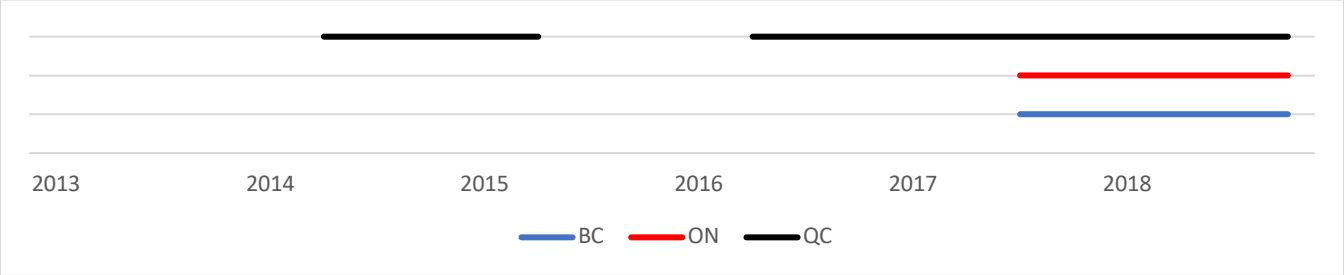
3.5.2 Analysis

Outcome: HCV treatment initiation was the primary outcome. The study period spanned between 2010 and 2018, therefore treatments included both pegylated interferon (peg-IFN) (in combination with ribavirin or DAAs) and interferon-free regimens DAAs included boceprevir/peg-IFN, telaprevir/peg-IFN, simeprevir/peg-IFN, sofosbuvir/peg-IFN,

sofosbuvir/simeprevir, sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir with/out dasabuvir, sofosbuvir/daclatasvir, sofosbuvir/velpatasvir, and elbasvir/grazoprevir. Eligible participants who did not achieve the outcome were censored on the date they were considered lost to follow-up (no study visits for at least 18 months), died, withdrew from the study, spontaneously cleared HCV infection or at the administrative end date (March 24, 2018). Since participants could initiate HCV treatment multiple times (i.e. failure, reinfection); treatment initiation was treated as a repeatable outcome. Only participants who initiated HCV treatment and achieved a sustained virologic response (SVR) were considered no longer at risk.

Exposure: The exposure of interest was the change in provincial policies that removed the criterion requiring presence of "significant liver fibrosis stage" for DAAs to be reimbursed by the provincial health plans. Figure 1 illustrates when policies changed in each province. In the province of Quebec, when simeprevir and sofosbuvir were available for treatment between June 2014-July 2015, there were no restrictions based on fibrosis stage. In 2016 when ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir/dasabuvir were approved, HCV treatment were restricted for people with advanced liver disease (>F3). However as of March 2016, these restrictions were removed for people co-infected with HIV allowing them early access to DAAs irrespective of fibrosis stage. In Ontario and British Columbia, fibrosis restrictions were only removed as of March 2017 for people co-infected with HIV.

Figure 3.2 **Time Varying Policy Changes by Province** [a,b,c,d,e]



[a] Solid lines represent calendar time when no fibrosis stage restrictions were in place. No line represents either significant (>F2) or advanced (>F3) liver fibrosis stage restrictions were required for reimbursement of DAAs.
[b] Before 2013, due to the lower efficacy and higher toxicity of interferon-based therapies in HIV-HCV co-infection, typically, only people with advanced fibrosis who were felt to be at increased risk for short term adverse liver–related outcomes were treated with pegylated-interferon
[c] Quebec: In 2014, simeprevir and sofosbuvir were unrestricted for patients living with HCV. Although HIV infection was a listed restriction, co-infected patients were usually granted access on a case by case basis through the "patient d'exception" process; As of 2016, people co-infected with HIV and HCV were considered a priority population and sofosbuvir/ledipasvir and ombitasvir/paritaprevir/ritonavir/dasabuvir were available without fibrosis stage restrictions; sofosbuvir/velpatasvir followed as of 2017
[d] British Columbia and Ontario: In 2017, after the pan-Canadian Pharmaceutical Alliance used collective bargaining to reduce DAA drug prices across Canada, provinces removed fibrosis stage restrictions as a criterion for treatment reimbursement.
[e] No sobriety restrictions were present in Canada.

Primary Analysis: Impact of removing fibrosis stage restrictions on HCV treatment initiation rates– We used a difference-in-differences approach to estimate the impact of removing significant liver fibrosis on HCV treatment initiation. This approach evaluates the difference between the average change in the exposure group (i.e. before and after policy change) and the average change over the same period of time in a control group (no policy changes)[164]. Focusing on changes within these groups over time controls for time-invariant characteristics of the exposed group, while including a control group controls for secular trends. The assumption that is made is, the post-intervention trend in the control group provides an accurate counterfactual for what would have happened in the absence of the exposure. This is verified by assessing whether the pre-intervention outcome trends are parallel[165]. We chose this study design because of the need to control for secular trends in HCV treatment uptake that co-occurred with policy

changes (DAA approval in 2013). A detailed explanation of the difference-in-differences study design and a discussion of its strengths and limitations follow in Chapter 4 (**Tutorial 1: Evaluating the Impact of Health Policies: Using a Difference-in-Differences Approach).**

The base difference-in-differences model includes three main variables: (1) Group (defined by province of residence; indicator variables for British Columbia (reference), Ontario or Quebec); (2) Time (indicator variables for each calendar year starting from time zero March 24th 2010 through to March 23rd 2018, the reference was March 24th 2013- 2014 (3) An interaction between Group and Time, which is equal to 1 in provinces and years when fibrosis stage restrictions are not in place, and equal to zero otherwise. The coefficient on this interaction term provides the difference-in-differences estimate of the policy effect (Equation 3.1). Since our analysis included multiple groups and time periods, the combination of group (province) and time-periods where fibrosis restrictions remained, form the control for this analysis. When QC was exposed to a policy change in 2014, BC and ON served as the control groups. Then when BC and ON were exposed to a policy change in 2017, QC served as their control (since there was no change in Quebec)

Equation 3.1:

$$\ln(\lambda) = \beta_0 + \beta_1(\text{province}) + \beta_2(\text{year}) + \beta_3(\text{policy})$$

I compared the DD estimator from the primary model with an adjusted model (equation 3.2) that included individual-level time-fixed and time-varying predictors of HCV treatment initiation.

Equation 3.2:

$$\ln(\lambda) = \beta_0 + \beta_1(\text{province}) + \beta_2(\text{year}) + \beta_3(\text{policy}) + \sum_{j=3}^{J} \beta_J \text{covariates}_{j=\text{fixed}} + \sum_{k=4}^{k} \beta \text{covariates}_{k=\text{time varying}}$$

The adjusted difference-in-differences model also included individual-level fixed and time-varying predictors of HCV treatment initiation. Fixed covariates included age (centered at mean), sex, men who have sex with men (MSM), HCV genotype (genotype 3 compared to genotype 1, 2 or 4). Time varying covariates included income (<$18,000 CAD)[166]; injection drug use (within the 6 months); undetectable HIV RNA (<50 copies/mL) and significant fibrosis. Significant fibrosis was determined using a hierarchical classification based on availability of a liver biopsy, clinical diagnosis, Fibroscan (>7.2 KPa)[67] or AST to Platelet Ratio Index (APRI) ≥1.5)[66].

I further evaluated the impact of the policy change among PWID by restricting the analytical sample only to participants who reported active injection drug use in the last 6 months.

Statistical Considerations: All difference-in-differences models were fit using negative binomial regression. The natural logarithm of each participant's time at risk (in years) was used as the offset. Generalized estimating equations were used to account for repeated outcomes, robust standard errors were used to adjust for clustering. Results are presented as Incidence Rate Ratios (IRR).

Sensitivity Analysis: (1) I evaluated if the parallel trends assumption necessary to make causal inference from a difference-in-differences analysis was reasonable. Since I used a non-linear

model, the parallel trends in HCV treatment initiations between the three provinces prior to the time varying policy changes were assessed on the logarithmic scale; (2) I evaluated if the policy reached the population that it was intended to reach (effect modification based on not having significant liver fibrosis) by performing a difference-in-difference-in-differences analysis. Here a triple interaction term (between the time-varying policy change, province and no significant fibrosis) was the estimator of interest; (3) I repeated our main analyses with a lead exposure indicator variable to evaluate if broad access to HCV treatments predated the policy change by one year. If the lead variable was associated with HCV treatment initiation rates, this would indicate that our results may be owing to time trends in our control groups (British Columbia and Ontario) that maybe systematically different from time trends in Quebec; (4) I tested a lagged exposure variable one year after provinces removed fibrosis stage restrictions to assess whether the effects of removing fibrosis stage restrictions persisted; and (5) I conducted a falsification test by assessing the association between the policy change and outcomes that we would not expect to be affected by changes broadening access to HCV treatments. Here I used serum creatinine levels (a marker for general health). If the policy was associated with serum creatinine, it would suggest that omitted variables affecting decisions to initiate DAAs were driving our results.

Secondary Analysis: Assessment of who is left to be treated? – Based on the eligibility criteria above, we summarized the proportion of participants who initiated treatment and those who remained eligible for treatment, by calendar year, significant fibrosis stage and active injection drug use. We then performed a cross-sectional analysis, using a modified Poisson regression model with robust standard errors to assess predictors of remaining HCV RNA positive at each

participant's last visit. Predictors included: (1) Socio-demographic – age, Indigenous ethnicity, women/ or MSM compared to heterosexual men, income, homelessness, incarceration (past 6 months) and province of residence (British Columbia as reference); (2) behavioural –active injection drug and alcohol use (3) clinical –undetectable HIV RNA, significant liver fibrosis, HCV genotype and psychiatric diagnosis (4) disengagement in care– defined as being lost to follow up. Lost to follow up was defined as not having a cohort visit within 18 months of our administrative censoring date (excluding those who had formally withdrawn from the study and those who died).

3.6 Manuscript 4: Impact of Direct Acting Antiviral Therapy on Health-Related Quality-of-Life

3.6.1 Analytical sample

Of the 1795 CCC participants recruited into the cohort by March 2018, 363 participants initiated oral DAAs. Oral DAAs were defined as regimens containing sofosbuvir/ribavirin, simeprevir/sofosbuvir, sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir/dasabuvir, sofosbuvir/daclatasvir, grazoprevir/elbasvir, or sofosbuvir/velpatasvir in the absence of interferon. After excluding participants who accessed DAAs through clinical trials (n=44), those for whom treatment response was missing (n=29), and those who did not participate in at least 1 visit before and 1 visit after DAA treatment (n=63), a total of 227 participants were included.

3.6.2 Analysis

Exposures: Successful treatment response, defined as a sustained virologic response (SVR); HCV RNA-negative 12 weeks post-EOT or treatment failure [defined as (i) EOT non-response (HCV RNA-positive), (ii) relapse (HCV RNA-negative at EOT, but HCV RNA-positive prior to SVR), or (iii) premature discontinuation (due to side effects or non-adherence)].

Outcome: Health Related Quality of Life (HR-QoL) was measured using the EuroQoL Group-5 Dimensional, 3-Level Version (EQ-5D-3L) instrument in English or French. The EQ-5D-3L is made up of two components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). In the EQ-5D-3L descriptive system, respondents report the extent of difficulty (no/some/extreme problems) in five health domains: mobility, self-care, usual activities, pain/discomfort, anxiety/ depression. The results from the five health domains are then converted into a composite utility score using a Canadian-based algorithm, using the eq5d command in Stata [167]. Utility scores range from 0 to 1, reflecting death (0) to full health (1). Results are reported as percentage points for ease of interpretability. The EQ VAS reflects the overall respondent's health state and ranges from the worst health state possible (0) to the best health state possible (100); results are reported in unit changes [168].

Statistical Analysis: Sociodemographic, clinical and treatment regimens were summarized for all participants who met the eligibility criteria at DAA treatment initiation. The five EQ-5D health domains were summarized at cohort entry, DAA initiation and the last visit (post-DAA response). Segmented generalized linear mixed models, also known as multiple baseline interrupted time series, allowing for individual random intercepts were used to evaluate the impact of treatment response on HR-QoL [169,170]. A detailed explanation of the segmented generalized mixed model and a discussion of its strengths and limitations follow in **Chapter 4** (**Tutorial 2: Segmented Generalized Mixed Models to Evaluate Health Outcomes).**

For the analysis, time zero was defined as the date on which DAA treatment was initiated (or the date of the closest cohort visit prior to initiating DAA treatment). The pre-treatment period included all observations from cohort entry to DAA initiation (while participants were HCV RNA-positive). The post-treatment period included all observations from the date treatment response was ascertained until the administrative censoring date (October 2017). As our objective was to evaluate the impact of the response to DAA therapy (SVR or non-response) as opposed to the impact of the treatment itself; we censored observations between treatment initiation and ascertainment of treatment response. By design, since the same individual is observed both before and after exposure, patients act as their own controls. In this approach, both known (e.g. sex, ethnicity, socioeconomic status) and unknown/unmeasured (e.g. genetics, motivation, determination) time-invariant confounders are accounted for[170].

Equation 3.3 summarizes the model used to estimate the conditional effect of SVR on HR-QoL for each individual (i) at time (j). The model included an intercept (baseline level of HR-QoL at treatment initiation), a pre-treatment slope (years), an indicator to reflect the immediate change in HR-QoL between treatment initiation and treatment response (Pre-Post), and a post-treatment slope (years)*(Pre-Post).

Equation 3.3:

$$\mathrm{E}[\mathrm{HR-QoL}] = \beta_{0+\beta i} + \beta_1(\mathrm{Pre-Post})_{ij} + \beta_2(\mathrm{years})_{ij} + \beta_3(\mathrm{years}) * (\mathrm{Pre-Post})_{ij}$$

Predictors of HR-QoL at DAA initiation were estimated using multivariate generalized linear mixed models. Models included the following fixed covariates at DAA initiation: age (centered at mean), sex, advanced fibrosis (defined as an AST to Platelet Ratio (APRI) score ≥1.5), and

prior HCV treatment exposure. Models also included the following time-varying covariates: undetectable HIV RNA (<50 copies/mL), diagnosis of a psychiatric disorder, income (dichotomized by greater/less than $1500 CAD/month), and recent injection drug use (in the last 6 months). Because of the limited number of individuals who did not respond to DAA therapy, I did not evaluate predictors of HR-QoL in this subgroup.

Sensitivity Analysis: I selected the pre-post study design to avoid the need to match patients who initiated DAA to those who did not since matching would only control for observed differences between the patients initiating and not initiating treatment and not unobserved confounders, and this may induce confounding by indication, since unmeasurable confounders such as motivation, perseverance, psychological state, socioeconomic status may be associated with the exposure and the outcome of interest. But time trends of EQ5D-VAS and utility score among people who did not initiate DAAs were also assessed to evaluate if they were similar to pre-treatment trends of the analytic sample (e.g. to assess generalizability of the analytic sample). For this sensitivity analysis time zero was defined at cohort entry, generalized linear mixed models, evaluating HR-QoL over time, showed no changes throughout patients follow up time. I further evaluated if there were any non-linear time relationships (including squared, cubic time variables) and even more flexibly using cubic B-splines and no significant improvements in model fit was observed.

All analyses were performed using STATA version 13/IC (manuscript 1 and 2) and version 15/IC (manuscript 3 and 4) (StataCorp LP, College Station, TX).

CHAPTER 4: QUASI-EXPERIMENTAL TUTORIALS

Tutorial 1: Evaluating the Impact of Health Policies: Using a Difference-in-Differences Approach. This tutorial describes the methods used in MANUSCRIPT #3

4.1 Preface to Tutorial 1

The difference-in-differences method emulates a randomized experimental design by measuring changes in outcomes over time between groups exposed to a "naturally" occurring intervention and control groups not exposed to the same intervention. Given a number of assumptions, researchers can estimate the causal impact of interventions in the absence of randomization. The difference-in-differences study design has been extensively used in economics and has gained considerable popularity in the clinical and epidemiology literature in the last ten years. Indeed, between 2008 and 2018 the number of articles indexed in PubMed with the key word "difference-in-differences" or "difference-in-difference" increased more than ten-fold. Despite the utility of this method, few non-technical papers with a public health focus are available. Therefore, this brief tutorial was written as an introductory paper targeted towards public health professionals evaluating public health interventions or policies. The tutorial includes a brief description of the study design, how to parametrize regression models, and analytical considerations.

This tutorial was published in January 2019, in the "Hints and Kinks" section of the International Journal of Public Health.

4.2 Evaluating the Impact of Health Policies: Using a Difference-in-Differences Approach (TUTORIAL 1)

Sahar Saeed, Erica EM Moodie, Erin C Strumpf and Marina B Klein

Constrained healthcare resources worldwide have made evaluating the impact of population health interventions increasingly important to maximize health and equity, while minimizing costs. However, the effects of population-level exposures such as health policies can seldom be evaluated through randomized controlled trials (RCTs). The following article will examine how the difference-in-differences method can be used to estimate the causal effect of such interventions. While this method was formalized and is extensively used in the field of economics [171], its first application is believed to have originated in the field of public health in 1855 [172]. The difference-in-differences method emulates a randomized design by measuring changes in outcomes over time between exposed and control groups. But unlike an RCT where the researcher randomly assigns exposure status, in a difference-in-differences design, researchers use "natural experiments" to assign exposure status, thus known as a quasi-experimental model [173,174]. Repeated outcome data are necessary to conduct a difference-in-differences analysis. The data can be in the form of longitudinal data (also known as panel data); sources may include payer/claims data, patient's electronic medical records or data from established cohort studies. Alternately, repeated cross-sectional data, such as national surveys (i.e. Demographic and Health Surveys (DHS)) can be used.

In this paper we describe the study design, how to parametrize regression models, and analytical considerations; we further provide published examples to illustrate the approach in practice. Like

all methods, the difference-in-differences approach comes with strengths, assumptions and limitations, which we discuss and direct the reader to other resources.

Motivating example

We start with a hypothetical example. A researcher is interested in evaluating the impact of universal access to influenza vaccination (the intervention) on hospital admissions (the outcome). Designing an RCT would be expensive, take a considerable amount of time and may not be generalizable. Fortunately, a natural experiment was already underway; as of December 2012, one state modified their state-level healthcare coverage to include universal influenza vaccination. One approach would be to conduct a pre/post design, where changes in outcomes post-intervention (after December 2012) are compared to pre-intervention (before December 2012) (Figure 4.2.1). If the unit of observation (aggregate hospital-level data or more granular individual-level data) was the same before and after the intervention, time-invariant confounders are controlled for by design [170,175]. However, for this study design to provide an unbiased association of the intervention, an implicit assumption is made that there are no time-varying confounders or underlying secular trends may influence the outcome -- a strong assumption that is rarely valid. For example, hospital admission rates could change regardless of the implementation of the new policy due to an ageing population or an acute health event such as a particularly bad influenza season. Failing to account for these underlying secular changes would lead to erroneous (and counterintuitive) conclusions that the policy was associated with an increased rate of hospital admissions, when in fact, other time-varying factors account for these changes. The difference-in-differences method takes the pre/post design one step further by

including an external control group. Using our example, states that did not experience the policy change in 2012 could be defined as controls.

The Design

As the name implies, this method compares the "difference" in outcomes of an exposed group, pre- and post- intervention, to the "difference" over the same time in a control group not subject to the intervention (Figure 4.2.1 (II))[173,175]. The crucial assumption to estimate an unbiased effect is that the only time-varying difference between the control and exposed groups is exposure to the intervention. Control groups should be chosen to be as similar in all ways to the treated group, except for the policy change, and, most importantly, the trends in the outcome pre-intervention. By including a control group, the secular trends common to both groups are subtracted from the association between the intervention and the outcome. The double difference between pre- and post-intervention and between the control and exposed groups is known as the difference-in-differences (DiD) estimate, summarizing the average impact of the intervention. Figure 4.2.1(II) illustrates the DiD estimate based on an average of multiple time points before and multiple time points after the policy implementation.

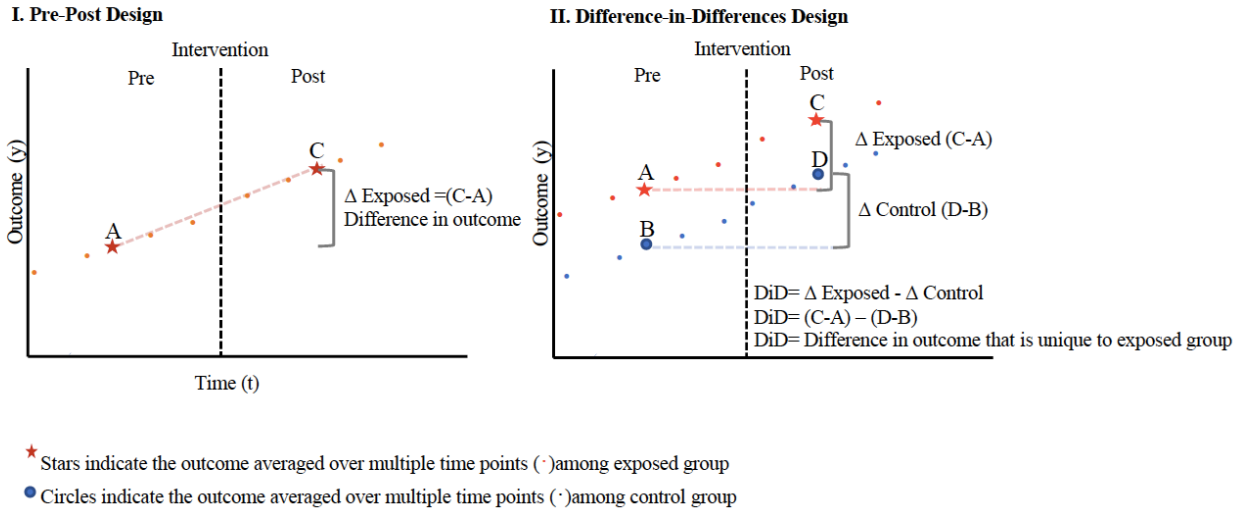


Figure 4.2.1 Graphical representation of Pre-Post (I) and Difference-in-Differences (II) study designs
Stars indicate the outcome averaged over multiple times (red ·) among the exposed group (before and after the intervention (A, B); Circles indicate the outcome averaged over multiple times (blue ·) among the control group (before and after the intervention (C, D)

Assumptions of Difference-in-Differences Approach

The strength of RCTs is that the randomization process should ensure that the exposed and control groups are exchangeable (both in terms of measured and unmeasured confounders) if the sample size is sufficient. Successful randomization is verified by comparing baseline characteristics of both groups (typically verified by results from a "Table 1"). By contrast, estimating an unbiased effect of an intervention with the difference-in-differences design requires the assumption that post-intervention trends of the control group provide an accurate counterfactual for "what would have happened in the absence of the exposure"[176]. Parallel pre-intervention trends (between the exposed and control groups) of the outcome are considered necessary and sufficient for this assumption to be reasonable. This assumption is verified by visually inspecting for parallel trends in the pre-intervention period [165], as illustrated in figure 4.2.2 (I). In contrast, figure 4.2.2 (II) illustrates examples of how non-parallel trends can either

result in counterfactual trends that either over-estimate or underestimate the impact of the interventions. Regression-based approaches can also be used to statistically test for parallel trends between the two groups in the pre-intervention period.

The validity of the difference-in-differences model also rests on the assumption that the intervention is as good as random, that is, independent of unobserved time-varying confounders, and that no other factors change differentially between the two groups over the study period. Supporting evidence for this assumption is provided by demonstrating minimal differences of observed characteristics between the exposed and control groups in the pre-intervention period, and by describing the motivation for, or the context of, the policy change. This is particularly important to rule out reverse causality – that is when changes in the outcome during the pre-period may have motivated the policy change.

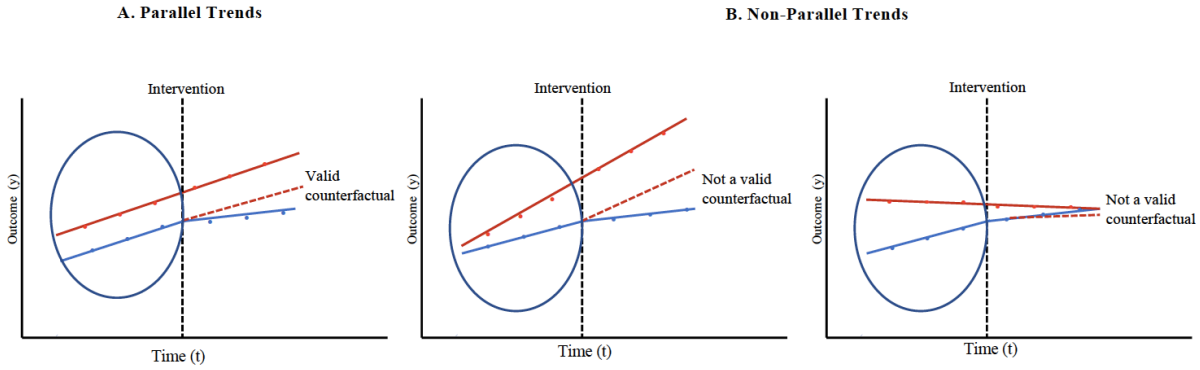


Figure 4.2.2 Parallel Trends Assumption of Difference-in-Differences Method
Blue line represents the exposed group, red line represents the control group and dashed red line represents the counterfactual trend (mirroring the control group). Panel I, illustrates parallel pre-intervention trends, resulting in a valid counterfactual. Panel II illustrates two examples of non-parallel trends resulting in invalid counterfactual trends.

Modeling and Statistical Considerations

While arithmetic can be used to calculate average changes in outcomes between two groups, regression-based modelling is commonly used to control for time-varying confounders and

efficiently calculate standard errors. Basic difference-in-differences models include three main variables in the regression models: an indicator variable for exposure (exposed group=1, control group=0), an indicator variable for time between pre- and post- intervention (post=1, post=0 (pre-intervention)) and the DiD estimator, which is the interaction between exposure and time:

$$Y = \beta_0 + \beta_1(\text{exposure}) + \beta_2(\text{post}) + \beta_3(\text{exposure}) * (\text{post}).$$

Figure 4.2.3 illustrates and provides interpretation of each coefficient of the regression model contrasting the pre-post and difference-in-differences designs. For linear regression models (used for continuous outcomes), the DiD estimator (β_3) describes the "excess" in outcome, controlling for secular trends (β_2) and time-invariant differences between the exposed and control groups (β_1) (see references [177-179] for examples of linear DiD models). When outcomes are binary or counts, logistic or Poisson models are used respectively, see references [180-183]. In contrast to the linear models, here β_3 describes a relative change as expressed as a change in odds, risk or rate ratios [184]. While the interpretation of the DiD estimator is similar in both linear and binary models, particular attention should be made when evaluating the parallel trends assumptions when using non-linear models. Specifically, outcome measurements should be plotted on the log scale to assess for parallel trends. Furthermore, since the same units of observation are repeatedly measured over time, outcomes will be correlated, violating the independence assumption of standard regression models [185]. Modelling decisions on the nature of the correlation matrix are described elsewhere [186] and should be taken into consideration.

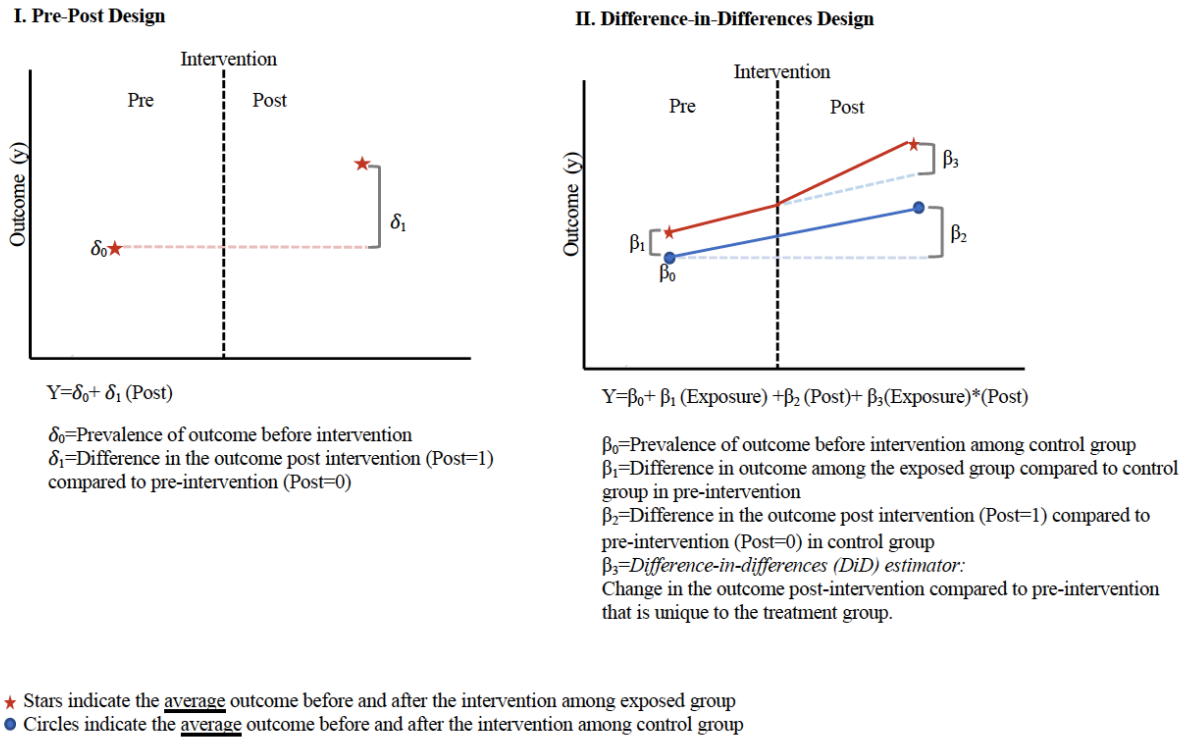


Figure 4.2.3 Graphical representation of regression models for Pre-Post (I) and Difference-in-Differences (II) study designs

Difference-in-differences models are flexible in the sense that they allow researchers to add multiple exposure/control groups, time periods, time-varying confounders and further evaluate effect modification [175,187]. Other extensions can include using a categorical variable indicating varying "intensities" of the intervention instead of binary exposures. For example, researchers evaluated the impact of varying degrees of seatbelt laws (none, primary and secondary enforcement) on traffic fatal accident rates [188]. While the difference-in-differences approach has the strength of controlling for secular trends and fixed differences between groups to provide unbiased estimates of the impact of the intervention, there are limitations specific to this study design, summarized in Table 4.2.1. Published work demonstrating solutions to these limitations or examples of sensitivity analyses are referenced.

Table 4.2.1 Limitations and Solutions specific to difference-in-differences models

Potential Limitations	Explanation	Solutions/ Sensitivity Analyses	Examples [Study Name, Country and Year of Study]
Inappropriate Control Group	The critical limitation to implementing a difference-in-differences design is finding the right control group, which can be difficult in practice. An inappropriate control group can include one where the parallel trends assumption is violated or if there is confounding by indication (the group that received the intervention was differentially chosen).	When appropriate control groups are not available, alternative methods using "synthetic controls" can be used to overcome this barrier. Synthetic controls aim to estimate treatment effects by constructing a weighted combination of control units, which represents what the treated group would have experienced in the absence of receiving the treatment [189]. Alternatively, researchers can carefully select a subset of control units that have an average pre-exposure outcome trend that is parallel to the exposed group.	Examples of how researchers used synthetic controls: Estimating the effect of California's Tobacco Control Program [Synthetic Control Methods for Comparative Case Studies: Estimating the Effect of California's Tobacco Control Program, USA, 2010][190] Using financial incentives for kidney donations [Financial incentives for kidney donation: A comparative case study using synthetic controls, USA, 2015] [191] Example of selecting a subset of control countries and averaging pre-exposure outcome trends [Removing user fees for facility-based delivery services: a difference-in-differences evaluation from ten sub-Saharan African countries, 10 sub-Saharan African countries, 2015] [192].
Lead time effect	It is possible that outcomes may begin to change in anticipation of the intervention. If so, this suggests that changes in outcomes may have preceded the intervention, which can result in a biased estimate of the intervention effect (either	Lead time effects can be assessed by evaluating whether changes already started to occur during the pre-intervention period.	Researchers interested in evaluating the association between same-sex marriage policies and adolescent suicide assessed changes in suicide attempts two-years before the policy changes [Difference-in-Differences Analysis of the Association Between State Same-Sex Marriage Policies and Adolescent Suicide Attempts, USA, 2017] [179] results available in supplemental materials

	attenuation or augmentation).		
Lagged effect	Interventions such as policies are not always implemented immediately. System-level changes such as policy implementations may have greater reach to populations, however their impact on individual health outcomes may not be immediate. This will result in a dilution, or underestimate, of the true effect of the intervention.	A priori, based on substantive knowledge, a lagged impact model can be parameterized if it is known how long the latency period should last.	In a study evaluating the association between user fees for facility-based delivery services and the portion of births delivered by caesarean section and neonatal mortality rates, researchers ran a series of regression models to test both lead and lagged effects and illustrated the impact visually at -3, -2, -1 years (pre-intervention) and +1 post-intervention [Removing user fees for facility-based delivery services: a difference-in-differences evaluation from ten sub-Saharan African countries, sub-Saharan African countries, 2015] [192].
Residual Confounding	Also known as a "shock" in the economics literature. A time varying confounder that differentially affects either the exposed or control group and coincides with the timing of the policy change of interest. This can result in a biased estimate of the intervention effect (either attenuation or augmentation).	Residual confounders need to be assessed based on substantive knowledge of the setting in which the policy is being assessed. Sensitivity analysis: The use of a placebo outcome or negative control test [193] (an outcome you would not expect to be affected by the exposure) may be used.	To identify whether uterine rupture impacted hospital's vaginal birth after cesarean delivery rate, researchers used gestational diabetes as a placebo outcome since there was no possibility of it being affected by the occurrence of uterine rupture. This was to test if there were any differential changes in outcome rates among the exposed hospitals at the time of the rupture, such as a change in hospital protocol procedures [Effect of uterine rupture on a hospital's future rate of vaginal birth after cesarean delivery, Canada, 2014][178].
Spill-over effect	Similar to clustered-RCT, there may be a	Alternative control groups can be assessed to test this hypothesis.	While studying the effect of a new law that required property owners of abandoned buildings to install working

	possibility of a "spill-over" effect. That is when outcomes in the control group (not exposed to the intervention) change due to proximity to the exposed group.	Of course, finding an alternative control group can be difficult in practice. Sensitivity analysis can be performed to evaluate if spill-overs have occurred (as described).	doors and windows in all structural openings on crime rates in Philadelphia, investigators were concerned that crimes may spill over to neighboring (unexposed) neighborhoods. They evaluated potential spill-overs by applying three varying degrees of contiguous radii expanding from each exposed site and then comparing the difference-in-differences estimates of the crime rates at each geographic level. A decrease in crimes immediately surrounding project sites, but increase in crimes in surrounding areas, would suggest a spillover or displacement of crimes. [A Difference-In-Differences Study of the Effects of a New Abandoned Building Remediation Strategy on Safety, United States, 2015][194]

Conclusion:

Quasi-experimental designs such as the difference-in-differences approach can provide an alternative to evaluating the impact of interventions such as public health policies when RCTs are not feasible. By including control group(s) to act as the counterfactual, time-varying confounders are controlled by design. In addition, this study design may be more intuitive and accessible to a diverse audience with the use of graphics to depict results. However, as we have reviewed in this article, there are specific assumptions and analytical considerations that need to be made when conducting a difference-in-differences design to accurately estimate the impact of the intervention of interest.

TUTORIAL 2: Segmented Generalized Mixed Effect Models to Evaluate Health Outcomes

This tutorial describes the methods used in MANUSCRIPT #4

4.3 Preface to Tutorial 2

Although Randomized Clinical Trials (RCTs) are considered the gold standard for studying causal relationships between exposures and outcome, they do have limitations. First, clinical trial populations may have limited generalizability to real-world populations. Second, trials are conducted for a finite period of time, potentially leading to overestimation or underestimation of the results. Finally, not all clinical trials are randomized. Open-label trials are subject to the Hawthorne effect, whereby individuals may modify aspects of their behavior in response to their awareness of being observed.

Observational studies can bridge knowledge gaps left by RCTs. Unlike chronic diseases or infections, DAA treatments are administered for a relatively short period of time and provide a virologic cure for the vast majority of the patients who initiate the treatments. This provides a unique opportunity to study the effect of curing HCV on health outcomes. The following tutorial explains how to utilize repeated outcome measures using a segmented generalized mixed model to evaluate the impact of acute individual-level exposures such as DAA treatments. I describe the advantages of using repeated measures over traditional pre-post designs, discuss what exposures are appropriate to analyze, and parameterize models. This tutorial provides an example of the impact of curing HCV on health-related quality of life, the example that was developed in more detail in Chapter 8 (Manuscript #4).

This tutorial was presented as a poster at the 22nd International Workshop on HIV and Hepatitis C Observational Databases (March 2018; Malaga, Spain). The tutorial was also published in April 2018 in the "Hints and Kinks" section of the International Journal of Public Health and has been cited 4 times.

4.4 Segmented Generalized Mixed Effect Models to Evaluate Health Outcomes (TUTORIAL 2)

Sahar Saeed, Erica EM Moodie, Erin C Strumpf and Marina B Klein

Introduction

Randomized placebo-controlled trials (RCTs) are considered the gold standard for assessing the effect of exposures (e.g. treatments) or interventions (e.g. policies) on a variety of outcomes. By design, randomization "controls" for confounders to yield internally valid inference. However due to high costs, feasibility issues and/or ethical considerations, the RCT study design may be unable to answer pertinent public health related research questions [195]. Such questions include real-world effectiveness of newly marketed medications or the evaluation of health policies. Observational studies can bridge knowledge gaps left by RCTs. The following article will explain how to extend a pre-post study design using a segmented generalized mixed model to evaluate the impact of acute individual-level exposures on health outcomes. We describe the advantages of using repeated measures over traditional pre-post designs, what exposures are appropriate to analyze, and how different impact models can be parameterized. Like all methods, this approach comes with strengths, assumptions and limitations, which we discuss.

Pre-Post Design

A simple pre-post study design compares outcomes at two periods in time: before and after the exposure. To understand how this design can measure the impact of an exposure, we introduce the notion of counterfactual or potential outcomes [196]. We would like to compare outcomes in the same people simultaneously: had they been exposed and had they not. This would eliminate any factors that confound the relation between exposure and outcome, but of course, this is not

possible. Instead, we seek an analytic design that mimics a scenario where we can observe what would have happened in the absence of an exposure. When repeated measures are available for the same individual, and the only factor that changes over time is the exposure, then the pre-exposure observations can act as the counterfactual for the post-exposure outcomes. By design, since the same individual is observed before and after exposure, they act as their own control, meaning time-invariant confounders both known (i.e. sex, ethnicity, socioeconomic status) and unknown/unmeasured (i.e. genetics, motivation, determination) are accounted for. A regression-based approach extends the simple pre-post design to model trends in outcomes as a function of time (or slopes); see figure 4.4.1. The difference between the estimated model for post-treatment slope based on the observed or "factual" data, and the counterfactual slope (extension of the pre-treatment slope) plus any immediate level change is attributed to the effect of the exposure.

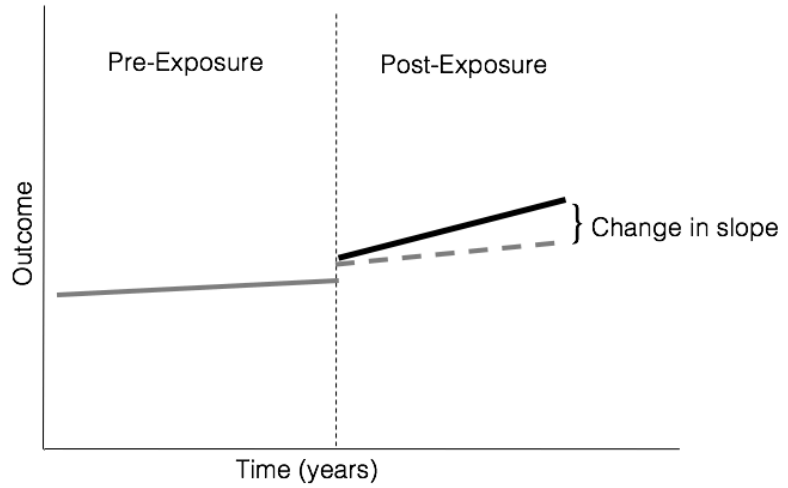


Figure 4.4.1 Pre-Post Design
Vertical dashed line illustrates time at which exposure occurs. Grey line illustrates the pre-exposure slope or trends in outcomes. The grey-dashed line is the counterfactual-extension of the pre-exposure trends to which the solid black line (the actual post-exposure trends) is compared. The difference between the two slopes (counterfactual and actual post-exposure) and the level shift at the intervention point combine to form the impact of outcome attributed to the exposure.

Exposure & Time

The pre-post study design combined with a segmented regression model requires systematic longitudinal data with precise dates of the exposure and outcomes. Since the main assumption is that nothing other than the exposure is changing over time, the exposure must be acute (abrupt or a shock) and uncorrelated with other covariates. Calendar time can be used as the time axis when an exposure impacts a population at a specific period in time such as a policy change many published examples exists [197-205]. Alternatively, and less common in the literature, is when time is centered for a given individual or cluster at a specific event, also known as a multiple-baseline time series [206,207]. Examples include critical biological periods (e.g. puberty, menopause) [208], acute physiological changes such as surgical transplants or viral clearance via curative treatments (the example we will use to illustrate this design).

Segmented Regression Impact model

The impact of the exposure on the outcome can be modelled in multiple ways. Figure 4.4.2 illustrates impact models (or expected outcomes) which may include: immediate changes, denoted as a jump or break between pre/post exposure [4.4.2(b), 4.4.2(c), 4.4.2(f)] and/or a more gradual change over time (slope change) [4.4.2(a), 4.4.2(b), 4.4.2(d), 4.4.2(e)]. The effect can also be modelled as a temporary [4.4.2(f)] or a delayed [4.4.2(e)] effect. The impact model should be determined a priori based on expert knowledge. A segmented model may also be called a piece-wise or broken-stick model; when evaluating population-level exposures with panel data, the pre-post design combined with segmented regression is known as an Interrupted Time Series design [197,198].

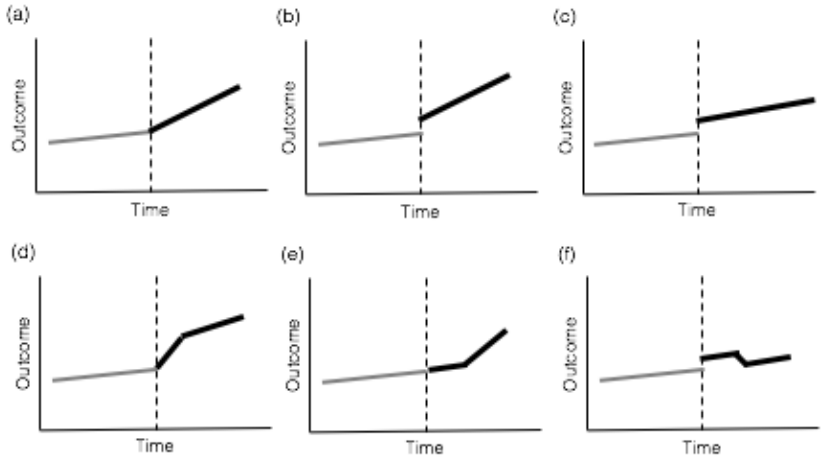


Figure 4.4.2 Segmented Regression Impact Models
(a) Slope change; (b) Level and slope change; (c) Level change; (d) Temporary slope change leading to a level change; (e) Slope change following a lag; (f) Temporary level change (Figure adapted from Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *International journal of epidemiology*. 2017;46(1):348-355).

Statistical Considerations

Generalized mixed models can be used in combination with a segmented design [169]. Clusters may refer to repeated measures of individual people or hierarchical groupings such as by jurisdictions, hospitals, or physicians. The use of random effects reflects natural heterogeneity across clusters, allowing for cluster-specific intercepts to be estimated efficiently by assuming they arise from a normal distribution [209], and by borrowing strength from those subjects with many data points to learn about individuals with fewer measurements. Fixed effects models are an alternative approach and require less stringent assumptions to produce consistent estimates [175], but are not statistically efficient since they require estimating separate parameters for each cluster. When models are linear, estimates from fixed versus mixed models are very similar. However, the interpretations from each model, especially when models are non-linear, and the properties of the estimators – most notably power – differ.

The basic segmented regression model (consistent with figures 4.4.2 a-c) that allows for immediate (level) and gradual (slope) changes has three model parameters relating to (1) $time_{ij}$, where each individual i has j observations; (2) $pre\text{-}post_{ij}$, an indicator variable to divide observations before and after exposure; (3) interaction term ($time_{ij}$*$pre\text{-}post_{ij}$) to allow for the post-exposure slope to change. Additional variables may be incorporated, letting X_{ij} denote a vector of confounders. Figure 4.4.3 illustrates the following model:

$$E[Yij] = (\beta 0 + {}_{bi}) + \beta 1 time_{ij} + \beta_2\ pre\text{-}post_{ij} + \beta_3\ time_{ij} * pre\text{-}post_{ij} + \beta_4\ X_{ij}.$$

Additional parameters are needed to capture relationships like those shown in figures 4.4.2 (d-f)

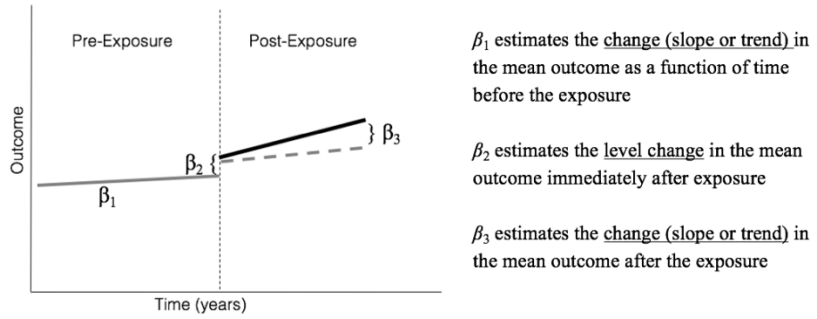


Figure 4.4.3 Visualization of Segmented Regression Coefficients

Example: Hepatitis C Virus (HCV) is the first chronic viral infection that can be cured using direct acting antivirals (DAAs). Although efficacious, it remains unknown what impact HCV cure will have on other health outcomes such as health-related quality of life (HR-QoL). Data was provided from a large prospective cohort of HIV-HCV co-infected individuals with repeated HR-QoL measures before and after treatment [158]. Participants self-reported current health from 0 to 100 (worst to best health) using the visual analog scale (VAS) of the EQ-5D-3L. A priori, we

assume the exposure/outcome relationship would resemble Figure 4.4.3. Stata code is provided (appendix 1). Between 2014-2016, 230 individuals (i) initiated DAA (exposure at time-zero). A total of 1741 observations (j); mean of 3.2 (SD 2.6) years were collected before treatment (pre-exposure) and 536 observations (j); 0.7 (SD 0.5) years were collected after treatment completion (post-exposure). The results are summarized in Table 4.4.1. Using a real-world population, we found some evidence of improvement in HR-QoL immediately following treatment. Patient's health state continued to increase post-treatment by 1.6 units/year (-1.3, 4.4), controlling for the immediate change and the pre-treatment trends.

Table 4.4.1 Results from a generalized linear mixed regression model of the impact of DAAs on HR-QoL

		(VAS units, 95% CI)
Baseline HR-QoL	β_0	68.3 (66.3, 70.3)
Pre-treatment HR-QoL Trends (change HR-QoL/year)	β_1	0.1 (-0.3, 0.4)
Immediate or level change of HR-QoL	β_2	2.0 (-1.0, 4.9)
Impact of DAAs on HR-QoL post-treatment (change HR-QoL/year)	β_3	1.6 (-1.3, 4.4)

Segmented regression assumes that any change in the outcome stems only from the exposure, and that the model correctly specifies the dependence of the outcome on time, the exposure, and other variables. Table 4.4.2 summarizes possible violations of these assumptions and solutions.

Table 4.4.2 Limitations and Solutions

Potential Limitations	Explanation or Practical Example	Solutions/Sensitivity Analyses
Presence of a lead-time effect	Since the exposure is not randomly assigned it is possible that outcomes may change in anticipation of the exposure.	This can be assessed by evaluating whether changes in the trend had already started to occur during the pre-exposure period. Sensitivity analysis: Change the time-axis to begin at some fixed interval prior to the exposure. This would provide a pre-treatment slope excluding any artificial changes attributable to the exposure.
Biased Counterfactual	The impact of the exposure is dependent on the pre-exposure trends estimating an unbiased counterfactual of post-exposure trends.	Pre-exposure trends need to be assessed by subject matter knowledge. Sensitivity analysis: If there are concerns that outcomes may be changing over time, an external control group (a group of people not exposed) can be used to evaluate trends over time; this is known as a "difference-in-difference" approach [175].
Presence of time-varying confounding	Although time-invariant confounders are accounted for by design when using repeated measures, time-varying confounders are not. These include factors that change over time associated with the exposure and outcome and not captured by the pre-exposure trend.	If time-varying confounders are measured these can be included into the regression model, provided these variables themselves are not affected by the change in exposure.
Exposure has a non-linear effect	The model equation described in this paper assumes a linear relationship of the outcome and time. However, this relationship may in fact be non-linear.	Visually examining the data is a first step to evaluate non-linearity. Flexible modelling of time can be a solution. Sensitivity analysis: A squared, or cubic form of time can be included in the model. The use of splines or other more flexible modeling may also be explored if data permits, however model interpretation becomes more difficult.

In this paper, we have demonstrated how a segmented generalized mixed model can be used to investigate impact of acute individual-level exposures on health outcomes. We illustrated this method using a real-world example of the impact of a curative HCV treatment on HR-QoL. The approach can easily be applied with any standard statistical software. The major strength of this

approach is that, by having repeated measures on the same individual before and after an exposure, by design both known and unknown time-invariant confounders are controlled. However, time-varying confounders and the possibility of lead-time effects may bias results. Therefore, caution should be exercised before interpreting the results causally.

Ethical approval: The data used to illustrate the study design comes from the Canadian HIV-HCV Coinfection Study (CCC) which has been approved by the community advisory committee of the Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network and by all institutional ethics boards of the participating centres.

CHAPTER 5: HOW GENERALIZABLE ARE THE RESULTS FROM TRIALS OF DIRECT ANTIVIRAL AGENTS IN THE REAL WORLD? (MANUSCRIPT 1)

5.1 Preface to Manuscript 1

When clinical trials are internally valid, they are considered the gold standard for estimating treatment effects. However, to make inferences to a wider population, results also need to be externally valid as well.

Clinical trials evaluating DAA treatments reported near-perfect cure rates (>95%), even in "hard to treat" co-infected patients. But as real-world studies were published, the efficacy of DAAs in HCV mono-infected populations was on average 5-15% lower than what was reported in phase 3 trials[95,96]. It is well known that individuals who participate in clinical trials tend to differ in key respects from individuals who do not participate; that is, they are usually more health-conscious and tend to be on average healthier. However, it remained questionable whether the difference between trial results and these real-world data were (1) due to a bona fide difference in the populations who choose to participate; or if (2) it was the eligibility criteria of trials themselves that hindered participation for certain individuals.

Before initiating my PhD, I spent close to 10 years working in the field of clinical research. One of my responsibilities was to evaluate how many patients from our clinic would be eligible to participate in pharmaceutical-sponsored clinical trials. It became very evident after reviewing trial protocols that eligibility criteria were very restrictive and in many instances without apparent clinically justifiable reasons. This raised the question: if a large proportion of patients were excluded from participating in clinical trials, how generalizable were the DAA trials? This

was particularly relevant because the very populations most at risk for HIV-HCV often face many health and social challenges that make this population potentially less adherent to treatment. The results from this study were the impetus of the rest of this thesis and highlighted the need to evaluate the real-world impact of DAAs on access to treatment and health outcomes.

This work was first presented orally at the International AIDS Society meeting (Vancouver, Canada; July 2015). Subsequently published in April 2016 as an Editor's Choice Manuscript in Clinical Infectious Disease (advance version available in January 2016). Since the publication of the results, this study has been cited 61 times. It has also been featured by the following general science news outlets:

2016/04/19	Study Exclusions Raise Questions About HCV Treatment Results in People With HIV, www.thebodypro.com/content/77459/study-exclusions-raise-questions-about-hcv- treatme.html
2016/02/22	For Those With HIV, Hep C Drug Trials Don't Offer Enough Real-World Data, www.hepmag.com/article/hiv-hep-c-drug-trials-offer-enough-realworld-data
2016/01/19	Anti-HCV drugs interact with evening dosing of HIV-1 protease inhibitors www.chronicliverdisease.org/reuters/article.cfm?article=20160119Scie1199584202&topic=scie
2016/01/12	How generalizable are the results from trials of Direct Antiviral Agents to people co-infected with HIV/Hepatitis C virus in the real world? www.mdlinx.com/infectious-disease/ medical-news-article/2016/01/12/direct-acting-antivirals/6488304/

5.2 How generalizable are the results from trials of Direct Antiviral Agents to people co-infected with HIV/Hepatitis C virus in the real world?

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Keywords: HIV-Hepatitis C coinfection, Direct Acting Antivirals, Generalizability, People Who Inject Drug, Clinical Trials

Running Title: Generalizability of DAAs trials

Summary: Trial results are used to support licensure, inform cost-effectiveness analyses and guide clinical decision-making. We found the majority of co-infected patients were not included in clinical trials of DAAs, raising concerns about the generalizability of these trial results.

Abstract: 247 words

Article: 2553 words

ABSTRACT

Background: Direct acting antivirals (DAAs) against hepatitis C virus (HCV) have been described as revolutionary. However, it remains uncertain how effective these drugs will be for individuals co-infected with HIV/HCV. Bridging this gap between efficacy and effectiveness requires a focus on the generalizability of clinical trials.

Methods: Generalizability of DAA trials was assessed by applying the eligibility criteria from 5 efficacy trials: NCT01479868; PHOTON-1 (NCT01667731); TURQUOISE-I (NCT01939197); ION-4 (NCT02073656) and ALLY-2 (NCT02032888) evaluating simeprevir; sofosbuvir; ombitasvir, paritaprevir/ritonavir and dasabuvir (3D); sofosbuvir/ledipasvir and daclatasvir/sofosbuvir respectively, to the Canadian Coinfection Cohort, representing ~23% of the total co-infected population in care in Canada.

Results: Of 874 active participants, 70% had chronic HCV, of whom 410, 26, 94, and 11 had genotypes 1, 2, 3, and 4, respectively. After applying trial eligibility criteria, only 5.9% (24/410) would have been eligible for enrolment in the simeprevir trial, 9.8% (52/530) in PHOTON-1, 6.3% (26/410) in TURQUOISE-I, and 8.1% (34/421) in ION-4. Eligibility into the ALLY-2 study was more inclusive, 43% (233/541) of the cohort would have been eligible. The most exclusive eligibility criteria across all trials with the exception of ALLY-2 were restriction to specific antiretroviral therapies (63-79%) and active illicit drug use (53-55%).

Conclusions: DAA trial results may have limited generalizability, since the majority of co-infected individuals were not eligible to participate. Exclusions appeared to be related to improving treatment outcomes by not including those at higher risk of poor adherence and reinfection—individuals for whom real world data is urgently needed.

INTRODUCTION

Worldwide approximately 5 million people are co-infected with HIV and Hepatitis C (HCV) [210]. Co-infected people are heterogeneous, have complex medical needs and are often socially disenfranchised. Injection drug use is responsible for the majority of both incident and prevalent cases in most developed countries. Despite effective HIV suppression and immune restoration, liver disease remains the leading cause of death in HCV co-infected individuals [3,4,41]. To reduce the clinical and healthcare burden of advanced liver disease, co-infected individuals need to be treated and cured of HCV [9-11]. Unfortunately, fewer than 10% of co-infected individuals have ever been treated [82,211].

The development of direct acting antivirals (DAAs) for HCV has been rightfully described as revolutionary. Based on compelling clinical trial results, multiple DAAs: simeprevir, sofosbuvir, ledipasvir, ombitasvir, paritaprevir/ritonavir and dasabuvir (3D), and daclatasvir have been approved by licensing authorities globally [16-22]. Clinical trial results show DAAs are well tolerated, more conveniently dosed and highly efficacious compared to earlier interferon-based HCV therapies. Among interferon-free DAA trials, with as little as 12 to 24 weeks of treatment, sustained virologic response (SVR) rates range between 91-97% across genotypes and fibrosis stages in co-infected individuals, representing a remarkable advance compared to previous therapies [23-25].

Trials evaluating these new agents have so far included relatively small numbers of participants (sub-groups ranging from 6-160) and have applied very strict eligibility criteria, likely excluding a substantial segment of the co-infected population. Substance abuse, comorbid medical and

psychiatric conditions, advanced liver disease, drug-drug interactions with antiretrovirals are common and are among some of the primary factors that may influence access to treatment and outcomes in the real world[212,213]. This raises the question: if a large proportion of co-infected patients are excluded from participating in clinical trials, how generalizable are DAA trials for people living with HIV-HCV co-infection?

METHODS

To evaluate the generalizability of DAA trials, we examined the eligibility criteria of trial protocols. We performed a review of all published phase three trials evaluating second generation DAAs in co-infected individuals with HIV and Hepatitis C coinfection as of November 2015, by searching PubMed and clinical trial registries (clinicaltrials.gov). DAAs that were identified were simeprevir; sofosbuvir; ledipasvir; grazoprevir/elbasvir; ombitasvir, paritaprevir/ritonavir/dasabuvir; faldaprevir; and daclatasvir. We further restricted trials to those where trial protocols were available. The following trials meeting our inclusion criteria were analyzed: NCT01479868; the PHOTON-1 trial (NCT01667731); the TURQUOISE-I trial (NCT01939197); the ION-4 trial (NCT02073656) and the ALLY-2 trial (NCT02032888) evaluating simeprevir; sofosbuvir; ombitasvir, paritaprevir/ritonavir and dasabuvir (3D); sofosbuvir/ledipasvir and daclatasvir/sofosbuvir respectively [23-25,90,91]. Specific eligibility criteria used to assess the generalizability of each trial are listed in Table 5.2. Supplemental table 5.1 summarizes permitted cART regimens by each trial. Supplemental Table 5.2 provides trial specific definitions of active drug use. We then used the Canadian Coinfection Cohort (CCC) as a representative population to evaluate the percentage of current cohort participants that would be eligible to participate in these trials.

As of April 1st, 2015, the CCC had enrolled 1423 HIV-HCV co-infected patients from 18 Canadian centers providing care to HIV infected persons. Details on the CCC have been published elsewhere [158]. Briefly, participating centers include large urban tertiary care and community-based hospitals, private clinics and street outreach programs in the attempt to capture a representative population in care. After obtaining informed consent, socio-demographic, behavioural and medical data are prospectively collected via self-administered questionnaires/chart review and blood is sampled every 6 months. Research involving this cohort was approved by all of the institutional ethics boards of the participating centres.

Of the 1423 cohort participants, we excluded those who died (n=184), withdrew from the study (n=107) and those lost to follow-up (defined as not completing a questionnaire within 18 months of the database closure; n=258). Of the 874 remaining participants, 615 (70%) had evidence of chronic HCV infection (HCV RNA positive, based on each center's standard of care). We further sub-divided the cohort into those who had a documented HCV genotype that reflected the trial populations. A total of 410 co-infected individuals were infected with genotype 1, 26 with genotype 2, 94 with genotype 3 and 11 with genotype 4. Participants with missing genotypes (n=74) were excluded from the analysis. The simeprevir and TURQUOISE-I trials evaluated patients infected with genotype 1 only. PHOTON-1 evaluated patients with genotypes 1, 2 or 3. The ION-4 trial evaluated those with genotypes 1 or 4 and the ALLY-2 study was open to co-infected patients with genotypes 1, 2, 3, 4, 5, or 6.

RESULTS

The diverse demographic, clinical and risk profiles of active CCC participants overall and subdivided by trial target populations according to eligible genotypes are presented in Table 5.1. Eighty percent of cohort participants had a history of injection drug use and 31% used injection drugs at their last cohort visit. Poverty and history of incarceration were very common. Despite these factors, 87% of the cohort received combination antiretroviral therapy (cART) and the majority maintained HIV viral suppression with high CD4 cell counts. cART regimens used were diverse; an equal proportion received tenofovir and abacavir-based backbones and the majority use boosted protease inhibitors or efavirenz-- drugs with potential for drug-drug interactions with some DAAs. The median duration of HCV infection was over 20 years, 15% had evidence of advanced fibrosis based on an APRI score of greater than 1.5 and 13% had a diagnosis of cirrhosis (clinically verified).

After applying all trial eligibility criteria to the CCC participants, only 5.9% (24/411) would have been eligible to be screened for the simeprevir trial, 9.8% (52/531) for the PHOTON-1 trial, 6.3% (26/411) for the TURQUOISE-1 trial, and 8.1% (34/421) for the ION-4 trial. The ALLY-2 trial stood out as being far more inclusive with 43% (233/541) of the cohort eligible for screening. Table 5.2 details the exclusive criteria leading to non-eligibility for each of the trials. The most common reasons for non-eligibility in all trials except the ALLY-2 trial were restriction to specific antiretroviral therapies that resulted in the exclusion of 63-79% of the cohort, followed by active drug use (excluding marijuana) which excluded 53-55% of the cohort. Figure 5.1 illustrates that even if antiretroviral eligibility criteria were not considered (e.g. assuming patients could be safely switched to other regimens compatible with DAAs under

study), 74-77% of the cohort would still have been excluded, primarily due to active drug use for 4 of the 5 trials. Among all trials, as many as 1 in 6 participants would have been excluded because of either: detectable HIV RNA (15-18%) and/or not meeting minimal CD4 count requirements (3-19%). Criteria related to safety concerns, specifically clinical cut-offs for anemia, renal and liver function resulted in relatively few exclusions. Despite the enhanced ease and tolerability of all oral interferon-free DAAs, eligibility into these trials was just as exclusive as the trial with pegylated-interferon and ribavirin with the notable exception of the ALLY-2 trial.

Figure 5.1 Proportion of CCC participants eligible to participate in clinical trials
Green represents the number of CCC participants that would be eligible to be screened in the trial evaluating simeprevir (NCT01479868); PHOTON-1: NCT01667731 (trial evaluating sofosbuvir); TURQUOISE-I: NCT01939197 (trial evaluating ombitasvir, paritaprevir/ritonavir and dasabuvir (3D)); ION-4: NCT02073656 (trial evaluating ledipasvir/sofosbuvir) and ALLY-2: NCT02032888 (trial evaluating daclatasvir/sofosbuvir). Light grey represents participants whose only exclusion was specific antiretroviral (ARV) therapies. Red represents participants not eligible regardless of ARV restriction.

DISCUSSION

When clinical trials are internally valid, they are considered the gold standard for estimating treatment effects. Trial results are used to support licensure, inform health authorities in

conducting cost-effectiveness analyses and guide clinical decision-making. However, to make these inferences to the wider population, trials also need to be externally valid. Here we have illustrated that the majority of HIV-HCV co-infected patients in clinical care would not be included in recent clinical trials evaluating HCV therapy and therefore DAA trial results may have limited generalizability.

In the last 5 years we have witnessed SVR rates previously unimaginable, especially in hard to treat co-infected patients. However, it is important to evaluate how trial efficacy translates to real world effectiveness. Effectiveness is driven by factors such as adherence, loss to follow up and co-morbidities [214]. Real world data on the effectiveness of DAAs in HCV mono-infected populations have been on average 5-15% lower than what was reported in phase 3 trials [95,96]. It is unclear what proportion of these lower SVR rates are explained by patients not adhering to their medications or being lost to follow-up as opposed to poorer efficacy. In one real-world analysis of interferon-free therapies in 151 HCV mono-infected patients, authors reported SVR rates of 88%; 7% relapsed and 4% were lost to post treatment follow-up and could not be assessed for SVR [215]. With the widespread use of DAAs into increasingly marginalized populations, higher failure rates than those seen in clinical trials could translate to hundreds of thousands of treatment failures with limited future treatment options.

Fundamentally, trial participants are different, they include highly motivated people who may receive compensation, extensive support from trial staff, including for adherence. Such extensive programs are not feasible in most real-world healthcare settings, although might serve as an effective model of care. Regardless of eligibility criteria, selection into clinical trials is not

random. Sites select patients who are more likely to comply with strict trial procedures. Additionally, we observed trial populations were on average "healthier" than the cohort population. This was evident by comparing baseline CD4 cell counts of trial participants to the CCC; regardless of minimum cut offs, trial participants had higher CD4 cell counts (between 31-139 cells/mL higher) than the average CCC participant [23-25,90,91].

While restriction into clinical trials for the purposes of protecting the safety of participants is legitimate, we found the majority of exclusionary criteria were not related to safety but appear to be aimed at maximizing treatment response rates. In particular, excluding active drug users may have been overly conservative as studies have shown they can achieve comparable SVRs as those not injecting drugs in well-supported settings [216]. Reinfection and interactions between illicit drugs and DAAs however remain a concern for the active drug using population. However, this should not prevent the inclusion of this important sub-group of individuals, especially when the eradication of HCV in developed countries is contingent on expanding treatment to active drug users. On the contrary, more data is urgently needed on the effectiveness of DAAs in this population to support scaling-up treatment strategies. The eligibility criteria for the ALLY-2 study appeared to be far more inclusive with respect to permitting enrolment of stable people who use drugs illustrating that it is possible to conduct studies that are more reflective of the target population. Despite these broader criteria however, there was actually no evidence that any drug users were included into the study. It will be important for future studies to report on the number of active drug users enrolled. Finally, given the prohibitive cost of treatments, restricting trials to ideal populations may also have profound effects on policy decisions as evidenced by the state level Medicaid restrictions of sofosbuvir where the majority of the U.S.

states require abstinence from drug and alcohol despite international guidelines stating the opposite[30].

For co-infected patients, HCV treatment is further complicated by potential drug-drug interactions between cART and DAAs [217]. While some drug-drug interactions are well documented and exclusion of individuals taking these medications is justifiable, others have either not been studied or have no basis for restriction[217]. Even if it were feasible to switch HIV regimens, the majority of the CCC participants would remain ineligible mostly due to active drug use and HIV viral load / CD4 cell count cut-offs or advanced liver disease. Even though the ALLY-2 trial permitted the majority of cART regimens and stable drug users, 57% of the cohort would still have been excluded from participating in this trial. This is particularly alarming given the CCC comprises individuals who are able to access care and maintain cART successfully.

To evaluate generalizability, we assumed the CCC is a representative population. The CCC is open to all HIV+ patients with evidence of HCV infection followed at participating sites without restriction and is estimated to include 23% of the total co-infected population in care in Canada. Since participants have access to universal healthcare, insurance does not restrict those who can attend clinics. Although other socioeconomic determinants may affect access to care this does not appear to be the case as cohort participants did have very high rates of substance abuse and poverty. Representativeness of this cohort can likely be extended to individuals with health insurance in the United States, and certain Europe countries where the prevalence of active illicit drug use is similar to Canada.

We focused on eligibility criteria listed in trial protocols. Additional factors such as overall willingness and motivation to participate in clinical trials were not assessed and may further reduce the proportion of co-infected trial participants. Other clinical criteria such as evidence of malignancies/other significant illnesses, electrocardiographic abnormalities, clinical cut offs for HCV RNA and glycosylated hemoglobin are data that has not been routinely collected as part of the CCC therefore they were not assessed. Moreover, historically HCV trial protocols in coinfection restricted participation into clinical trials based on presence of HIV resistance. This was only an exclusionary criterion for the TURQUOISE-I trial ("Past virologic failure to more than 1 HIV-1 ART regimen and specifically darunavir resistance"). Additionally, documentation on previous HCV treatment failures and clinical definitions of what constituted cirrhotic vs. non-cirrhotic patients, could also have further excluded trial participation. Taken together, our estimate of trial eligibility is likely to be conservative.

We restricted our analysis to phase 3 trials. Trial populations from the PHOTON-2 trial, evaluating sofosbuvir (NCT01783678) and the C-EDGE Co-infection trial evaluating Grazoprevir/Elbasvir (NCT02105662) were not included in this analysis because trial protocols were not published. Based solely on the limited eligibility criteria available from published papers and publicly from clinical trial registries we would estimate that only 12.6% of cohort participants would have been eligible to be screened to the PHOTON-2 trial and 10.2% for the C-EDGE trial. Similar to the other trials the most exclusive eligibility criteria was restriction to specific antiretroviral regimens, excluding 63% of the CCC from PHOTON-2 and 80% from the C-EDGE trials[17,218]. Thus, for the co-infected population, drug-drug interactions will remain a limiting factor for those who cannot be safely switched to alternative regimens.

HCV is the first chronic viral disease that can be cured. However, many paradoxes exist. DAAs are the most expensive antivirals ever to be developed on a per pill basis costing between $54,000-122,000 per treatment course in Canada. HCV disproportionately affects the poorest and most disenfranchised populations globally. Clinical trials have demonstrated very high efficacy in people that do not reflect target populations and in ideal trial settings. Despite breakthroughs in HCV treatments, many psychosocial disadvantages still require intervention in order to increase treatment uptake and obtain successful outcomes. Unless mandated to do so, the pharmaceutical industry has little incentive to evaluate DAAs in representative populations and even when restriction is more inclusive, there is still no guarantee of enrolling representative populations. Therefore, observational study designs that estimate unbiased treatment effects in the co-infected population will be essential to determine how effective these therapies will be in the real-world[219]. This work illustrates the need to evaluate the external validity of all marketed pharmaceuticals in order to determine whether trial populations represent target populations. If generalizability is found to be limited, then targeted phase 4 studies need to be considered.

The advent of DAAs and especially interferon free regimens has given hope that the burden of liver disease can be reduced among HIV-HCV individuals and that HCV can ultimately be eliminated. It remains to be seen how effective these therapies will be for the average patient who urgently requires them.

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Ethics: Approval from each center's ethics committee was obtained and informed consent from each participant of the CCC.

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Author contributions: As the corresponding author, Dr. Klein has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 5.1 Characteristics of the Canadian Coinfection Cohort Participants at last visit and according to specific trial target populations

	Total Active patients (N=874)	Simeprevir & TURQUOISE-I Genotype 1 (N=410)	PHOTON-1 Genotype 1, 2, or 3 (N=530) GT1=410 GT2=26 GT3=94)	ION-4 Genotype 1 or 4 (N=421) GT1=410 GT4=11	ALLY-2 Genotype 1, 2, 3, 4, 5, 6 (N=530) GT1=410 GT2=26 GT3=94 GT4=11
Age, median (IQR), years	49 (43, 55)	47 (42, 52)	49 (43, 55)	49 (44, 54)	49 (43, 55)
Female, No. (%)	244 (28%)	102 (25%)	147 (28%)	108 (26%)	153 (28%)
Aboriginal, No. (%)	171 (20%)	81 (20%)	113 (21%)	81 (19%)	113 (21%)
Gross annual income* <$18,000 CAD, No. (%)	634 (73%)	311 (76%)	308 (76%)	317 (75%)	412 (76%)
History of incarceration, No. (%)	489 (64%)	234 (65%)	308(65%)	236 (64%)	310 (57%)
Current psychiatric diagnosis, No. (%)	80 (9%)	55 (13%)	65 (12%)	55 (13%)	65 (12%)
Currently living in shelter or homeless, No. (%)	73 (8%)	43 (10%)	47 (9%)	43 (10%)	47 (9%)
History of IDU, No. (%)	703 (80%)	336 (82%)	438 (82%)	336 (80%)	438 (81%)
Current IDU[b], No. (%)	259 (30%)	130 (32%)	68 (32%)	130 (31%)	168 (31%)
Current alcohol use, No. (%)	497 (57%)	213 (52%)	278 (52%)	220 (53%)	285 (53%)
Current alcohol abuse[§], No. (%)	132 (15%)	61 (15%)	81 (15%)	62 (15%)	82 (15%)

Time since HIV diagnosis, median (IQR), (years)	15.8 (9.6, 21.4)	15.8 (8.7, 21.5)	15.7 (8.5, 21.2)	15.7 (8.8, 21.5)	15.7 (8.5, 21.3)
Undetectable HIV RNA, No. (%)	680 (78%)	292 (71%)	388 (73%)	301 (72%)	397 (73%)
CD4 T-cell count, median (IQR), (cells/mm^3)	500 (332, 690)	490 (300, 674)	480 (298, 670)	490 (300, 680)	480 (300, 675)
Currently cART Naïve, No. (%)	23 (3%)	13 (3%)	17 (3%)	13 (3%)	17 (3%)
On cART, No. (%)	752 (86%)	356 (87%)	455 (86%)	366 (87%)	465 (86%)
NRTI backbone, No. (%)					
Tenofovir/emtricitabine	318 (36%)	147 (36%)	191 (36%)	153 (36%)	197 (36%)
Abacavir/lamivudine	317 (36%)	142 (35%)	186 (34%)	146 (35%)	190 (35%)
NNRTI-based, No. (%)					
Efavirenz	127 (15%)	54 (14%)	67 (12%)	57 (14%)	70 (13%)
Nevirapine	20 (2%)	11 (3%)	11 (2%)	12 (3%)	12 (2%)
Ripilvirine	22 (4%)	19 (5%)	23 (5%)	19 (5%)	23 (3%)
Etravirine	36 (4%)	18 (4%)	25 (5%)	18 (4%)	25 (5%)
PI/Ritonavir, No. (%)					

Atazanavir	164 (19%)	75 (18%)	100 (19%)	76 (18%)	101 (19%)
Lopinavir	76 (9%)	30 (7%)	42 (8%)	32 (8%)	44 (8%)
Darunavir	159 (18%)	79 (19%)	103 (19%)	81 (19%)	105 (19%)
Integrase Inhibitors					
Raltegravir	190 (22%)	90 (22%)	117 (22%)	93 (22%)	120 (22%)
Dolutegravir	27 (3%)	17 (4%)	17 (3%)	17 (4%)	17 (3%)
Elvitegravir	43 (5%)	19 (5%)	23 (4%)	19 (5%)	23 (4%)
Duration HCV Infection, median (IQR), years	21.7 (13.7, 30.0)	21.4 (13.0, 29.1)	21.3 (13.2, 29.3)	21.0 (13.0, 29.0)	21.0 (13.0, 29.0)
Prior HCV treatment experience, No. (%)	334 (38%)	113 (28%)	148 (28%)	119 (28%)	152 (28%)
Current APRI >1.5, No. (%)	130 (15%)	78 (19%)	109 (21%)	81 (19%)	112 (21%)
History of cirrhosis (clinical diagnosis), No. (%)	115 (13%)	64 (16%)	78 (15%)	66 (16%)	80 (15%)
History of ESLD diagnosis, No. (%)	129 (15%)	74 (18%)	89 (17%)	76 (18%)	91 (17%)

Trials restricted participation to specific genotypes therefore the cohort is sub-divided into those genotypes. The Simeprevir and TURQUOISE-I trial's evaluated patients infected with genotype 1. PHOTON-1 evaluated patients with genotypes 1, 2, or 3. The ION-4 trial evaluated those with genotypes 1, or 4 and the ALLY-2 study was open to co-infected patients with genotypes 1, 2, 3, 4, 5, or 6.

Active Patients (n=874) includes all active cohort participants.

Undetectable HIV RNA (RNA<50 copies/mL) Abbrev. GT- genotype; IDU- Injection drug use; cART- combined antiretroviral therapy; NNRTI- Non-nucleoside reverse-transcriptase inhibitors; PI- Protease Inhibitors; HCV-Hepatitis C Virus; APRI- AST to Platelet Ratio Index; ESLD-End Stage Liver Disease (ascites, bleeding esophageal varices, portal hypertension, hepatocellular carcinoma, spontaneous bacterial peritonitis)

* Single person poverty is considered annual income of less than $18,421/yr CAD

ᵬCurrent IDU: Use of any injection drugs within 6 months of last cohort visit (self-reported)
§ Current Alcohol Abuse: Drinking more than 2 units of alcohol on a "typical day" within 6 months of last cohort visit (self-reported)

Table 5.2 Selection of Exclusion Criteria (Each Exclusive)

Criteria	Trial Specific Exclusion Criteria	Simeprevir Trial (GT1) N=410 No. (%)	PHOTON-1 Trial (GT 1, 2, or 3) N=530 No. (%)	TURQUOISE-I Trial (GT 1): N=410 No. (%)	ION-4 Trial (GT 1 or 4) N=421 No. (%)	ALLY-2 Trial (GT 1, 2, 3, or 4) N=541 No. (%)
cART Regimens[1,2,3,4,5]	Supplemental Table 1	291 (71)	336 (63)	301 (73)	334 (79)	44 (8)
Active illicit drug use (excluding marijuana)	Supplemental Table 2	221 (54)	294 (55)	221 (54)	223 (53)	NA
CD4 T-cell count (cells/mm^3)	<300[1]; <200[2, 3, 5] <100[4]	77 (19)	57 (11)	39 (9)	12 (3)	47 (9)
HIV RNA (copies/mL)	>50[1,2,4,5]; >40[3]	70 (17)	82 (15)	73 (18)	71 (17)	80 (15)
Active Psychiatric Disorder¶		NA	NA	NA	NA	65 (12)
Neutrophils (cells/mm^3)	<1.5[1]; <1.2[3]; <0.75[5]	35 (9)	NA	10 (2)	NA	2(<1)
Albumin (g/dL)	<3.3[1]; <3.0[2,4,5]; <2.8[3]	53 (11)	25 (4)	12 (3)	19 (5)	22 (4)
Hemoglobin (g/dL)	<110 (female) or <120 (male)[1,2,3,4] <100[5]	44 (11)	47 (9)	35 (9)	36 (9)	9 (2)
Platelets (cells/mm^3)	<90,000[1] <60,000[2,3] <50,000[4,5]	33 (8)	NA	8 (2)	7 (2)	8 (2)
Decompensated Liver Disease[ᵬ]		30 (7)	38 (7)	30 (7)	31 (7)	39 (7)

AIDS illness[§]		14 (3)	16 (3)	14 (3)	14 (3)	21 (4)
Hypertension	Systolic blood pressure ≥160 mmHg Or diastolic blood pressure ≥100 mmHg	NA	NA	NA	NA	14 (3)
Co-Infection with Hepatitis B	HbsAg positive	13 (3)	17 (3)	13 (3)	14 (3)	18 (3)
Serum Creatinine (mg/dL) or Cockcroft-Gault Equation	<1.5[1]; <60 mL/min[2,3,4] <50 mL/min[5]	9 (2)	56 (11)	40 (10)	43 (10)	41(8)
Age (years)	<18[2, 4, 5]; <18 & >70[1,3]	5 (1)	3 (<1)	5 (1)	2 (<1)	3(<1)
BMI (kg/m^2)	<18[2,4]; ≤18 &>38[3] ≤18 &>35[5]	NA	22 (4)	20 (5)	20 (5)	40 (7)
Bilirubin	>3 mg/dL[1,2,3,4] > 2 mg/dL[5]	3 (<1)	3 (<1)	3 (<1)	3 (<1)	3 (<1)
International normalized ratio (INR)	>1.5	4 (<1)	4 (<1)	4 (<1)	5 (<1)	NA
Alpha-Fetoprotein	<50 ng/mL[1] <100 ng/mL[3,5]	6 (1)	NA	4(<1)	NA	4(<1)
Aspartate Aminotransferase (U/L)	<10x ULN[1,2,4]; <7x ULN[3]	3 (<1)	5 (<1)	5 (1)	3 (<1)	NA
Alanine Aminotransferase (U/L)	<10x ULN[1,2,4,5]; <7x ULN[3]	1 (<1)	1 (<1)	7 (2)	1 (<1)	1 (<1)

n (%) represent the excluded population based on each of the individual criteria cART-combined antiretroviral therapy; ULN-upper limit of normal; BMI-body mass index; INR-International normalized ratio

[1] Simeprevir trial allowed: raltegravir, efavirenz and ripilvirine; [2] PHOTON-1 trial (sofosbuvir) allowed: tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, efavirenz, raltegravir or ripilvirine; [3] TURQUOISE-I trial (ombitasvir, paritaprevir/ritonavir and dasabuvir) allowed: tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, raltegravir; [4] ION-4 trial (ledipasvir/sofosbuvir) allowed: tenofovir/emtricitabine with efavirenz, raltegravir or ripilvirine; [5] ALLY-2 trial (daclatasvir/sofosbuvir) only excluded unboosted protease inhibitors and cobicistat ¶ Active severe psychiatric disorders including but not limited to, schizophrenia, psychosis, bipolar disorder, post-traumatic stress disorder, mania etc.[b]Decompensated liver disease including but not limited to, radiologic criteria a history or presence of ascites, bleeding varices, or hepatic encephalopathy [§]Presence of AIDS-defining opportunistic infections

5.3 Appendix to Manuscript 1: Supplemental Data

Supplemental Table 5.1 Permitted antiretroviral regimens in trials evaluating HCV therapy in HIV-HCV co-infection

Trial (treatment)	Permitted cART regimens
Simeprevir in combination with pegylated interferon and ribavirin	NRTIs: tenofovir/emtricitabine or tenofovir/lamivudine or abacavir/ lamivudine in combination with either: Integrase: raltegravir NNRTIs: efavirenz or ripilvirine
PHOTON-1 (sofosbuvir in combination with pegylated interferon and ribavirin)	NRTIs: tenofovir/emtricitabine in combination with either: Integrase: raltegravir NNRTIs: efavirenz or ripilvirine PIs: darunavir/ritonavir or atazanavir/ritonavir
TURQUIOSE-1 (ombitasvir, paritaprevir, dasabuvir and ribavirin (3D))	NRTIs: tenofovir/emtricitabine or tenofovir/lamivudine in combination with either: Integrase: raltegravir PIs: darunavir/ritonavir or atazanavir/ritonavir
ION-4 (ledipasvir/ sofosbuvir)	NRTIs: tenofovir/emtricitabine in combination with either: Integrase: raltegravir NNRTIs: efavirenz or ripilvirine
ALLY-2 (daclatasvir/ sofosbuvir)	NRTIs: tenofovir, emtricitabine, lamivudine, abacavir, zidovudine Integrase: dolutegravir, raltegravir NNRTIs: efavirenz, nevirapine or rilpivirine PIs: atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir Entry Inhibitors: maraviroc, enfuvirtide

NRTIs-Nucleoside/Nucleotide Reverse Transcriptase Inhibitors;
NNRTIs-Non Nucleoside/Nucleotide Reverse Transcriptase Inhibitors;
PIs-Protease Inhibitors

Supplemental Table 5.2 Definitions used for excluding illicit drug users from trials evaluating HCV therapy in HIV-HCV co-infection

Trial (treatment)	Definitions	Drug/Alcohol Screen at Screening visit
Simeprevir in combination with pegylated interferon and ribavirin	A current or past abuse of alcohol and/or recreational or narcotic drugs, which in the investigator's opinion would have compromised the subject's safety and/or compliance with the study procedures.	Yes
PHOTON-1 (sofosbuvir in combination with pegylated interferon and ribavirin)	Clinically- relevant drug or alcohol abuse within 12 months of screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator	Yes
TURQUIOSE-1 (Ombitasvir, Paritaprevir, Dasabuvir and Ribavirin) (3D)	Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol	Yes
ION-4 (ledipasvir/ sofosbuvir)	Clinically- relevant drug or alcohol abuse within 12 months of screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator	Yes
ALLY-2 (daclatasvir/ sofosbuvir)	Active substance abuse as defined by DSM-IV*, Diagnostic Criteria for Drug and Alcohol Abuse, which in the opinion of the investigator would make the candidate inappropriate for participation in this study. *Criteria for Alcohol & Substance Abuse: 1. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period: a. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household) b. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use) c. Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct) d. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights) 2. The symptoms have never met the criteria for Substance Dependence for this class of substance.	No

CHAPTER 6: DISPARITIES IN DAA UPTAKE (MANUSCRIPT 2)

6.1 Preface to Manuscript 2

The development of DAAs generated enthusiasm that HCV can one day be eliminated. However, the gap between near-curative treatments for individuals and virus elimination at the population level is immense if only a small segment of the population initiates treatment.

Given the results from Chapter 5, it was unknown if access to treatment had expanded to include marginalized populations that were largely excluded from clinical trials. In addition, it was not clear if the efficacy rates of DAAs published from the clinical trials would be replicated in real world populations. The second objective of this thesis was to evaluate treatment uptake among key vulnerable HIV-HCV co-infected populations, in a publicly funded healthcare setting with no explicit system-level barriers to access DAA treatment based on socio-demographic characteristics or health behaviors. The World Health Organization (WHO) defines key populations as those "most-at-risk of HIV and viral hepatitis transmission". Such key populations include PWID and men who have sex with men (MSM), in addition to country-specific populations considered to be vulnerable. Since this study was based in Canada, the key populations also included women and people of Indigenous ethnicity. I answered the following research questions: Has treatment uptake increased in the DAA era? What are predictors of second-generation DAA initiation? Finally, how effective are DAAs in key populations of interest in the real world?

The results from this objective were first presented in a poster at the 24th Conference on Retroviruses and Opportunistic Infections 2017 (CROI 2017; February 2017, Seattle, USA), for which I received a

Young Investigator's Award. The final results were then presented orally at the 21st International Workshop on HIV and Hepatitis C Observational Databases, March 2017 in Lisbon, Portugal and at the Canadian Association for HIV Research, April 2017 in Montreal. The final results were published in the Journal of the International AIDS Society November 2017. Since the publication of the results this study has been cited 17 times and has been featured by the following general science news outlet:

2017/03/10	Major Disparities Seen in Hep C Treatment Uptake Among Canadians With HIV, www.poz.com/article/major-disparities-seen-hep-c-treatment-uptake-among-canadians-hiv

6.2 Disparities in Direct Acting Antivirals Uptake in HIV-Hepatitis C Coinfected Populations in Canada

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Keywords: HIV-Hepatitis C co-infection, Direct Acting Antivirals (DAA), People Who Inject Drug (PWID), Disparities, Indigenous peoples, Women, Men who have Sex with Men (MSM)

ABSTRACT

Background: Direct acting antivirals (DAAs) have revolutionized hepatitis C (HCV) treatment with >90% cure rates even in real-world studies, giving hope that HCV can be eliminated. However, for DAAs to have a population-level impact on the burden of HCV disease, treatment uptake needs to be expanded. We investigated temporal trends in HCV treatment uptake and evaluated factors associated with second-generation DAA initiation and efficacy among key HIV-HCV co-infected populations in Canada.

Methods: The Canadian HIV-HCV Co-Infection Cohort Study prospectively follows 1699 participants from 18 centres. Among HCV RNA+ participants, we determined the incidence of HCV treatment initiation per year overall and by key populations between 2007-2015. Key populations were based on World Health Organization (WHO) guidelines including: people who actively inject drugs (PWID) (reporting injection drug use, last 6 months); Indigenous people, women and men who have sex with men (MSM). Multivariate Cox models were used to estimate adjusted hazard ratios (aHR) and two-year probability of initiating second-generation DAA for each key population.

Results: Overall, HCV treatment initiation rates increased from 8 (95% CI, 6-11) /100 person-years in 2013 to 28 (95% CI, 23-33) /100 person-years in 2015. Among 911 HCV RNA + participants, there were 202 second-generation DAAs initiations (93% with interferon-free regimens). After adjustment (aHR, 95% CI), active PWID (0.60, 0.38-0.94 compared to people not injecting drugs) and more generally, people with lower income (<$18,000 CAD/year) (0.50, 0.35-0.71) were less likely to initiate treatment. Conversely, MSM were more likely to initiate 1.95 (1.33-2.86) compared to heterosexual men. In our cohort, the population profile with the lowest two-year probability of initiating DAAs was

Indigenous women who inject drugs (5%, 95% CI 3-8%). Not having any of these risk factors resulted in a 35% (95% CI 32-38) probability of initiating DAA treatment. Sustained virologic response (SVR) rates were >82% in all key populations.

Conclusion: While treatment uptake has increased with the availability of second-generation DAAs, marginalized populations, already engaged in care, are still failing to access treatment. Targeted strategies to address barriers are needed to avoid further health inequities and to maximize the public health impact of DAAs.

INTRODUCTION

Broad access to combination antiviral therapy (cART) lead to tremendous improvements to the lives of people living with Human Immunodeficiency Virus (HIV), including dramatic reductions of Acquired Immune Deficiency Syndrome (AIDS) related morbidity and mortality [1,2]. However, despite controlled HIV viremia and immune restoration, liver disease has now emerged as a leading cause of death among HIV positive individuals largely due to Hepatitis C virus (HCV) coinfection[41]. HIV-HCV coinfection affects approximately 2.3 million people worldwide and represents a particular challenge in Eastern Europe and Russia, in Indigenous communities in Canada and in rural North America where injection drug use drives the emerging epidemic [67,220,221].

The development of oral direct acting antivirals (DAAs) revolutionized HCV treatment with over 90% cure rates even in real-world settings, giving hope that HCV can be eliminated [222-228]. However, for DAAs to have a population-level impact on the burden of HCV disease, treatment uptake needs to be expanded [101,229]. Historically, HCV treatment uptake in North America and Europe among HIV-HCV co-infected individuals was as low as 1% [80,82,83,86,230,231]. This is particularly true among people who inject drugs (PWID), a key population to target if the goal is to reduce incident HCV infections [101,232].

Barriers to accessing HCV treatment emerge at each step of the HCV care continuum [135]. A combination of patient-, provider- and system-level barriers have previously been identified as reasons why patients fail to access treatment [83]. Patient-level barriers include competing priorities, lack of awareness and co-morbidities [80]. Preconceived fears of poor adherence and risk of reinfection have been reported as reason for provider-level barriers [80]. Although improved efficacy and tolerability of DAAs have addressed many clinical barriers to treatment initiation, these have largely been replaced by

financial ones [87]. Indeed, in many countries, financial barriers are the principal reasons for reduced access to HCV therapy. Since Canada's healthcare system is publicly funded, it should be less driven by an individual's ability to pay, however, other factors such as lower socio-economic status (SES) and Aboriginal identity, have been associated with health disparities [144,145]. The extraordinary cost of DAAs has led to policies restricting access to HCV treatments worldwide, resulting in system-level barriers [28-30]. Despite international guidelines to treat 'all' populations infected with HCV [233], considerable variability in DAA reimbursement exists [228]. Reimbursement of DAAs in Canada, varies across provinces by liver disease stage, HCV genotype and prescriber type [28]. While in other jurisdictions such as in the United States, patient characteristics such as illicit drug and alcohol use are used as a restriction, due to concerns about potential for non-adherence and reinfection [30].

Currently limited data exists on treatment initiation rates among key HIV-HCV co-infected populations. The World Health Organization (WHO) defines key populations as those "most-at-risk of HIV and viral hepatitis transmission" which include PWID and men who have sex with men (MSM) in addition to country specific populations considered to be vulnerable [159]. In Canada, Indigenous peoples are almost three times more likely to acquire HIV compared with other Canadians and can therefore be considered a key population [42] Women may also face unique barriers to treatment and are often not enrolled in clinical trials. Developing strategies to treat all co-infected populations is essential to both manage incident cases of HCV [55,101,232] and reduce morbidity and mortality in those at greatest risk for liver disease progression [9,11]. The purpose of this study was to investigate if disparities in HCV treatment initiation rates exist among key HIV-HCV co-infected populations already engaged in care and to identify factors associated with failure to initiate second-generation DAAs.

METHODS

Study Population

The Canadian Co-infection Cohort Study (CCC) is a publicly funded prospective cohort of 1699 HIV-HCV co-infected individuals from across Canada [158]. Enrolment of HIV positive adults with evidence of HCV infection (antibody positive) began in 2002. In 2006, the cohort expanded nationally and continues to recruit actively from 18 centres. Participating centres comprise of urban tertiary care and community-based hospitals, private clinics, and street outreach programs in the attempt to capture a representative sample of patients in care [158]. After obtaining informed consent, socio-demographic, behavioral, and clinical data are collected prospectively via self-administered questionnaires and chart review every six months. Since 2012 the main focus of the CCC has been to study the "real-world" impact of DAAs on health outcomes in HIV-HCV coinfection. Details on HCV treatments and subsequent responses are extracted from participant's medical records using standardized case report forms. The CCC is approved by the community advisory committee of the Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network and by all institutional ethics boards of participating centres.

Key populations (main exposures): Key populations were identified a priori based on WHO guidelines [159]. Definitions were extracted from self-reported data collected by semi-annual questionnaires. Key populations included active PWID as defined as injection drug use within the last 6 month); Indigenous people of Canada defined as either people of First Nations, Inuit or Metis origins; women based on biological sex and MSM.

Outcomes: All outcomes (defined below) were examined overall and by key populations of interest.

Temporal Trends in HCV Treatment Initiation Rates

Participants were potentially eligible to initiate any HCV treatment if they were both actively participating in the CCC (alive, with a cohort visit within 1 year) and HCV RNA positive. HCV RNA was measured in local laboratories using either a qualitative assay (COBAS® Ampliprep/TaqMan® HCV Test, v2.0, Roche Molecular Systems, or other local lab assays; lower limit of detection varied by assay and year) or quantitative assay (Abbot RealTime PCR; Abbott Molecular Inc, or other local lab assays; lower limit of detection varied by assay and year). HCV treatment initiation rates were calculated from January 1st, 2007 until December 31st, 2015.

Uptake of second-generation DAAs

Second-generation DAAs were defined as Health Canada approved regimens containing simeprevir, sofosbuvir, ledipasvir, ombitasvir/paritaprevir/ritonavir or daclatasvir. Participants were potentially eligible to initiate second generation DAAs if they were both HCV RNA positive as of November 21, 2013 (date Health Canada approved simeprevir) and had not accessed second generation DAAs through a clinical trial. Participants were followed until DAA initiation or censored if lost to follow-up (no study visit for at least 1.5 years), died, withdrew or at the end of the study period (December 31st, 2015).

Efficacy Second-generation DAAs

Sustained virologic response (SVR) was defined as documented negative HCV RNA result at least 12 weeks after completing HCV treatment. SVRs results were determined up until December 31, 2016.

Statistical Analysis

HCV treatment incidence rates were reported as per 100 person-years, by calendar year. Demographics,

SES, illicit drug and alcohol consumption, HIV and HCV related treatments and clinical factors were compared between people who initiated second generation DAAs to those who did not initiate treatment. SVR rates were compared between key populations using Fisher's exact test.

We estimated unadjusted and adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for time to second-generation DAA initiation using Cox proportional hazards models. The adjusted Cox model included the key exposures of interest (indicators for Indigenous status, sex, active injection drug use and MSM) along with other predictors of treatment initiation selected a priori. Predictors included: (1) socio-demographic – age (centered at mean) and income (<$18,000 CAD)[166]; (2) behavioural – past (but not current) injection drug use and current alcohol use (within the last 6 months); (3) clinical – HCV genotype 2, 3 or 4 compared to genotype 1, advanced fibrosis (measured as an AST to Platelet Ratio Index (APRI) score ≥1.5) and undetectable HIV RNA (<50 copies/mL); and (4) healthcare systems – Canadian province of residence (Saskatchewan, Alberta/Ontario and Quebec compared to British Columbia; grouped to reflect DAA policy restrictions [28]). Robust standard errors were used to adjust for possible clustering by centre. Multiple imputation by chained equations was used to impute missing data on HCV genotype (89/712 were missing genotypes) in multivariate models [161]. The imputation model included all covariates in the multivariable model, an indicator for DAA initiation, and a measure of the cumulative baseline hazard using the Nelson-Aalen estimator. Twenty imputed data sets were created and Rubin's rules were used to combine regression results [162]. Using the adjusted Cox model, the baseline survival function at 2 years was estimated using post-estimation commands (predict) to calculate probabilities of second-generation DAA initiation and 95% CI [160]. The two-year probability of second-generation DAA initiation was summarized graphically for the key groups of interest who were less likely to initiate treatment (combination of being Indigenous, a women and active injection drug use). As a sensitivity analysis, stratified Cox models were evaluated independently for each of the key

populations. Graphical methods were used to check the proportional hazards assumption of Cox models. All statistical analyses were performed using STATA version 13.

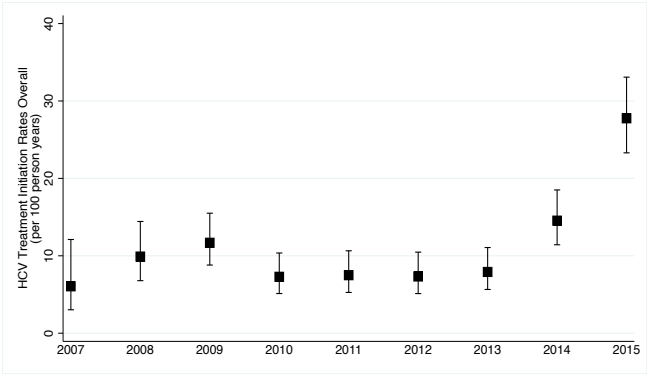
RESULTS

As of September 30, 2016, 1699 participants had enrolled into the CCC. The median age of cohort participants at baseline was 45 years old (IQR 39, 51) and 81% had a history of injection drug use (IDU). Twenty-eight percent were women, 21% were Indigenous and 23% were MSM.

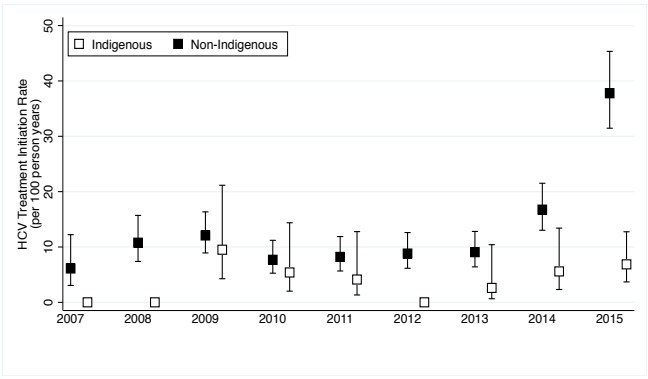
Trends in overall HCV Treatment Initiation Rates

HCV treatment initiation rates remained relatively stable (5-11 initiations per 100 person-years) between 2007 until 2013. With the introduction of second-generation DAAs, initiation rates increased more than threefold between 2013 and 2015, from 8 (95% CI: 6, 11) to 28 (95% CI: 23, 33) per 100 person-years (Figure 6.1, Panel A). After stratifying initiation rates by key populations, HCV treatment uptake was markedly lower among Indigenous peoples (Panel B), active PWID (Panel C) and women (Panel D) compared to non-Indigenous peoples, non-active PWID, heterosexual men respectively. Conversely, MSM (Panel D) initiated HCV treatment at a higher rate compared to heterosexual men.

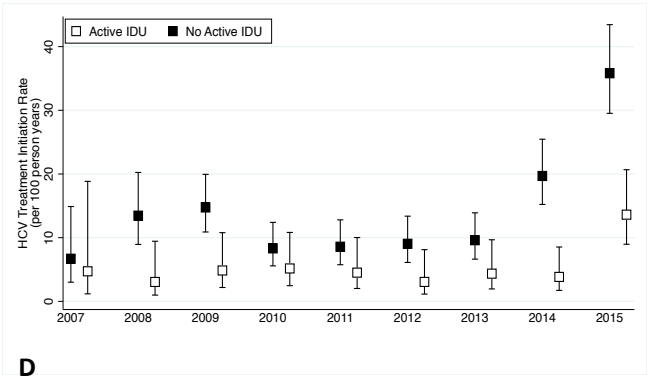
A


HCV Treatment Initiation Rates Overall
(per 100 person years)
0
10
20
30
40
2007
2008
2009
2010
2011
2012
2013
2014
2015

B


Indigenous
Non-Indigenous
HCV Treatment Initiation Rate
(per 100 person years)
0
10
20
30
40
50
2007
2008
2009
2010
2011
2012
2013
2014
2015

C


Active IDU
No Active IDU
HCV Treatment Initiation Rate
(per 100 person years)
0
10
20
30
40
2007
2008
2009
2010
2011
2012
2013
2014
2015

D

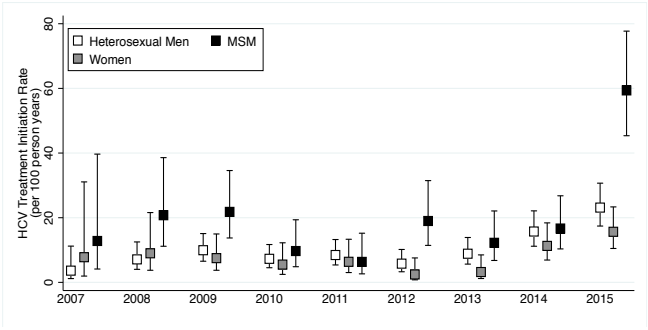

Heterosexual Men
MSM
Women
HCV Treatment Initiation Rate
(per 100 person years)
0
20
40
60
80
2007
2008
2009
2010
2011
2012
2013
2014
2015

Figure 6.1 HCV Treatment Initiation Rates between 2007-2015
A: Overall among the Canadian Co-Infection Cohort; B: Indigenous (white box) compared to Non-Indigenous people (black box); C: Active PWID (white box) compared to non-Active PWID (black box); D: Women (grey box) and MSM (black box) compared to heterosexual men (white box). Rates per 100 person years, whiskers represent 95% confidence intervals. Abbreviations: People who inject drugs (PWID); Men who have sex with men (MSM)

Factors associated with second-generation DAA Initiation

Our DAA treatment eligible cohort consisted of 911 participants (Supplemental Figure 6.1). Characteristics of participants excluded from this analysis (those lost/withdrew before time zero and who accessed DAAs through a clinical trial) are summarized in Supplemental Table 6.1. The median follow-up time was 2.1 years (IQR 1.9-2.1). There were a total of 202 second-generation DAAs initiations– 3 people initiated twice. Of the 712 participants who did not initiate DAAs, 120 participants were censored (83 (9%) were lost to follow up, 8 (<1%) withdrew and 29 (3%) died) and the remaining 592 participants were followed until the end of the study. Demographic, behavioral, HIV and HCV clinical characteristics of the 199 participants who initiated second-generation DAAs were compared to the 712 who did not initiate (Table 6.1).

Table 6.1 Baseline characteristics of the Canadian Coinfection Cohort Participants who initiated second-generation DAA treatments compared to those who did not

	Initiated DAA **N=199[a, b]**	**Eligible for treatment but did not initiate DAAs** **N=712[c]**
Age, median (IQR), years	50 (47, 55)	47 (40, 53)
Women, No. (%)	39 (19%)	228 (32%)
Indigenous people, No. (%)	19 (9%)	228 (32%)
Men who have sex with men (MSM), No. (%)	82 (41%)	121 (17%)
Single, No. (%)	132 (65%)	490 (69%)
Education (>high school diploma), No. (%)	79 (39%)	148 (21%)
Gross annual income[d], <$18,000 CAD, No. (%)	131 (65%)	569 (80%)
Canadian Provinces [28], No. (%)		
British Columbia	58 (29%)	198 (28%)
Saskatchewan	1 (<1%)	146 (21%)
Alberta	4 (2%)	17 (2%)
Ontario	50 (25%)	158 (22%)
Quebec	87 (43%)	192 (27%)
Nova Scotia	2 (1%)	1 (<1%)
Current psychiatric diagnosis, No. (%)	39 (19%)	163 (23%)
Currently living in shelter or homeless, No. (%)	14 (7%)	90 (13%)
Ever injection drug use (IDU), No. (%)	144 (71%)	616 (87%)
Past PWID[e], No. (%)	105 (52%)	340 (48%)
Active PWID[f], No. (%)	39 (19%)	273 (38%)
Current alcohol use, No. (%)	106 (53%)	387 (54%)
Current alcohol abuse[g], No. (%)	21 (10%)	150 (21%)
Current tobacco smokers, No. (%)	161 (80%)	663 (93%)
Time since HIV diagnosis, median (IQR), (years)	17 (12, 23)	13 (7, 19)
Undetectable HIV RNA, No. (%)	174 (86%)	499 (70%)
CD4 T-cell count, median (IQR), (cells/mm^3)	440 (270, 630)	456 (269, 650)
On cART, No. (%)	190 (94%)	604 (85%)
Duration HCV Infection, median (IQR), years	22 (12, 31)	21 (12, 29)
HCV Genotype, No. (%)		
1	161 (80%)	467 (66%)
2	11 (5%)	28 (4%)
3	23 (11%)	119 (17%)
4	7 (4%)	9 (1%)
Missing	0	89 (13%)
Prior HCV treatment experience, No. (%)	78 (39%)	85 (12%)
Missing	8 (4%)	
Current APRI >1.5, No. (%)	71 (35%)	128 (18%)
History of ESLD diagnosis, No. (%)	78 (39%)	100 (14%)

Footnotes:
a- Included the following regimens [133 initiations were with ledipasvir/sofosbuvir; 28 with sofosbuvir/ribavirin; 19 with sofosbuvir/ simeprevir +/- ribavirin; 13 with sofosbuvir/ribavirin/peg-interferon; 4 with ombitasvir/paritaprevir/ ritonavir/ribavirin; 3 with sofosbuvir/daclatasvir and 2 simeprevir/ribavirin/peg-interferon]
b-199 unique people initiated treatment, 3 people initiated twice (n=202 initiations)
c-Includes all active participants, with a positive HCV RNA result, who did not initiate DAAs (see supplemental table 1 for details)
d-Single person low income is considered annual income of less than $18,421/yr CAD [166]
e-Active PWID: Use of any injection drugs within 6 months of last cohort visit (self-reported)
f-Past PWID: Not actively injecting drugs (as defined above) however exposure to injection drugs while participating in the CCC study (self-reported)
g-Current Alcohol Abuse: Drinking more than 2 units of alcohol on a "typical day" within 6 months of last cohort visit (self-reported)
h- ESLD-End Stage Liver Disease (clinical diagnosis of: ascites, bleeding esophageal varices, portal hypertension, hepatocellular carcinoma, spontaneous bacterial peritonitis)

Abbreviations: Undetectable HIV RNA (RNA<50 copies/mL) HCV- Hepatitis C Virus; IDU- Injection drug use; PWID- Person who injects drugs; cART- combined antiretroviral therapy; NNRTI- Non-nucleoside reverse-transcriptase inhibitors; PI- Protease Inhibitors; HCV-Hepatitis C Virus; APRI- AST to Platelet Ratio Index

The vast majority of DAA regimens were interferon free (93%): 133 initiations were with ledipasvir/sofosbuvir; 28 with sofosbuvir/ribavirin; 19 with sofosbuvir/simeprevir +/- ribavirin; 13 with sofosbuvir/ribavirin/pegylated-interferon; 4 with ombitasvir/paritaprevir/ritonavir/ribavirin; 3 with sofosbuvir/daclatasvir and 2 simeprevir/ribavirin/pegylated-interferon. Those who initiated HCV treatment were less likely to be Indigenous, women and active PWID (Table 6.1). Participants who initiated HCV treatment were more likely to be MSM, have a gross annual income above the low-income threshold [166], undetectable HIV viral load, more advanced liver disease (based on an APRI score >1.5), and to have previous exposure to HCV treatment. After adjustment, active PWID, low-income, drinking alcohol, and living in the province of Saskatchewan were associated with lower rates of DAA treatment initiation (Table 6.2).

Table 6.2 Predictors of second-generation direct acting antiviral treatment initiation

	Unadjusted Model HR (95% CI)	**Adjusted Model aHR (95% CI)**
Age (per 10-year)	1.60 (1.37, 1.87)	1.12 (0.93, 1.35)
Indigenous people	0.23 (0.14, 0.37)	0.70 (0.43, 1.15)
Sex (Reference Heterosexual Men)		
Women	0.71 (0.48, 1.04)	0.85 (0.53, 1.36)
MSM	2.38 (1.74, 3.24)	1.95 (1.33, 2.86)
Injection Drug Use (Reference non-PWID)		
Active PWID[a]	0.26 (0.18, 0.40)	0.60 (0.38, 0.94)
Past PWID[b]	0.54 (0.39, 0.75)	0.88 (0.58, 1.33)
Income (<$18,000/year)	0.45 (0.34, 0.61)	0.50 (0.35, 0.71)
Alcohol Use	0.96 (0.73, 1.27)	0.74 (0.58, 0.94)
Undetectable HIV Viral Load (<50 copies/mL)	2.55 (1.70, 3.83)	1.73 (1.20, 2.50)
Significant Liver Fibrosis (APRI>1.5)	2.60 (1.94, 3.48)	2.28 (1.64, 3.16)
HCV Genotype (Reference Genotype 1)		
2	1.21 (0.66, 2.24)	1.12 (0.57, 2.18)
3	0.59 (0.38, 0.92)	0.69 (0.42, 1.13)
4	2.48 (1.15, 5.22)	1.51 (0.66, 3.16)
Province of Residence [c] (Reference British Columbia)		
Saskatchewan	0.02 (0.00, 0.17)	0.04 (0.01, 0.11)
Alberta/ Ontario	1.00 (0.69, 1.44)	0.58 (0.24, 1.41)
Quebec	1.60 (1.15, 2.23)	1.52 (0.66, 3.51)

Adjusted model included all predictors listed in table 6.2

a-Active PWID: Use of any injection drugs within 6 months of cohort visit (self-reported)

b-Past PWID: Not actively injecting drugs (as defined above) however exposure to injection drugs (self-reported)

Undetectable HIV RNA (RNA<50 copies/mL) HCV- Hepatitis C Virus; PWID-Person who Inject Drugs; MSM-Men who have Sex with Men; APRI- AST to **P**latelet **R**atio Index

c-Canadian province of residence (British Columbia, Saskatchewan, Alberta/Ontario and Quebec; based on DAA policy restrictions [28])

Indigenous peoples, women and non-active PWID also tended to have lower treatment rates. Conversely, MSM were more likely to initiate DAAs as were people with significant liver fibrosis and controlled HIV viremia. Stratified Cox models confirmed the results of the adjusted model summarized in Table 6.2 (results not shown).

Figure 6.2 illustrates the 2-year probability of initiating second-generation DAA treatment by 8 population profiles based on the multivariate Cox model. Across all three factors of interest (women,

Indigenous peoples and active PWID) the clearest delineation in uptake exists between Indigenous peoples compared to other ethnicities. Among our cohort the profile with the lowest probability (5%, 95% CI 3-8%) of initiating second-generation DAAs were female, Indigenous, PWID. Not having any of these risk factors resulted in a 35% (95% CI 32-38) probability of initiating DAA treatment. Supplemental Table 6.2 summarizes the unadjusted initiation rates per 100 person-years by key populations.

As these risk factors may occur together, we attempted to isolate which was most responsible for lower rates of DAA initiation by creating a hypothetical cohort with fixed characteristics of those more likely to initiate treatment. As illustrated in supplemental figure 6.2, it appears that IDU drove most of the effect although being Indigenous and a woman additionally contributed to the lower probability of initiating DAAs.

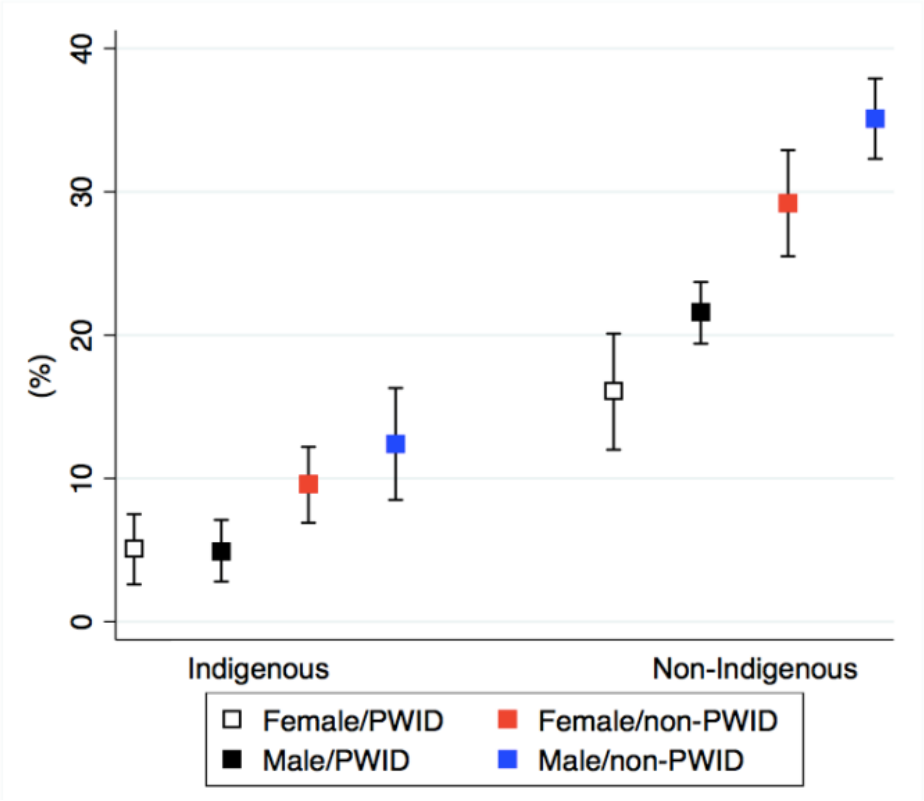
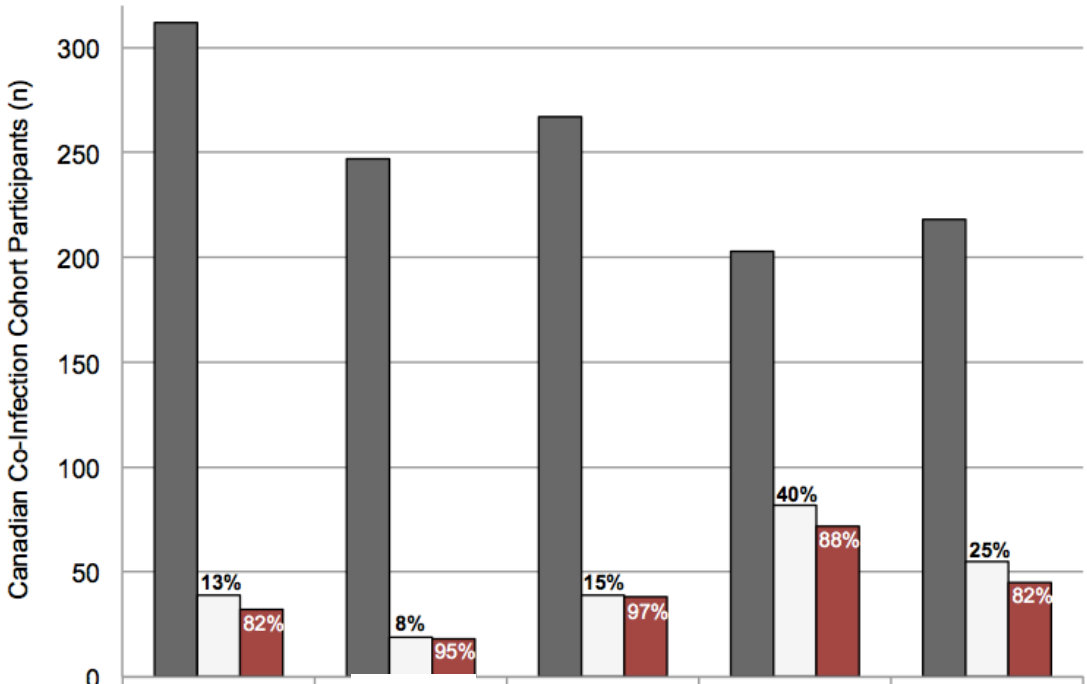


Figure 6.2 Two-Year Probability of Second-Generation DAA initiation by Population Profile
Probability (%), whiskers represent 95% confidence intervals. Abbreviations: PWID, People who Inject Drug

Second-generation DAA Treatment Response

Figure 6.3 illustrates the cascade of HCV treatment among CCC participants who were eligible, initiated and achieved SVR. Overall, SVR rates were 87% (176/202). By definition, 26 people were classified as non-responders (null (n=8), breakthrough (n=6), partial response (n=4), deaths (n=3), relapse (n=1) and missing post treatment HCV RNA (n=4)). Despite low treatment uptake among the key populations of interest, SVR rates were high: 82% in active PWID (32/39, 1 missing), 90% among Indigenous peoples (18/19), 97% among women (38/39), and 88% (72/82) in MSM. For comparative purposes, a category defined as 'other' was created to include populations who were not Indigenous, women, active PWID or MSM. Again, although this group had a higher rate of initiation, SVR rates (82%; 45/55, 3 missing) were similar to the overall cohort. No clear associations were observed between non-response and clinical characteristics or specific treatment regimens.



	Active PWID	Indigenous	Female	MSM	Other
Eligible for Treatment	312	247	267	203	218
Initiated Second-Generation DAA	39	19	39	82	55
Sustained Virologic Response	32	18	38	72	45

Figure 6.3 Second Generation DAA Treatment Cascade
Bar graph represents overall numbers of patients eligible for treatment, initiate second-generation DAAs, and achieved SVR by key populations. Abbreviations: CCC, Canadian Co-Infection Cohort; PWID, People who Inject Drugs; MSM, Men who have sex with men; SVR, Sustained Virologic Response

DISCUSSION

The development of DAAs has generated enthusiasm that HCV can be eliminated. However, the gap between even near 100% curative treatments and viral elimination is immense if only a small segment of the population initiates treatment [234]. HCV treatment cascades among HCV mono-infected individuals highlight the need for better screening, diagnosis and linkage to care to ultimately cure HCV [133-135]. HIV-HCV co-infected populations are generally well identified and already engaged in HIV care therefore easier to reach compared to HCV mono-infected populations. In a publicly funded healthcare setting with no overt restrictions limiting DAA uptake by socio-demographic or behavioral factors, we found significant disparities existed among key HIV-HCV co-infected populations engaged in care. Although HCV treatment uptake was rapid after second-generation DAA were approved, the MSM population largely drove this trend. In contrast PWID, and more generally, people of lower SES were far less likely to initiate treatment. Despite low treatment uptake in some groups, SVR rates were high in all key populations. Results from this study suggest that despite the advent of highly efficacious and well-tolerated second-generation DAA therapies, patient- system- and provider- barriers may still remain for many HIV-HCV co-infected populations.

Patient-Level Barriers

In high-income countries, HIV-HCV co-infection affects marginalized populations who are often socially disenfranchised with many competing priorities. Lower SES, substance abuse and mental illness have previously been associated with barriers to accessing healthcare [82,83,85]. Results from our study provide evidence that patient-related factors (IDU, low income and alcohol use) remain barriers to HCV treatment initiation in the DAA era. Disparities are also evident in Indigenous compared to non-Indigenous individuals. High rates of IDU, predominantly among young Indigenous people, have

recently increased rates of co-infection significantly in Canada, specifically in the province of Saskatchewan [55]. Similarly in Australia newly diagnosed HCV among Aboriginal people has increased by 38% from 2010 to 2014; in contrast during the same time period, notification rates among non-Aboriginal people has decreased by 15% [56]. While in Canada there are no system-level barriers that limit treatment of PWID, our results suggest active PWID, and to a certain extent, past PWID are not accessing DAAs at the same rate as non-PWID. Modeling studies have shown treating PWID to be cost-effective, because treatment may also act as prevention [101,232]. Furthermore, women face unique barriers to accessing treatment and care. Among women who inject drugs, reasons for not accessing healthcare and treatment may include child-bearing, child care responsibilities, ongoing sex work, higher rates of mental health issues, and lower access to harm-reduction programs [148].

MSM with HIV form an emerging risk group for HCV acquisition [235]. We found MSM were far more likely to initiate treatment suggesting that broad treatment in this group is possible and could result in reduced HCV transmission. MSM in our cohort were more likely to have higher income and be more educated and were less likely to inject drugs— all factors associated with initiating DAAs.

System-Level Barriers

The extraordinary cost of DAAs has led many countries to restrict access to DAAs based on a variety of factors. Compared to the multi-payer system in the United States where considerable variation in DAA coverage exists, specifically in regard to active substance use, coverage policies across Canada are more homogeneous. Although all Canadian citizens and permanent residents have insurance coverage for in-hospital and physician services, medication coverage varies across the 10 provinces and 3 territories, with a mix of both public and private sources of insurance depending on individual characteristics. For example, people on social assistance receive public coverage for medications with no or minimal co-

payments and Indigenous people receive medication coverage from the First Nations and Inuit Health Branch (FNIHB). During the period of study, all provinces and territories in Canada, with the exception of Quebec, restricted the reimbursement of DAAs to those with advanced liver fibrosis (F2 or greater) [28]. Consistent with this, the strongest predictor of treatment initiation in our study was having advanced liver fibrosis. In addition, DAA initiation varied by province; for example, a larger proportion of co-infected individuals were treated in Quebec compared to other provinces. Quebec was the first province to reimburse simeprevir and sofosbuvir with no liver fibrosis restrictions (in 2014) and later introduced a tiered reimbursement strategy that allowed all co-infected individuals access to ledipasvir/sofosbuvir and paritaprevir/ombitasvir/dasabuvir regardless of liver fibrosis stage. Even with Quebec's more inclusive insurance coverage of DAAs, PWID compared to people not reporting IDU were still less likely to initiate treatment while MSM and people with advanced liver fibrosis were more likely to initiate treatment (data not shown). In contrast, people residing in Saskatchewan initiated DAAs at a significantly lower rate than in other provinces. In Saskatchewan patients tended to be younger PWID with less advanced liver disease illustrating how even though significant liver fibrosis requirements may seem like, a non-discriminatory policy restriction, however it may still lead to social and health inequities.

Provider-Level Barriers

Providers are faced with the challenge of managing clinically and socially complex co-infected patients and navigating administrative hurdles to access treatments. We found HCV genotypes were missing for 10% of our cohort, indicating that even though engaged in care, such people were not being considered for treatment. Those with unknown genotypes were more likely to be PWID and Indigenous. Even though IDU has been characterized as a chronic relapsing brain disease, PWID may continue to face

stigma and discrimination from health professionals [149]. It is also possible providers may have concerns about poor adherence and reinfections among PWID [42,82,150]. Based on successful HCV treatment trials and economic analyses, international guidelines now recommend that the treatment of PWID be made a priority [236,237]. We found similar SVR rates in active PWID compared to non-PWID in a real world setting, further supporting international guidelines to treat PWID.

Previous published reports exist on DAA treatment disparities using data from the Veterans Affairs (VA) and TRIO Network cohorts [155,238]. In the VA cohort, black patients and younger women were less likely to initiate DAA treatment [238]. However, it is difficult to generalize results from the VA cohort to other healthcare systems since this cohort is primarily male and has broader access to healthcare and HCV treatment compared to other American cohorts [239,240]. The TRIO network compared receipt of DAAs according to type of insurance providers (Medicaid or commercial) and, as in other studies, found that Medicaid prescribers faced more barriers to treatment due to processes related to insurance coverage and financial reasons [30,154,155]. Our study focuses specifically on HIV-HCV co-infected individuals, a unique population that arguably stands to benefit the most from HCV viral clearance [11,100,241]. We used data from a representative, prospective cohort of co-infected individuals already engaged in care that included active and past PWID, women, and Indigenous peoples. Furthermore, patient characteristics and treatment information were based on prospective data collection and not secondary data extraction from billing codes. Most recently Janjua et al. described shifts in the characteristics of people who received interferon-based HCV regimens compared to DAAs, using a population-based cohort in British Columbia, Canada and found HIV-HCV co-infected individuals were more likely to initiate DAA treatment compared to the interferon era [138]. Results from our study highlight the heterogeneity of the

HIV-HCV co-infected population and the importance of evaluating uptake among specific key populations.

Our study has limitations. Overlapping patient-level barriers make it difficult to identify independent reasons for treatment disparities and due to our sample size, it was not possible for us to explore formal statistical tests to identify synergistic relationships between Indigenous ethnicity, IDU and/or sex. Having supplemental healthcare insurance coverage (third party private insurance) maybe another important predictor of treatment initiation, however not routinely collected. Though the vast majority of this cohort was making less than $18,000/year therefore qualified for provincial drug assistance. Furthermore, 4 people (2%) who initiated treatment had a missing treatment response. This could mean the overall SVR rates may be underestimated, if in fact the missing responses were undetectable. Finally, we focused on a population already in care - that is, at the end of the cascade of care. To evaluate the population level impact of DAAs, it will be important to evaluate each step of the care continuum, including ongoing surveillance of reinfections. Close follow up to document treatment response and reinfections will be important as treatments are rolled out more broadly.

Conclusions

In this study we found important disparities in DAA uptake existed among key HIV-HCV co-infected populations already engaged in care in a publicly funded healthcare system, in particular PWID and more generally people of low SES. Low rates of treatment cannot be justified based on SVR rates, which were relatively high in all sub-groups. Availability of generics in developing countries and recent pricing agreements in developed countries should mean wider access to these curative therapies in the near future. However, if patient-level barriers are not addressed, even in high-income countries, we will

fail to make headway in reaching HCV elimination targets set out by the WHO by 2030. The next steps will be to develop targeted interventions that can be ultimately scaled-up to address unique patient-level barriers and to educate providers and policy makers to reduce stigma against treating key co-infected populations worldwide.

Competing interests

None of the authors feel in conflict of interest with regards to this study and there was no pharmaceutical industry support to conduct this study. Sahar Saeed, Erin C Strumpf, Erica Moodie, Jim Young and Roy Nitulescu have no conflicts of interest to declare. Marina Klein has received research grants for investigator-initiated trials from Merck and ViiV Healthcare; consulting fees from ViiV Healthcare, Bristol-Meyers Squibb, Merck, Gilead and AbbVie. Joseph Cox received consulting fees from Bristol-Meyers Squibb; grants from ViiV Healthcare and Gilead; and payment for lectures from Merck. Alex Wong received consulting and honoraria from Merck, Gilead Sciences, Bristol Myers Squibb, Pfizer, Janssen, Boehringer-Ingelheim, and AbbVie. Funding for regional and provincial programming was received from Merck, Gilead Sciences, Bristol Myers Squibb, ViiV, Janssen, and AbbVie. Sharon Walmsley received grants, consulting fees, lecture fees, nonfinancial support and fees for the development of educational presentations from Merck, ViiV Healthcare, GlaxoSmithKline, Pfizer, Gilead, Abbvie, Bristol-Myers Squibb and Janssen. Curtis Cooper reports consulting fees from AbbVie, Gilead, and Merck; and grants from AbbVie and Gilead. Marie-Louise Vachon has received consulting fees from Boehringer Ingelheim and Merck; consulting fees and lecture honoraria from Janssen Pharmaceuticals, Gilead, Hoffman–La Roche and Vertex Pharmaceuticals; and speaker fees from Gilead. Valérie Martel- Laferrière reports consulting fees from Merck and Gilead; grant from Gilead; and lecture fees from AbbVie, Merck and Gilead. Mark Hull, received grant support from National Institute on Drug Abuse (NIDA R01DA031043-01). Honoraria were received from (speaking engagements and/or consultancy) AbbVie, Bristol Myers Squibb, Gilead, Merck, Ortho-Janssen, and ViiV. Brian Conway reports grants, travel support, personal fees for speakers bureau and advisory board participation from AbbVie, Gilead, and Merck.

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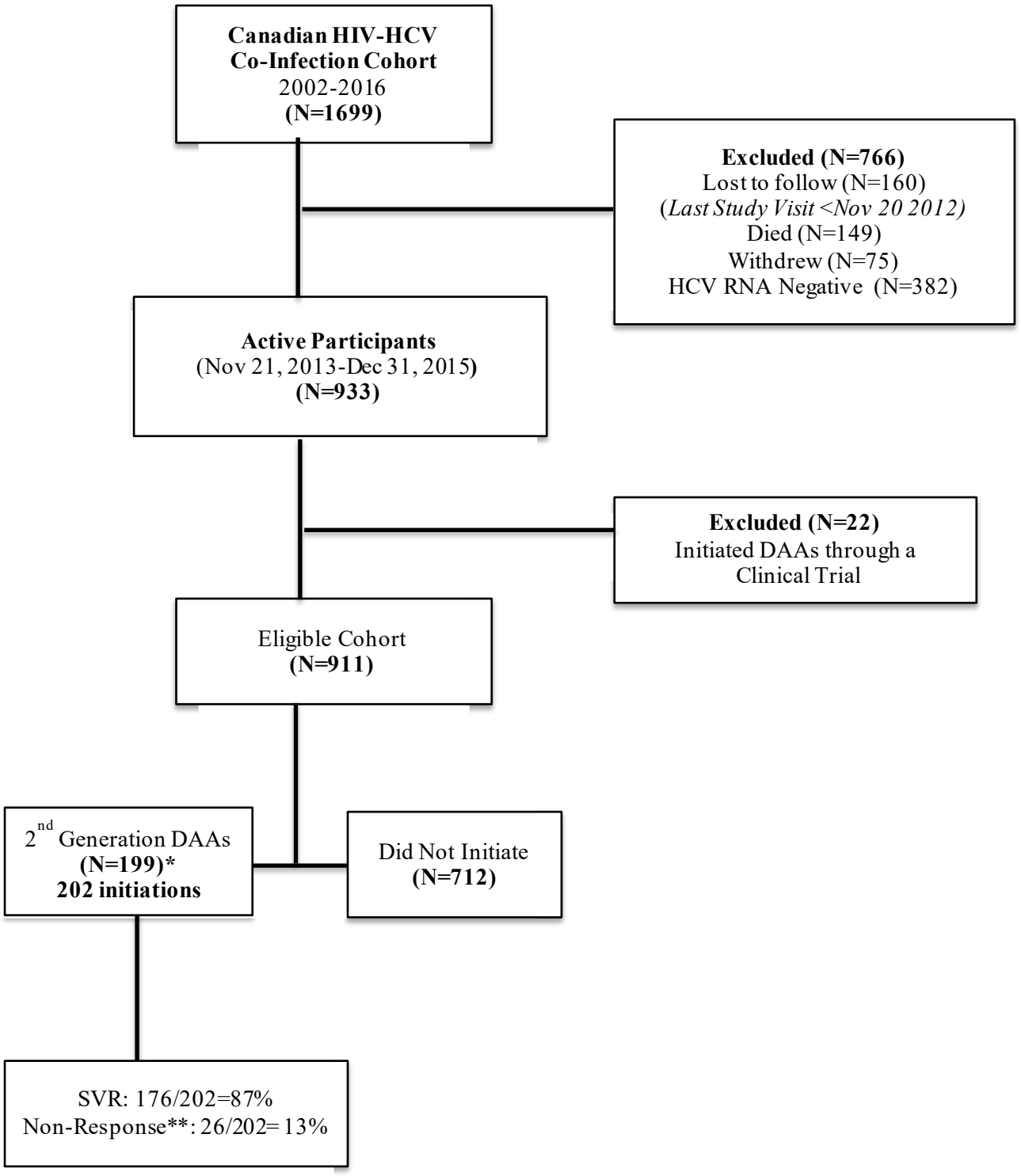
Author contributions

As the corresponding author, Dr. Klein has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Sahar Saeed & Marina Klein; Acquisition, analysis, or interpretation of data: Sahar Saeed, Marina Klein, Erin Strumpf, Erica Moodie, Jim Young, Joseph Cox, Alexander Wong, Sharon Walmsely, Curtis Cooper, Marie-Lousie Vachon, Valerie Martel-Laferriere, Mark Hull, Brian Conway Drafting of the manuscript: Sahar Saeed; Critical revision of the manuscript for important intellectual content: Sahar Saeed, Marina Klein, Erin Strumpf, Erica Moodie, Jim Young, Roy Nitulescu, Joseph Cox, Alexander Wong, Sharon Walmsely, Curtis Cooper; Statistical analysis: Sahar Saeed; Obtained funding: Marina Klein

6.3 Appendix to Manuscript 2: Supplemental Data

Supplemental Figure 6.1 Participant Flow Diagram



*199 participants initiated second generation DAAs, 3 people initiated twice therefore there were a total of 202 initiations
**Non-response included: Null (n=8) Breakthrough (n=6) Partial Response (n=4) Deaths (n=3) Relapse (n=1) Missing (n=4)--(All 4 did completed treatment) Abbreviations: HIV, Human Immunodeficiency Virus; HCV Hepatitis C Virus; DAA, Direct Acting Antivirals; SVR, Sustained Virologic Response

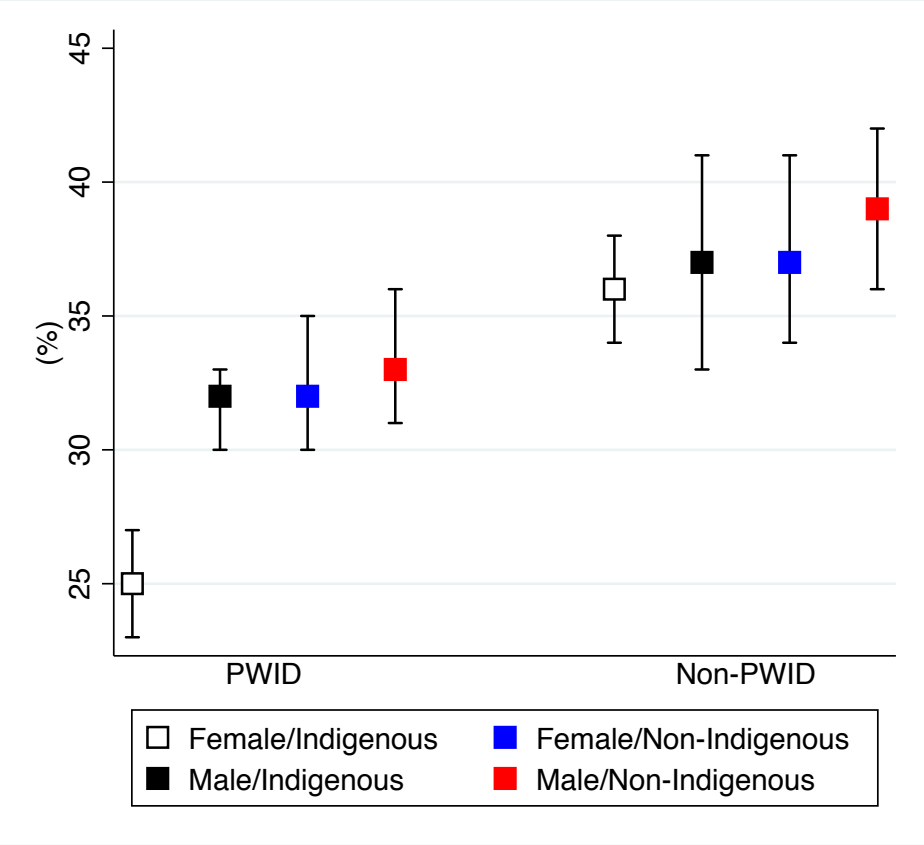
Supplemental Table 6.1 Participants excluded from study population

	Left Censored (Lost to follow up/ Withdrew) No. (%) **N=235**	**Clinical Trial Participant** No. (%) **N=22**
Age (years, IQR)	45 (39, 51)	51 (47, 55)
Indigenous	37 (16%)	3 (14%)
Women	56 (24%)	8 (36%)
MSM	49 (21%)	5 (23%)
Active PWID	68 (29%)	3 (14%)
Past PWID	119 (51%)	15 (68%)
Income (<$18,000/year)	176 (75%)	15 (68%)
Alcohol Use	122 (52%)	11 (50%)
Undetectable HIV Viral Load (<50 ɛs/mL)	150 (64%)	19 (86%)
Significant Liver Fibrosis (APRI>1.5)	39 (17%)	22 (100%)
HCV Genotype		
1	131 (56%)	18 (82%)
2	9 (4%)	1 (5%)
3	30 (13%)	2 (9%)
4	7 (3%)	1 (5%)
Missing	58 (25%)	0
Province of Residence		
British Columbia	72 (31%)	9 (41%)
Alberta	7 (3%)	0
Ontario	56 (24%)	8 (36%)
Quebec	99 (42%)	5 (23%)

Undetectable HIV RNA (RNA<50 copies/mL) HCV- Hepatitis C Virus; PWID-Person who Inject Drugs; MSM-Men who have Sex with Men; APRI- AST to Platelet Ratio Index

Supplemental Table 6.2 DAA Second Generation DAA Initiations by Population Profile

		Number of Initiations (numerator)	**Total number of people**	**Total follow-up time (years)**	**Rates per 100 person-years**
Indigenous	Female/PWID	3	49	98	3
	Male/PWID	1	56	114	1
	Female/non-PWID	5	64	131	3
	Male/non-PWID	5	51	96	5
Non-Indigenous	Female/PWID	4	45	87	5
	Male/PWID	18	113	206	9
	Female/non-PWID	27	101	87	31
	Male/non-PWID	54	204	180	30



Supplemental Figure 6.2 Two-Year Probability of DAA Second Generation DAA Initiation (Fixed Covariates)
Probability was calculated for hypothetical participants most likely to initiate treatment (i.e. 47 year old, with significant liver fibrosis (APRI>1.5), genotype 1, undetectable HIV viral load (<50 copies/ml), income greater than $18,000/per, living in the province of Quebec and no alcohol consumption. Abbreviations: PWID-Person who Inject Drug

CHAPTER 7: IMPACT OF REMOVING FIBROSIS STAGE RESTRICTIONS ON HCV TREATMENT UPTAKE (MANSCRIPT 3)

7.1 Preface to Manuscript 3

Even though clinical guidelines from multiple international agencies unilaterally recommend treating all HCV-viremic patients, the high costs of DAAs have led healthcare insurers worldwide to limit access. One of the most common eligibility criteria that remains is having significant liver fibrosis (>F2) to be eligible for treatment. Any country that has any restrictions on DAA treatment is automatically excluded from the WHO's list of "countries on track to HCV elimination". In addition to having no restrictions on DAA treatment, countries need to treat at least 7% of their infected population each year to make the list. Currently only 12 countries are on track to HCV elimination (out of the 194 countries that signed the WHO agreement to eliminate HCV as a public health threat in 2016). One pragmatic approach to the massive undertaking of identifying and treating a sizable population of people living with HCV is to focus on micro-populations to achieve micro-eliminations. One such micro-population that has been identified are people co-infected with HIV and HCV.

In Chapter 7, I quantify the impact of removing fibrosis stage restrictions on treatment initiation rates. Furthermore, I evaluate how sustainable treatment rates are after the removal of initiation restrictions and determine who remains left to be treated. Most provinces restricted access to treatment using significant liver fibrosis when DAAs were first approved in 2013. In the province of Quebec, there were no restrictions by fibrosis stage between June 2014 to July 2015 and then as of March 2016 restrictions were permanently removed for people co-infected with HIV. After price negotiations between the Pan Canadian Pharmaceutical Alliance and the leading pharmaceutical companies who manufacture DAAs in 2016, restrictions were gradually removed in other provinces. In Ontario and British Columbia, restrictions were removed as of March 2017 for people co-infected with HIV. This variation in time and

geography created a natural experiment that I use to evaluate the causal impact of removing advance fibrosis stage restrictions for DAA treatment on HCV treatment initiation rates overall and among PWID.

7.2 Eliminating Structural Barriers: Impact of Removing Fibrosis Stage Restrictions on HCV Treatment Uptake among People Living with HIV

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Keywords: HIV-Hepatitis C Co-Infection, Direct Acting Antivirals, People who Inject Drugs, Unrestricted Access, Quasi-experimental methods

Running Title: Impact of Unrestricted Access on DAA Uptake

Summary: People co-infected with HIV-HCV were 1.8 times more likely to initiate treatments after fibrosis stage restrictions were removed, after controlling for temporal trends. However marginalized populations remain to be treated and as well as those disengaged from care.

Abstract Word Count: 250

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ABSTRACT:

Background: High costs of direct acting antivirals (DAAs) led healthcare insurers to limit access worldwide. Using a natural experiment, we evaluated the impact of removing fibrosis stage restrictions on hepatitis C (HCV) treatment initiation rates among people living with HIV and then examined who was left to be treated.

Methods: Using data from the Canadian HIV-HCV Co-Infection Cohort, we applied a difference-in-differences approach. Changes in treatment initiation rates following the removal of fibrosis stage restrictions was assessed using a negative binomial regression with generalized estimating equations. The policy change was then specifically assessed among people who inject drugs (PWID). We then identified characteristics of participants who remained to be treated using a modified Poisson regression.

Results: Between 2010-2018, there were a total of 585 HCV initiations among 1130 eligible participants. After removing fibrosis stage restrictions, DAA initiations increased by 1.8-fold (95% CI 1.3, 2.4) controlling for time-invariant differences and secular trends. Among PWID the impact appeared even stronger; adjusted incidence rate ratios (aIRR) (95% CI), 3.6 (1.8, 7.4). However, this increased treatment uptake was not sustained. One year following universal access, treatment rates declined, 0.8 (0.5, 1.1). Marginalized participants (PWID and Indigenous ethnicity) and those disengaged from care were more likely to remain HCV RNA positive.

Conclusion: After the removal of fibrosis restrictions HCV treatment initiations nearly doubled immediately but this treatment rate was not sustained. To meet the WHO elimination targets, minimization of structural barriers and adoption of tailored interventions are needed to engage and treat all vulnerable populations.

INTRODUCTION:

Deaths due to viral hepatitis are soon projected to surpass HIV, tuberculosis and malaria [242]. Given the advent of direct acting antivirals (DAAs) and the significant public health burden of viral hepatitis, the WHO set targets to eliminate viral hepatitis by 2030. Countries "on track to HCV elimination" have (1) unrestricted access to DAAs and (2) treat at least 7% of their overall infected population per year [128]. Only 12/194 countries are on track to meeting these targets[128]. High costs of DAAs, have led health authorities to continue to restrict access. Despite clinical guidelines, one of the most common eligibility criteria for treatment reimbursement globally remains the presence of significant liver fibrosis [28,30,156,157]. An unintentional consequence of fibrosis stage restrictions may be that younger people who inject drugs (PWID) and men who have sex with men (MSM)– who are clinically less advanced but at ongoing risk of transmitting HCV – may differentially face barriers to treatment.

Globally, an estimated 2.3 million people living with HIV (PLWH) are co-infected with HCV of whom 80% are people who inject, or previously injected drugs [5]. Despite the rapid advances in HCV treatment, barriers to elimination remain across each step of the care continuum. In high-income settings, people co-infected with HIV-HCV are generally well identified and most are already engaged in HIV care, therefore the only remaining step to curing HCV is initiating treatment. This is an ideal "micro-population" to achieve the WHO targets [136].

Health care services in Canada are universal but medication coverage is not. The decision as to what medications are reimbursed and under what circumstances is made independently by provincial health authorities. When DAAs were first approved for use most provinces required people living with HCV to have significant liver fibrosis to access treatment. These limitations on access have been variably

removed overtime. This variation of policy change by time and geography creates a natural experiment and an opportunity to estimate the impact of unrestricted access to DAAs, on treatment initiation rates. We then examined the characteristics of participants that remained to be treated to estimate how close we are to eliminating HCV among PLWH.

METHODS:

Study Population: The Canadian Co-infection Cohort Study (CCC) is an open publicly-funded prospective cohort of PLWH with evidence of HCV infection recruited from 18 centres [158]. Details on study procedures and the representativeness of the cohort have been published elsewhere [158]. To date, it is estimated the CCC has enrolled 23% of the total HIV co-infected population in care in Canada. The CCC is approved by a community advisory committee and by all institutional ethics boards of the participating centres.

Eligibility: CCC participants who were HCV RNA positive, with one visit as of March 24, 2010 (time zero) from either, British Columbia, Ontario or Quebec were included in this analytic sample. Participants from Saskatchewan, Alberta and Nova Scotia were excluded because at time zero less than 20 active participants represented the province.

Primary Analysis: Impact of removing fibrosis stage restrictions on HCV treatment initiation rates

Outcome: HCV treatment initiation was the primary outcome. The study period spanned between 2010 and 2018, therefore treatments included both pegylated interferon (in combination with ribavirin or DAAs) and interferon-free regimens. DAAs included boceprevir, telaprevir, simeprevir, sofosbuvir,

sofosbuvir/simeprevir, sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir with/out dasabuvir, sofosbuvir/daclatasvir, sofosbuvir/velpatasvir, and elbasvir/grazoprevir. Eligible participants who did not achieve the outcome were censored on the date they were considered lost to follow-up (no study visits for at least 18 months), died, withdrew from the study, spontaneously cleared HCV infection or at the administrative end date (March 24, 2018). Since participants could initiate HCV treatment multiple times (i.e. failure, reinfection); treatment initiation was treated as a repeatable outcome. Once participants initiated HCV treatment and achieved a sustained virologic response (SVR), they were censored unless they became reinfected, at which time they could again contribute person time at risk for treatment.

Exposure: The exposure of interest was the change in provincial policies that removed the criterion requiring presence of "significant liver fibrosis stage" for DAAs to be reimbursed by three provincial health plans. Figure 7.1 illustrates when policies changed in each province (details listed as footnotes). Briefly, in Quebec, when simeprevir and sofosbuvir were available for treatment between June 2014-July 2015, there were no restrictions based on fibrosis stage. In 2016 when ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir/dasabuvir were approved, treatments were restricted to people with advance liver disease (>F3), but as of March 2016, these restrictions were permanently removed for PLWH. In Ontario and British Columbia, fibrosis restrictions were removed as of March 2017 for PLWH. There were never any sobriety restrictions for reimbursement of DAAs in any province in Canada[28].

Statistical Analysis: We applied a quasi-experimental method known as a difference-in-differences (DD) approach to estimate the impact of removing significant liver fibrosis restrictions on HCV

treatment initiation. This approach compares the difference between the average change in treatment initiations before and after the intervention between an exposed and control group [164]. Focusing on changes within these groups over time controls for time-invariant characteristics of the exposed group, while including a control group controls for secular trends. The assumption made is that the post-intervention treatment trend in the control group provides an accurate counterfactual for "what would have happened in the absence of the exposure". This is verified by assessing for parallel trends before the intervention [165]. We chose this design because of the need to control for secular trends in HCV treatment uptake that co-occurred with policy changes (DAA approval in 2013).

The base difference-in-differences model includes three main variables: (1) Group (defined by province of residence; British Columbia (reference), Ontario or Quebec); (2) Time (calendar year from time zero –March 24, 2010 through to March 23, 2018; the reference was March 24, 2013-2014; (3) an interaction between Group and Time, which is equal to 1 in provinces and years when fibrosis stage restrictions are not in place. The coefficient on this interaction term provides the difference-in-differences estimate of the policy effect. Since our analysis included multiple groups and time periods, the combination of group (province) and time-periods where fibrosis restrictions remained, form the control for this analysis. When QC was exposed to a policy change in 2014, BC and ON served as the control groups. Then when BC and ON were exposed to a policy change in 2017, QC served as their control (since there was no change in Quebec)[243].

The adjusted DD model also included both individual-level fixed and time-varying predictors of HCV treatment initiation. Fixed covariates included age, sex, MSM, Indigenous ethnicity, HCV genotype. Time varying covariates included income (<$18,000 CAD) [166], injection drug use (within 6 months), undetectable HIV RNA (<50 copies/mL) and significant liver fibrosis. Significant liver fibrosis was

determined using a hierarchical classification based on availability of a liver biopsy, clinical diagnosis of cirrhosis, fibroscan (>7.2 kPa) [67] or AST to Platelet Ratio Index (APRI) ≥1.5. A definition of a confounder in a DD analyses is a predictor associated with the exposure (policy change) and the outcome (treatment initiation) that differentially changes over time by groups (province).

We next evaluated the impact of the policy change among PWID by restricting the analytical sample only to participants who reported active injection drug use in the last 6 months prior (time updated).

All DD models were fit using negative binomial regression. The natural logarithm of each participant's time at risk (in years) was used as the offset. Generalized estimating equations were used to account for repeated outcomes, robust standard errors were used to adjust for clustering. Results are presented as adjusted Incidence Rate Ratios (aIRR).

We conducted several robustness checks, we evaluated: (1) the parallel trends assumption; (2) if the policy reached the intended population (i.e. effect modification based on not having significant liver fibrosis) (3) "lead effect" to assess if HCV treatment uptake pre-dated the policy change; (4) " lagged effect" to assess the sustainability of the policy change; and (5) " falsification test" to assess whether omitted variables affecting decisions to initiate DAAs were driving our results. Here we used serum creatinine levels.

Secondary Analysis: Assessment of who is left to be treated?

Based on the eligibility criteria above, we summarized the proportion of participants who initiated treatment and those who remained eligible for treatment, by calendar year, significant fibrosis stage and

active injection drug use. We then performed a cross-sectional analysis, using a modified Poisson regression model with robust standard errors to assess predictors of remaining HCV RNA positive at each participant's last visit. Predictors included: (1) Socio-demographic – age, Indigenous ethnicity, women/ or MSM compared to heterosexual men, income, homelessness, incarceration (past 6 months) and province of residence (British Columbia as reference); (2) behavioural –active injection drug and alcohol use (3) clinical –undetectable HIV RNA, significant liver fibrosis, HCV genotype and psychiatric diagnosis (4) disengagement in care– defined as being lost to follow up. Lost to follow up was defined as not having a cohort visit within 18 months of our administrative censoring date (excluding those who had formally withdrawn from the study and those who died).

All analyses were performed using Stata 15/IC (StataCorp LP, College Station, TX).

RESULTS:

Primary Analysis: Impact of removing fibrosis stage restrictions on treatment initiation rates

As of March 2018, 1843 co-infected individuals had been recruited to the CCC. After applying the eligibility criteria, a total of 1130 CCC participants from British Columbia (n=414), Ontario (n=326) and Quebec (n=390) were HCV RNA+ as of March 24, 2010 (supplemental figure 7.1). Between March 24, 2010 and March 23, 2018, there were 585 HCV treatment initiations by 543 participants (458 participants achieved SVR). The majority (n=390, 67%) of participants were treated with all oral DAA regimens; 100 (17%) with first and second generation DAAs in combination with pegylated-interferon and 72 (12%) with pegylated-interferon regimens alone. There were 23 (4%) regimens that could not be classified because patients were enrolled in blinded clinical trials or information on regimens was missing. Censoring reasons were similar across provinces (supplemental table 7.1). Table 7.1 illustrates

the baseline characteristics of the analytic sample, comparing the three provinces. Clinical factors were comparable across provinces, but sociodemographic characteristics such as the proportion of participants of Indigenous ethnicity, women and those with low income differed between the provinces. Behavioral characteristics, such as proportion of active PWID and MSM, also differed at baseline but proportions did not vary over time (results not shown). Forty-four participants were treated within clinical trials, but participation did not differ by province.

Figure 7.2 illustrates the temporal trends in HCV treatment initiations between 2010-2018. Before second-generation DAAs were available, treatment rates were low across all provinces. Following the introduction of oral DAAs, treatment initiation rates rose appreciably in all provinces, but rates began to diverge. Treatment rates in Quebec followed a distinct trajectory compared to those in British Columbia and Ontario. Uniquely, in Quebec between 2014 and 2015, there were no restrictions to reimburse DAAs by fibrosis stage and rates rose compared to the other provinces. Between 2015 and 2016, temporary restrictions were put in place and treatment rates declined to levels comparable to Ontario and British Columbia, where restrictions to treatment persisted. As restrictions were permanently removed in Quebec in July 2016, rates increased once more, but then dropped considerably between 2017 and 2018. Treatment rates in Ontario and British Columbia followed similar trends to each other. There was an initial increase between 2013 and 2016, followed by a slight decline in rates between 2016 and 2017. One year following unrestricted access to DAAs as of March 2017, treatment uptake appeared to be rising in Ontario but plateauing in British Columbia.

Accounting for shared temporal trends and time-invariant differences between the provinces, removing fibrosis stage restrictions increased overall HCV treatment rates by 1.8 times (95% CI, 1.4, 2.4). Among

PWID, the effect of the policy change was even more pronounced: IRR 3.8 (95% CI, 2.0, 7.3). Adjustment for covariates did not change the impact of the policy change (Table 7.2).

The results of sensitivity analyses are presented in supplemental tables 7.3 to 7.5. The parallel trends assumption was verified visually and statistically (supplemental figure 7.2). We then evaluated if there was effect modification by presence of significant liver fibrosis and found, following removal of restrictions, those without significant fibrosis were 1.5-times more likely to initiate treatment (supplemental table 7.3). A lead indicator for provinces implementing removal of fibrosis stage restrictions one year before the actual policy change, was not associated with treatment initiations, IRR 1.0 (95% CI, 0.7, 1.4). A one-year lagged indicator for provinces removing fibrosis stage restrictions indicated that treatment initiation rates may not be sustainable, IRR 0.8 (95% CI 0.5, 1.1) (supplement table 7.4). Our falsification test demonstrates changes in the reimbursement policy was not associated with changes in serum creatinine (supplemental table 7.5).

Who still remains to be treated?

Figure 7.3 illustrates the increase in the proportion of treatments occurring among people without significant fibrosis and among PWID over time. Using data from the participant's last visit, we evaluated predictors of remaining HCV RNA positive and found associations of sociodemographic, behavioral and clinical characteristics (supplemental table 7.6 summarizes participants characteristics). Figure 7.4 illustrates the adjusted prevalence risk ratio (aPRR; 95% CI) of all the covariates listed. People of Indigenous ethnicity compared to any other ethnicity (1.17; 1.01, 1.34); reporting homelessness (1.31; 1.14, 1.51); PWID compared to people who do not report actively injecting drugs within 6 months (1.21; 1.08, 1.36); and those who disengaged from care (lost-to-follow up) were (2.12;

1.92, 2.33) more likely to remain HCV RNA positive, therefore still requiring HCV treatment. Factors associated with achieving an HCV cure were: self-identification as an MSM (0.88; 0.76, 1.02), having an undetectable HIV RNA (0.80; 0.72, 0.90) and having significant liver fibrosis (0.83; 0.73, 0.95).

DISCUSSION:

The cost of DAAs has led many payers worldwide to restrict access -- this remains a significant impediment to universal access to treatment. In this study, we capitalized on a natural experiment occurring in Canada but with international implications. We found that co-infected people were nearly two-times more likely to initiate treatment after fibrosis stage restrictions were removed, after controlling for fixed differences across provinces and shared temporal trends. Among this population already engaged in health care, we found annual treatment rates peaked at 25% (between 2015 and 2016) but by 2018 had decreased to 17%. If maintained, this rate could be sufficient to achieve micro-elimination among HCV co-infected PLWH in Canada. However, it is unclear if these rates can be sustained, as we also found that the population that remains to be treated is marginalized and largely disengaged from care.

Reimbursement restrictions

The first review of DAA coverage among Medicare recipients in the United States (US), found the vast majority of states restricted access to DAAs for a variety of reasons including clinical and behavioural criteria [30]. Four years later, despite advocacy efforts and threats of legal action, a recent study suggests that both public and private health insurers in the US continue to deny coverage for DAAs at increasingly high rates [30,153,154]. While these studies did not examine the reasons for the increase in absolute denial, authors did speculate the constrained budgets of payers continue to contribute to insurers having to prioritize treatments. Similar reviews of DAA coverage were conducted in Canada

and Europe where it was found that fewer restrictions were in place than the US (specifically in regards to sobriety) but the majority of countries still required patients to have significant liver fibrosis [28,154-157]. Since 2017, following pricing negotiations, reimbursement criteria for DAAs has progressively changed across Canada.

Most strikingly, PWID were 3.6 times more likely to initiate treatment following unrestricted coverage. In addition to patient-level benefits of treatment initiation and HCV viral clearance, there is a particular public health impact of treating PWID. Modeling studies have shown in high prevalence settings that treatment can also act as prevention [101]. These studies indicate that restricting access to treatment by advanced fibrosis and/or by drug use status, would likely limit the impact on preventing transmission among PWID [244,245]. One study estimated that in a city with 65% HCV prevalence and widespread harm reduction, two new cases of HCV could be averted for every case treated if treatments are scaled to 98 per 1,000 PWID annually [102].

Warehousing effect

Removing structural barriers such as medication access, is an important step in HCV elimination. However, we found unrestricted DAA access may not alone lead to sustained treatment rates. After the initial surge in treatment initiation following unrestricted access in Quebec, treatment rates declined considerably. One explanation for this decline may be a "warehousing effect" – that is physicians were aware of existing patients eligible and likely to adhere treatment, treating them as soon as access was expanded. Once most of the "warehoused patients" have been treated, the people remaining are those who continue to be more difficult to reach, inconsistently engaged in health care or perceived to be socially unstable resulting in a reluctance to initiate treatment. Our results are consistent with decreased treatment rates observed in countries such as Australia where access to treatment had been universal

since 2016 [142]. As the prices of DAAs continue to decrease and as generic treatments become broadly licensed, our study suggests that universal access may not be enough to meet WHO targets.

Who is left to treat?

The underlying principle of the WHO response to viral hepatitis is the promotion of healthcare equity. As we report, following unrestricted access to treatment, PWID were more likely to access treatments. However, this was not sufficient to achieve equity (Figure 7.4). The objective of the secondary analysis was to identify characteristics of the participants engaged in healthcare and who had not yet accessed treatment in the era of DAAs. We found that the strongest predictor of remaining HCV RNA positive was becoming disengaged from care of whom, 90% (228//254) remained HCV RNA positive. Consistent with previous studies, among those remaining in care, people of Indigenous ethnicity and who report injecting drugs were still more likely to be HCV RNA positive at the end of this study [138,238,246]. Although this analysis could not elicit the reasons why participants with these characteristics had not accessed treatment, a recent survey of Canadian providers identified poor access to harm-reduction services and mental-health treatments as the most important barriers to initiating HCV treatments [152].

The strengths of our study were leveraging detailed longitudinal data on a generalizable HIV-HCV co-infected population in combination with the use of quasi-experimental methodology. Without pre-policy longitudinal data collection, the proposed methodology would not be possible. The time-varying changes before and after DAA reimbursements within provinces allowed us to make plausible causal conclusions of the impact of removing fibrosis stage restrictions on treatment uptake among PLWH. Several sensitivity analyses confirmed the result of the primary analysis.

Our study also has limitations. Results are based on participation in the CCC Study, which may not reflect those who have yet to be linked to healthcare, possibly representing up to 15% of the total coinfected population in Canada [136]. This unengaged population most likely represents people who are more marginalized and vulnerable, meaning our results may be optimistic if we generalized to the broader HIV-HCV coinfected population. While our secondary analysis provides insight as to who remains eligible for treatment, this analysis was not designed to attribute causality. Further research is needed to elucidate the individual-level barriers to accessing DAA treatment. Furthermore, our study, and specifically the exposure of interest, coincides with the emerging opioid epidemic [247]. While this crisis has not yet directly impacted death rates in our study population (Supplement Table 7.1), it is possible that physicians may also have been more hesitant to treat active PWID if they believed overdose or reinfection was inevitable. Finally, loss-to-follow-up rates were high, although non-differential between the provinces. If participants who disengaged from care were less likely to have initiated treatment, censoring could be informative, which would lead to an overestimation of our estimates. In contrast, it is also possible that people who were lost-to follow-up may have been treated outside of the CCC. Finally, the impact of universal access to HCV treatments on treatment uptake was limited to three provinces and an average of three years post-policy change in Quebec and only one year in British Columbia and Ontario. More follow up time is required to evaluate if this impact is sustainable.

CONCLUSION:

Using a quasi-experimental design, we show removal of fibrosis restrictions markedly increased treatment access in the short term, particularly for the priority population of PWID to levels that could

result in HCV elimination in HIV-HCV co-infected persons. However, these rates may not be sustainable. To reach elimination, an emphasis on finding innovative ways to address persistent disparities in treatment uptake among vulnerable populations is needed.

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Sharon Walmsley, University Health Network, Toronto, Ontario; and Alex Wong, Regina Qu'Appelle Health Region, Regina General Hospital, Saskatchewan. We thank all study coordinators and nurses for their assistance with study coordination, participant recruitment and care.

Author contributions: As the corresponding author, Dr. Klein has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sahar Saeed

Acquisition, analysis, or interpretation of data: Sahar Saeed, Erin Strumpf, Erica EM Moodie, Leo Wong, Joseph Cox, Sharon Walmsley, Mark Tyndall, Curtis Cooper, Brian Conway, Mark Hull, Valerie Martel-Laferriere, John Gill, Alexander Wong, Marie-Louise Vachon, Marina B Klein

Drafting of the manuscript: Sahar Saeed

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Statistical analysis: Sahar Saeed

Obtained funding: Marina Klein

Study supervision: Marina Klein, Erin Strumpf, Erica Moodie

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Healthcare and AbbVie, and lecture fees from ViiV Healthcare and Gilead. Sharon Walmsley received grants, consulting fees, lecture fees, nonfinancial support and fees for the development of educational presentations from Merck, ViiV Healthcare, GlaxoSmithKline, Pfizer, Gilead, Abbvie, Bristol-Myers Squibb and Janssen. John Gill received personal fees for being a member of the national advisory boards of Abbvie, Gilead, Merck, Janssen, ViiV Healthcare and Bristol-Myers Squibb. Mark Hull has served as a consultant for Merck, Vertex Pharmaceuticals, Pfizer, Viiv Healthcare and Ortho-Jansen. He has received grants from the National Institute on Drug Abuse, and he has received payment for lectures from Merck and Ortho-Janssen. Joseph Cox received grants from ViiV Healthcare and Gilead and personal fees from Bristol-Myers Squibb, Merck and Gilead. Curtis Cooper has received personal fees for being a member of the national advisory boards of Gilead, Merck, Janssen, and Bristol-Myers Squibb

Table 7.1 Baseline Characteristics of CCC participants included in this study

	British Columbia (BC) N= 414	**Ontario (ON) N=326**	**Quebec (QC) N= 390**
Time at risk, (person-years)	1426	1230	1476
Age, median (IQR)	47 (42, 53)	48 (41, 52)	48 (42, 53)
Indigenous	136 (33%)	54 (17%)	11 (3%)
Heterosexual men	190 (46%)	129 (40%)	208 (53%)
Female	140 (34%)	72 (22%)	84 (22%)
Men who have sex with men	80 (19%)	125 (38%)	96 (25%)
Injection drug use (past 6 months)	174 (42%)	79 (24%)	141 (36%)
Income <$18,000 CAD/year	323 (79%)	207 (64%)	326 (84%)
Homelessness	43 (10)	17 (5)	67 (17)
Incarceration (past 6 months)	172 (41)	97 (30)	144 (37)

Alcohol use (past 6 months)	200 (48)	194 (60)	246 (63)
Significant Liver Fibrosis [a]	119 (29%)	113 (35%)	134 (34%)
HCV Genotype			
1	279 (67%)	221 (68%)	252 (64%)
2	19 (5%)	12 (4%)	14 (4%)
3	73 (17%)	38 (12%)	69 (18%)
4	2 (<1%)	17 (5%)	15 (4%)
Missing	41 (10%)	36 (11%)	40 (10%)
HIV RNA undetectable [b]	270 (76%)	240 (82%)	274 (79%)
CD4 cell count, median (IQR)	420 (250, 620)	480 (284, 690)	442 (280, 640)

*Baseline characteristics of the analytical sample. The median date of entry was July 13, 2011 (IQR, Aug 5, 2010, 12 May 2014)

[a] Significant fibrosis was determined using a hierarchical classification, based on availability of a liver biopsy, clinical diagnosis, fibroscan (>7.2 KPa) or AST to Platelet Ratio Index (APRI) ≥1.5)

[b] Proportion based on people on cART

Table 7.2 Relative impact in HCV treatment initiation rates following removal of significant liver fibrosis restrictions

	Relative impact of removing significant liver fibrosis restrictions, Incidence Rate Ratios (IRR)	Adjusted[b] Relative impact of removing significant liver fibrosis restrictions (IRR)
All CCC participants	1.8 (1.4, 2.4)	1.8 (1.3, 2.5)
PWID[c]	3.8 (2.0, 7.3)	3.6 (1.8, 7.4)

[a] Each cell represents a separate regression analysis, for each we included fixed effects for province and year. The natural logarithm of each participant's time at risk (in years) was used as an offset. Standard errors are clustered by individuals. Full regression tables for each analysis in supplemental tables 2

[b] Adjusted models included fixed covariates included age (centered at mean), sex, men who have sex with men (MSM), HCV genotype. Time varying covariate included income (<$18,000 CAD)[166]; injection drug use (within the 6 months); undetectable HIV RNA (<50 copies/mL) and significant fibrosis.

[c] People who inject drugs (PWID) were defined as self-reporting injection drug use within the 6 months of cohort visit. This was treated as time-varying variable.

Figure 7.1: Time Varying Policy Changes by Province

Solid lines represent calendar time when no fibrosis stage restrictions were in place. No line represents either significant (>F2) or advanced (>F3) liver fibrosis stage restrictions were required for reimbursement of DAAs. BC-British Columbia; ON-Ontario and QC-Quebec

Figure 7.2. Hepatitis C Treatment Initiation Trends by Canadian Provinces between 2010 and 2018

Shaded areas represent time when the access to DAAs were not restricted by fibrosis stage in Quebec (grey)* and in British Columbia** (blue) and Ontario** (red)

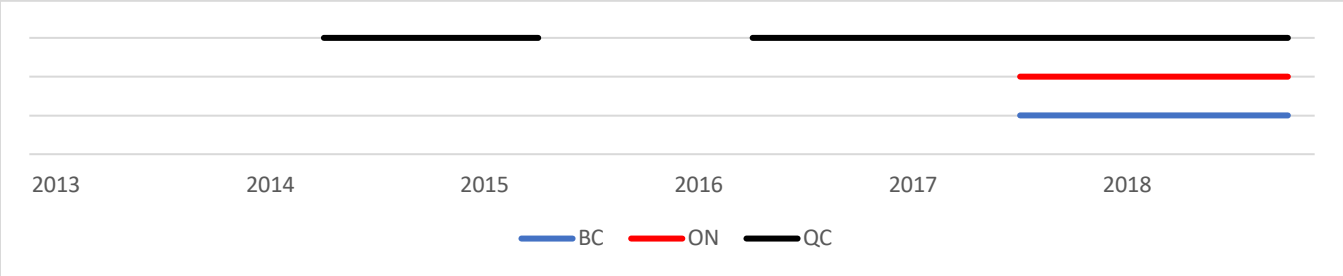
Figure 7.3. Treatment initiations by Fibrosis Stage and Active Injection Drug Use between 2012 and 2018

Figure 7.4. Predictors of remaining HCV RNA+ (Prevalence Risk Ratios) among people living with HIV between 2010-2018

Circles are point estimates; bars are 95% Confidence Intervals. Vertical line indicates the null value of 1.

Incarceration (past 6 months); MSM– Men who have sex with men; active PWID– people who inject drugs (past 6 months); undetectable HIV VL– (<50 copies/mL); HCV Genotype 3 compared to Genotype 1, 2 or 4; ON- Ontario QC- Quebec compared to the province of British Columbia; Loss-to-follow-up (no visit within 18 months of administrative censoring date)

Figure 7.1 Time Varying Policy Changes by Province [a,b,c,d,e]



BC-British Columbia; ON-Ontario and QC-Quebec

[a] Solid lines represent calendar time when no fibrosis stage restrictions were in place. No line represents either significant (>F2) or advanced (>F3) liver fibrosis stage restrictions were required for reimbursement of DAAs.

[b] Before 2013, due to the lower efficacy and higher toxicity of interferon-based therapies in HIV-HCV co-infection, typically, only people with advanced fibrosis who were felt to be at increased risk for short term adverse liver–related outcomes were treated with pegylated-interferon

[c] Quebec: In 2014, simeprevir and sofosbuvir were unrestricted for patients living with HCV. Although HIV infection was a listed restriction, co-infected patients were usually granted access on a case by case basis through the "patient d'exception" process; As of 2016, people co-infected with HIV and HCV were considered a priority population and sofosbuvir/ledipasvir and ombitasvir/paritaprevir/ritonavir/dasabuvir were available without fibrosis stage restrictions; sofosbuvir/velpatasvir followed as of 2017

[d] British Columbia and Ontario: In 2017, after the pan-Canadian Pharmaceutical Alliance used collective bargaining to reduce DAA drug prices across Canada, provinces removed fibrosis stage restrictions as a criterion for treatment reimbursement.

[e] No sobriety restrictions were present in Canada.

Figure 7.2 Hepatitis C Treatment Initiation Trends by Canadian Provinces Trends between 2010 and 2018

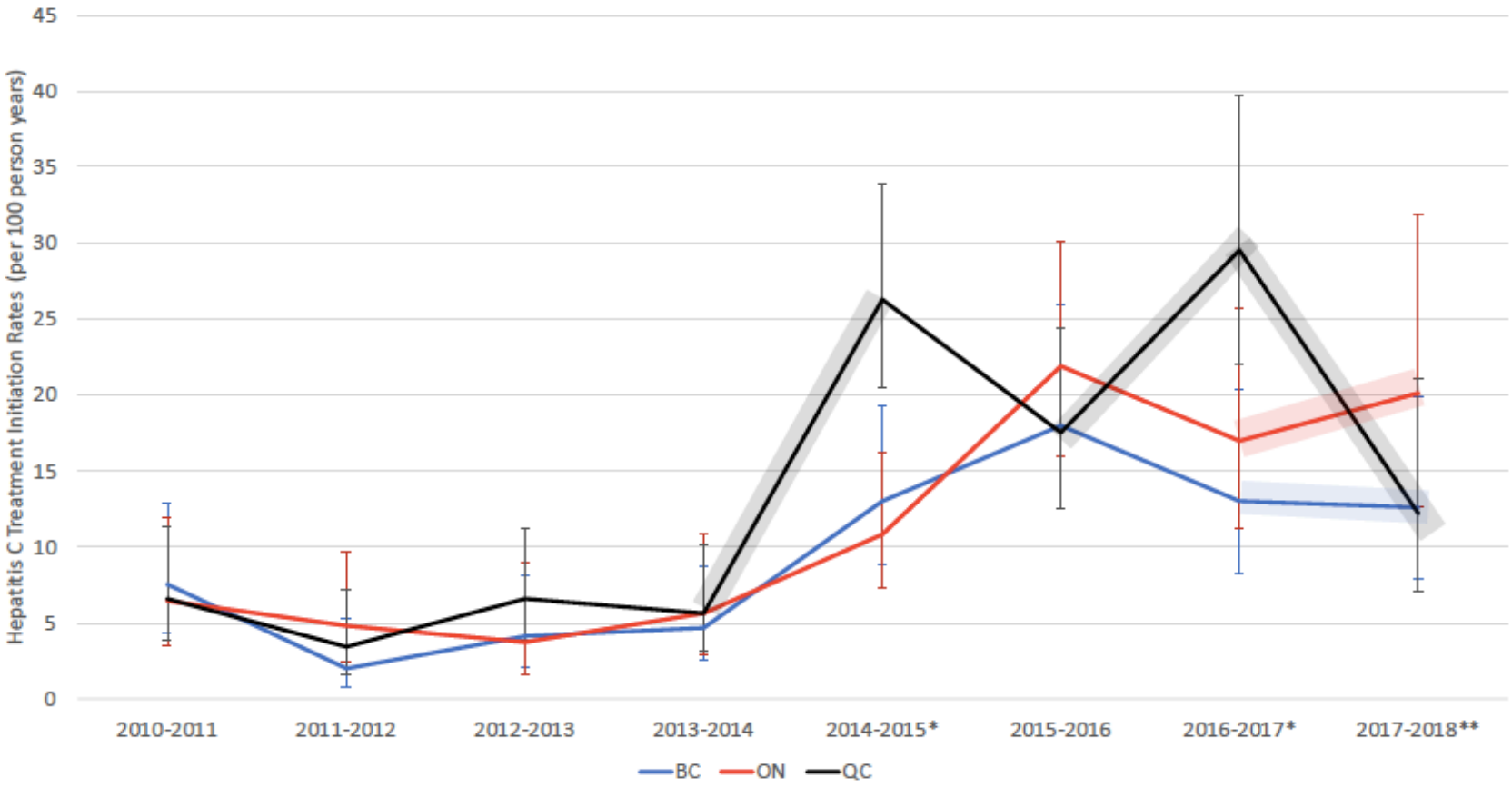


Figure 7.3 Treatment initiations by Fibrosis Stage and Active Injection Drug Use between 2012 and 2018

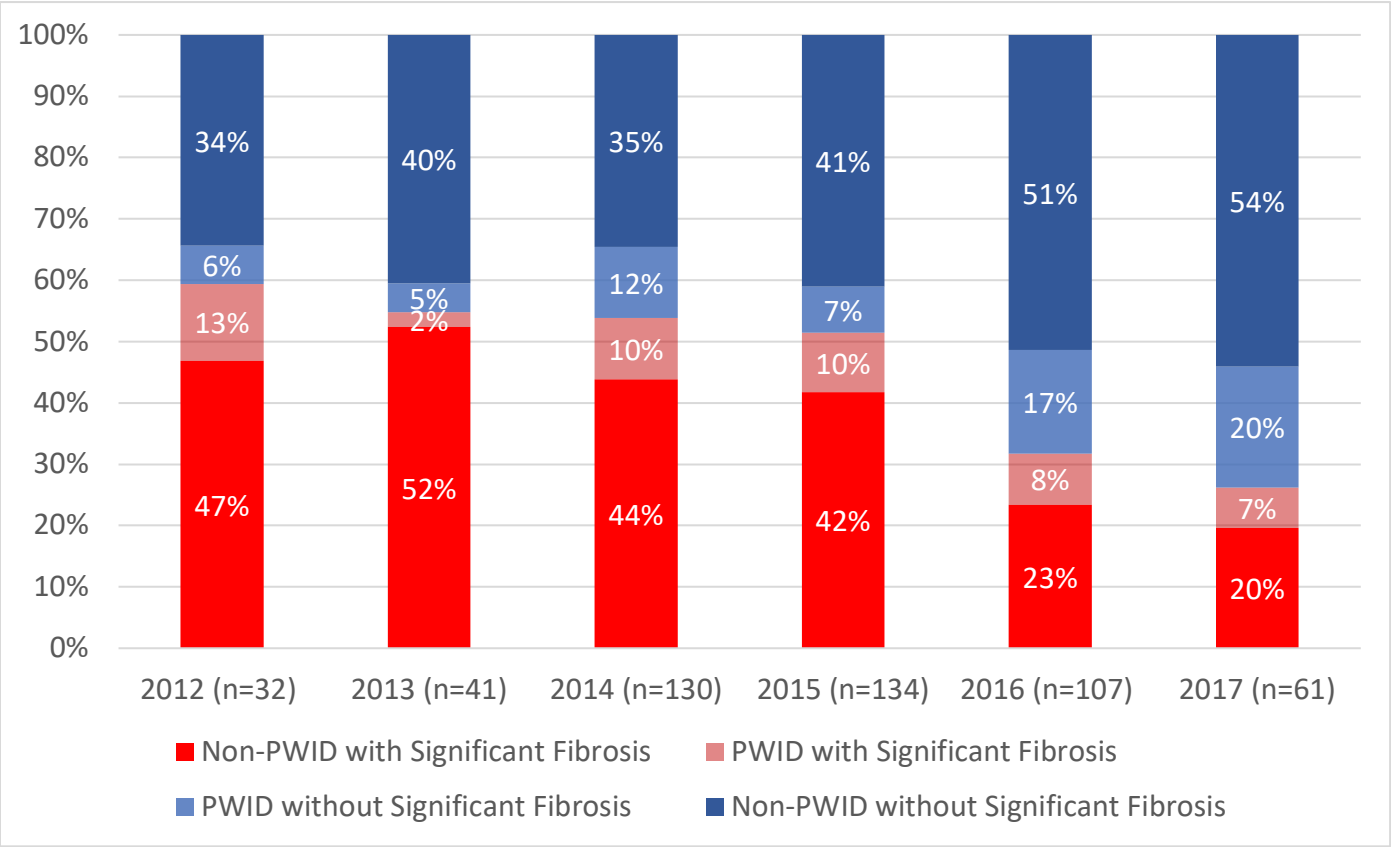
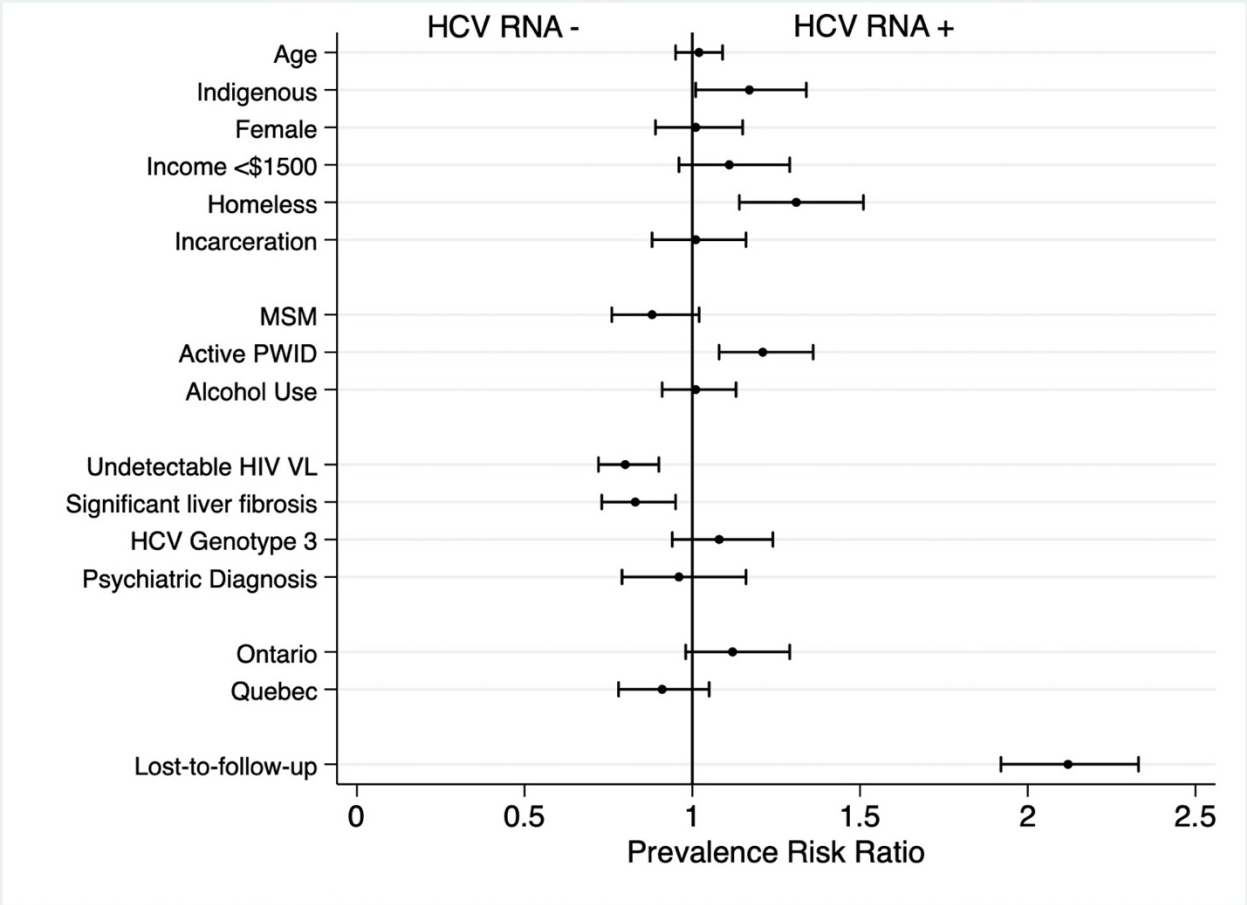
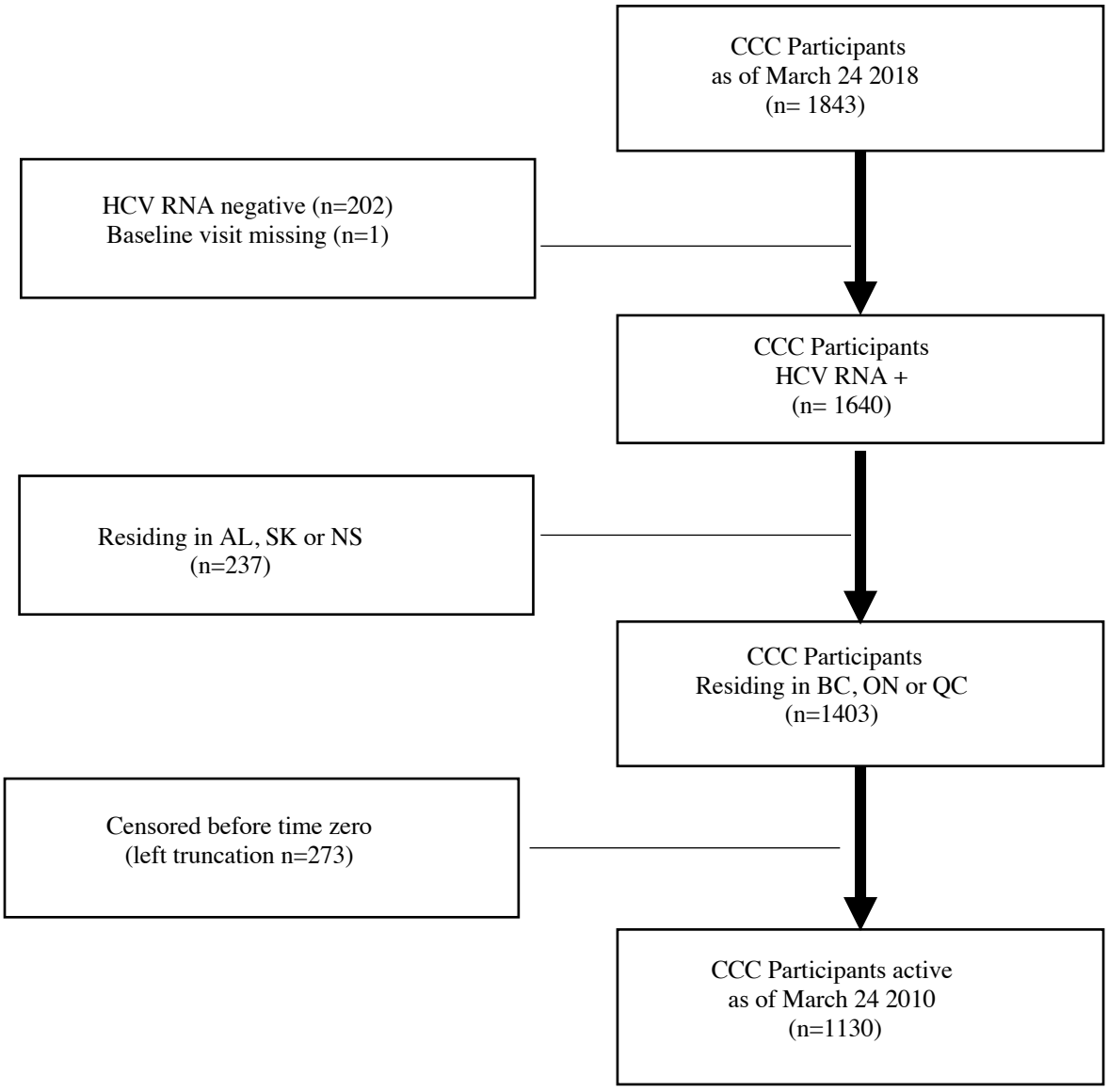


Figure 7.4 Predictors of remaining HCV RNA+ (Prevalence Risk Ratios) among people living with HIV between 2010-2018

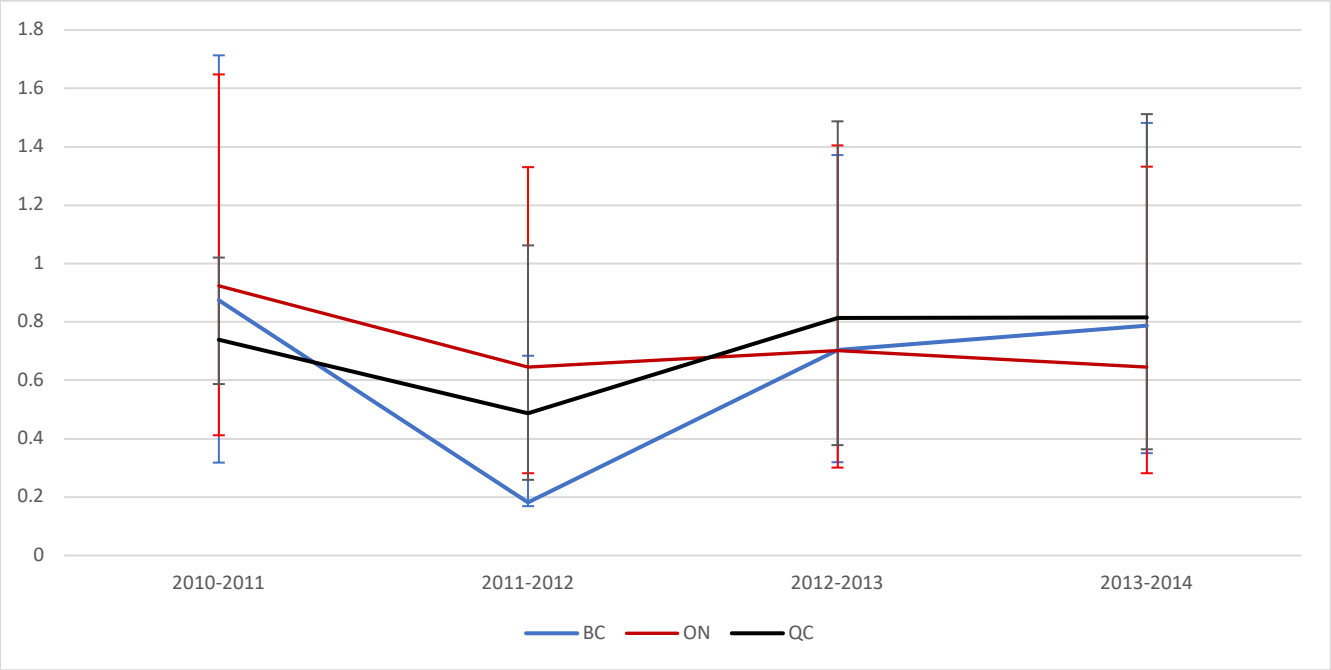


7.3 Appendix to Manuscript 3

Supplemental Figure 7.1 Selection of Analytical Sample



Supplemental Figure 7.2 Parallel Trends Assumption verified on logarithmic Scale. Treatment initiations before fibrosis stage restrictions removed



Supplemental Table 7.1 Censoring Reasons across Provinces

Censoring	Overall N=631	BC N=253	ON N=189	QC N=188
Administrative Censoring	259 (41%)	112 (44%)	70 (37%)	77 (41%)
Lost-Follow Up	254 (40%)	111 (44%)	73 (39%)	70 (37%)
Withdraw	29 (5%)	11 (4%)	13 (7%)	5 (3%)
Death	92 (15%)	21 (8%)	33 (17%)	38 (20%)
Spontaneous Clearance	38 (6%)	17 (7%)	10 (5%)	11 (6%)

Supplemental Table 7.2 Impact of removing fibrosis stage restrictions on hepatitis C treatment initiation rates overall and among people who inject drugs (PWID), full regression models

	Overall IRR (95% CI)	Adjusted Overall IRR (95% CI)	PWID IRR (95% CI)	Adjusted PWID IRR (95% CI)
Year Ref: 2013-2014				
2011-2012	1.0 (0.6, 1.6)	1.0 (0.6, 1.6)	4.5 (1.2, 16.8)	4.1 (1.1, 15.8)
2012-2013	0.9 (0.6, 1.4)	0.9 (0.6, 1.5)	2.6 (0.7, 10.5)	2.6 (0.6, 10.3)
2014-2015	2.5 (1.7, 3.6)	2.8 (1.9, 4.0)	5.5 (1.7, 18.2)	5.9 (1.8, 19.4)
2015-2016	3.5 (2.5, 5.0)	4.1 (2.8, 5.9)	7.9 (2.3, 26.5)	8.4 (2.5, 28.0)
2016-2017	2.7 (1.8, 3.9)	3.4 (2.3, 5.0)	6.1 (1.8, 20.6)	7.4 (2.2, 24.6)
2017-2018	1.3 (0.8, 2.2)	1.9 (1.1, 3.1)	2.1 (0.5, 7.9)	2.5 (0.6, 10.1)
Province Ref: BC				
ON	0.9 (0.7, 1.2)	0.5 (0.4, 0.7)	0.8 (0.4, 1.7)	0.5 (0.2, 1.0)
QC	0.7 (0.5, 1.0)	0.6 (0.4, 0.8)	0.4 (0.2, 0.7)	0.3 (0.1, 0.5)
DD estimator [a] Time-varying policy change	1.8 (1.4, 2.4)	1.8 (1.3, 2.5)	3.8 (2.0, 7.3)	3.6 (1.8, 7.4)
Age (per 10 yrs)		0.9 (0.7, 1.0)		1.0 (0.7, 1.3)
Income (<$1500 CAD/month)		0.7 (0.5, 0.9)		0.6 (0.3, 1.1)
Female Ref: Heterosexual men		0.9 (0.7, 1.0)		0.9 (0.5, 1.7)
MSM Ref Heterosexual men)		2.0 (1.5, 2.6)		2.3 (1.3, 4.1)
Indigenous		0.7 (0.5. 1.0)		0.6 (0.3, 1.1)
Active injection drug use (last 6 months)		0.6 (0.4, 0.7)		NA
Significant liver fibrosis		2.4 (1.9, 3.0)		3.1 (1.8, 5.1)
Genotype 3		1.0 (0.7, 1.3)		0.8 (0.4, 1.4)
Undetectable HIV viral load		1.7 (1.3, 2.3)		2.6 (1.4, 4.6)

[a](Year of policy change*Province that implemented changes)

Supplemental Table 7.3 Robustness check effect measure modification by fibrosis stage

	IRR (95% CI)
Year Ref: 2013-2014	
2011-2012	1.0 (0.6, 1.6)
2012-2013	0.9 (0.6, 1.4)
2014-2015	2.6 (1.8, 3.7)
2015-2016	3.8 (2.6, 5.4)
2016-2017	3.0 (2.1, 4.4)
2017-2018	1.5 (0.9, 2.5)
Fixed Province (Ref: BC)	
ON	0.8 (0.6, 1.0)
QC	0.7 (0.5, 0.9)
No Fibrosis Reference: Significant fibrosis	0.4 (0.3, 0.5)
DD estimator [a] Time-varying policy change	1.4 (0.9, 2.0)
DDD estimator [b]	1.5 (1.0, 2.2)

[a](Year of policy change*Province that implemented changes)
[b](Year of policy change*Province that implemented changes*no significant fibrosis)

Supplemental Table 7.4 Robustness check Difference-in-Differences "Lead" and "Lag"

	Lead Model[a] IRR (95% CI)	Lag Model[b] IRR (95% CI)
Fixed Year (Ref: 2012-2013)		
2010-2011	1.0 (0.6, 1.6)	1.0 (0.6, 1.6)
2011-2012	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)
2013-2014	3.1 (2.2, 4.3)	3.1 (2.2, 4.3)
2014-2015	3.8 (2.7, 5.5)	4.2 (2.9, 6.0)
2015-2016	3.5 (2.3, 5.5)	3.6 (2.5, 5.2)
2016-2017	2.5 (1.6, 4.0)	2.8 (1.8, 4.2)
Fixed Province (Ref: BC)		
ON	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
QC	1.0 (0.7, 1.3)	1.0 (0.8, 1.4)
Time-varying policy change DD estimator (Year of policy change*Province that implemented changes)	1.0 (0.7, 1.4)	0.8 (0.5, 1.1)

[a] To assess if HCV treatment uptake pre-dated the policy change. As if policy changed in June 2013 (in Quebec); March 2016 (in British Columbia and Ontario)
[b] To assess the sustainability of the policy change. This was limited to one-year post policy change in Quebec (two time periods) only since other provinces did not have more than one-year of follow up post policy change.

Supplemental Table 7.5 Falsification Tests, linear regression

	Creatinine μmol/L
Intercept	80 (75.5, 84.5)
Fixed Year (Ref: 2012-2013)	
2010-2011	0.2 (-3.5, 3.9)
2011-2012	-0.6 (-4.3, 3.1)
2013-2014	2.8 (-1.1, 6.7)
2014-2015	4.4 (0.4, 8.3)
2015-2016	5.4 (0.7, 10.1)
2016-2017	7.3 (0.5, 14.0)
Fixed Province (Ref: BC)	
ON	-2.1 (-7.7, 3.6)
QC	0.5 (-4.9, 6.0)
Time-varying policy change DD estimator (Year of policy change*Province that implemented changes)	-0.8 (-5.3, 3.8)

Supplemental Table 7.6 Characteristics of CCC participants (HCV RNA+) who remain to be treated.

	Active[a] (n=259)	Lost-to-Follow-up[b,c] (n=228)	Overall (n=487)
Age (yrs)	50 (44, 56)	49 (43, 55)	49 (43, 55)
Indigenous	67 (26)	35 (15)	102 (21)
Female	78 (30)	61 (27)	139 (29)
Income (<$1500 CAD/month)	198 (76)	176 (79)	374 (77)
Homelessness	39 (15)	30 (13)	69 (14)
Incarceration (in the last 6 months)	44 (17)	53 (24)	97 (20)
MSM	58 (22)	44 (19)	102 (21)
PWID	96 (37)	87 (39)	183 (38)
Alcohol use	132 (51)	129 (56)	261 (54)
Province British Columbia Ontario Quebec	 110 (42) 70 (27) 74 (29)	 98 (43) 64 (28) 66 (29)	 208 (43) 134 (28) 140 (29)
CD4 (cells/mm3)	481 (280, 725)	480 (280, 652)	480 (280, 690)
Undetectable HIV Viral Load (<50 copies/ml)	175 (68)	159 (70)	334 (69)
Significant fibrosis	61 (24)	60 (26)	121 (25)
Genotype 3	58 (22)	34 (15)	92 (19)
Psychiatric Diagnosis	19 (7)	25 (11)	44 (9)

Continuous variables are summarized as IQR and dichotomized variables are n (%)

[a] CCC participants from the analytical sample with a visit within 18 months of administrative censoring date (March 2018)

[b] CCC participants from the analytical sample without a visit within 18 months of administrative censoring date.

[c] Median years lost-to-follow was 2.9 years (IQR 1.4, 4.4)

CHAPTER 8: REAL-WORLD IMPACT OF DAA THERAPY ON HEALTH-RELATED QUALITY OF LIFE (MANUSCRIPT 4)

8.1 Preface to Manuscript 4

The results of this thesis so far have suggested that HCV treatment uptake has rapidly increased with the introduction of DAAs and that access has expanded more broadly than the populations studied in clinical trials. Furthermore, we can expect high cure rates in all populations. This motivated an evaluation of the individual level benefits of DAA therapy.

Chapter 8 evaluates the real-world impact of DAAs on Health-Related Quality of Life (HR-QoL). HR-QoL is a patient-centered outcome that has gained worldwide recognition as an important metric for examining the relationship between cost and value. Results from clinical trials of DAAs reported significant improvements of HR-QoL, but the extent to which these results are broadly generalizable to a real-world setting is unknown (Chapter 4). Very few studies evaluated HR-QoL among marginalized populations (such as individuals co-infected with HIV) who face many issues such as low socioeconomic status, active substance abuse and mental health disorders that potentially impact HR-QoL. Although curing HCV is an acute exposure, it is important to distinguish the immediate effect of treatment response (which may reflect the patients' positive perceptions of being cured) from the long-term impact of successful treatment on HR-QoL due to viral clearance. Furthermore, previous studies had reported chronic HCV to be associated with extra-hepatic conditions including insomnia, pain and neurological effects that could impact quality of life. Using quasi-experimental methodology and longitudinal data from the CCC, I assessed the impact of successful treatment with oral DAA therapy on HR-QoL in the following chapter.

The results of this objective were presented orally at the Canadian Association for Health Services Research (May 2018, Montreal). This work was also published in the Journal of Viral Hepatitis in December 2018 (available via early access in September 2018).

8.2 Real-World Impact of Direct Acting Antiviral Therapy on Health-Related Quality of Life in HIV/Hepatitis C Co-Infected Individuals

Running Title: Impact of DAAs on HR-QoL

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Conflict of Interest Statement

None of the authors feel in conflict of interest with regards to this study and there was no pharmaceutical industry support to conduct this study. Sahar Saeed, Erin C Strumpf and Erica Moodie, have no conflicts of interest to declare. Marina Klein has received research grants for investigator-initiated trials from Merck, ViiV Healthcare and Gilead; consulting fees from ViiV Healthcare, Bristol-Meyers Squibb, Merck, Gilead and AbbVie. John Gill has received personal fees for being a member of the national advisory boards of AbbVie, Gilead, Merck, Janssen, and ViiV Healthcare. Alex Wong received consulting and honoraria from Merck, Gilead Sciences, Bristol Myers Squibb, Pfizer, Janssen, Boehringer-Ingelheim, and AbbVie. Funding for regional and provincial programming was received from Merck, Gilead Sciences, Bristol Myers Squibb, ViiV, Janssen, and AbbVie. Sharon Walmsley received grants, consulting fees, lecture fees, nonfinancial support and fees for the development of educational presentations from Merck, ViiV Healthcare, GlaxoSmithKline, Pfizer, Gilead, Abbvie, Bristol-Myers Squibb and Janssen. Curtis Cooper reports consulting fees from AbbVie, Gilead, and Merck; and grants from AbbVie and Gilead. Valérie Martel- Laferrière reports consulting fees from Merck and Gilead; grant from Gilead; and lecture fees from AbbVie, Merck and Gilead. Mark Hull received grant support

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ABSTRACT

Clinical trial results of direct acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) have shown improvements in health-related quality of life (HR-QoL). However, the extent to which these results are broadly generalizable to real-world settings is unknown. We investigated the real-world impact of oral DAA therapy on HR-QoL among individuals co-infected with HIV/HCV. We used data from the Canadian HIV-HCV Co-Infection Cohort Study that prospectively follows 1795 participants from 18 centers. Since 2007, clinical, lifestyle, and HR-QoL data have been collected biannually through self-administered questionnaires and chart review. HR-QoL was measured using the EQ-5D instrument. Participants initiating oral DAAs, having at least one visit before treatment initiation and at least one visit after DAA treatment response was ascertained were included. Successful treatment response was defined as a sustained viral response (SVR). Segmented multivariate linear mixed models were used to evaluate the impact of SVR on HR-QoL, controlling for pre-treatment trends. 227 participants met our eligibility criteria, 93% of whom achieved SVR. Before treatment, the EQ-5D utility index decreased 0.6 percentage-point/year (95% CI, -0.9, -0.3) and health state was constant over time. The immediate effect of SVR resulted in an increase of 2.3-units (-0.1, 4.7) in patients' health state and 2.0 percentage-point increase (-0.2, 4.0) in utility index. Health state continued to increase post-SVR by 1.4 units/year (-0.9, 3.7), while utility trends post-SVR plateaued; over the observation period. Overall using real-world data, we found modest improvements in HR-QoL following SVR, compared to previously published clinical trials.

Key Words: Direct Acting Antivirals (DAAs), HIV, Hepatitis C, EQ-5D, Health-Related Quality of Life (HR-QoL)

INTRODUCTION:

Direct acting antivirals (DAAs) revolutionized the clinical management of hepatitis C virus (HCV) [15]. HCV is now the first chronic viral infection that can be cured; which is achieved in >90% of all infected individuals using oral DAA therapy, with almost no side effects [15].

It is estimated that 2.3 million (interquartile range (IQR) 1.3–4.4) people worldwide are co-infected with HIV and HCV, of whom 59% are people who inject drugs (PWID) [5]. Arguably individuals who are co-infected with HIV and HCV stand to benefit the most from DAA therapy, as they progress faster to end stage liver disease if HCV infection is left untreated [11,100,241]. While clinical trials have demonstrated DAAs to be highly efficacious and associated with improvements in patient-reported outcomes (PROs) in HCV mono-infection, it remains unknown if similar benefits will be observed in the real-world settings. More specifically, it is unknown if patients co-infected with HIV will experience similar improvements as they may have additional co-morbidities that impact quality of life.

PROs are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response" [104]. PROs include multidimensional constructs, such as Health-Related Quality of Life (HR-QoL), that assess the well-being (including physical, emotional, and social functioning) of individuals. HR-QoL has gained worldwide recognition as a patient-centered outcome of healthcare interventions and has become an increasingly important metric for examining the relationship between treatment cost and value [104]. Results from clinical trials evaluating DAA-based regimens have shown improvements in a variety of PROs, including HR-QoL, in patients' mono-infected with HCV

[106-124]. However, as we and others have noted, clinical trial populations have limited generalizability to real-world populations, and therefore the results of clinical trials may not necessarily be transferable [248]. Exclusion of active substance users and people co-infected with HIV from clinical trials are likely to impact changes in HR-QoL. In addition, while PROs are usually assessed in clinical trials at baseline, multiple times during treatment, the end of treatment (EOT), and when treatment response is ascertained (12 weeks post-EOT), they are seldom evaluated afterwards [249]. Finally, some clinical trials that reported the impact of HCV treatment on PROs were open-label (i.e. without a placebo group). Therefore, changes in PROs may have been subject to the Hawthorne effect, whereby individuals may modify aspects of their behavior in response to their awareness of being observed. To our knowledge, no clinical trials or observational studies have investigated changes in HR-QoL after ascertainment of treatment response following oral DAA treatment. We therefore investigated the impact of successful DAA therapy on HR-QoL in a real-world cohort of individuals co-infected with HIV-HCV.

METHODS:

Study Population: The Canadian Co-infection Cohort Study (CCC) is a publicly-funded prospective cohort of 1795 HIV-positive adults with evidence of HCV infection (HCV antibody-positive) recruited from 18 centres across Canada [158]. Participating centers comprise of urban tertiary care and community-based hospitals, private clinics, and street outreach programs with the goal of capturing a representative sample of patients in care [158]. After obtaining informed consent, socio-demographic variables, PROs, and clinical data are collected prospectively via self-administered questionnaires and chart review every six months. Details on HCV treatments and subsequent responses are extracted from participants' medical records using standardized

case report forms. The CCC is approved by the community advisory committee of the Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network and by all institutional ethics boards of the participating centres.

Eligibility: CCC participants who initiated oral DAA therapy through standard of care, had at least one questionnaire completed before initiating DAAs (pre-treatment), and at least one questionnaire completed following ascertainment of treatment response (post-treatment) were included. Participants who initiated DAAs through clinical trials were excluded.

Exposures: Oral DAAs were defined as regimens containing sofosbuvir/ribavirin, simeprevir/sofosbuvir, sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir/dasabuvir, sofosbuvir/daclatasvir, grazoprevir/elbasvir, and sofosbuvir/velpatasvir in the absence of interferon. Successful treatment response was defined as a sustained virologic response (SVR); HCV RNA-negative 12 weeks post-EOT. Treatment failure was defined as (i) EOT non-response (HCV RNA-positive), (ii) relapse (HCV RNA-negative at EOT, but HCV RNA-positive prior to SVR), or (iii) premature discontinuation (due to side effects or non-adherence).

Outcome: HR-QoL was measured using the EuroQoL Group-5 Dimensional, 3-Level Version (EQ-5D-3L) instrument in English or French. The EQ-5D-3L is made up of two components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system, respondents reported the extent of difficulty (no/some/extreme problems) in five health domains: mobility, self-care, usual activities, pain/discomfort, anxiety, or depression. The results from the 5 health domains are then converted into a composite utility score using a

Canadian-based algorithm [167]. Utility scores ranged from 0 to 1, reflecting death (0) to full health (1) results in the manuscript are reported as percentage-points for ease of interpretability, in the Table 8.1 results are reported as beta coefficients to be consistent with the literature. The EQ VAS reflects the overall respondents' health state and ranges from the worst health state (0) to the best health state possible (100) results are reported as a unit change [168].

Statistical Analysis: Sociodemographic, clinical and treatment regimens were summarized for all participants who met eligibility criteria at DAA treatment initiation. The five individual health domains of EQ-5D were summarized at cohort entry, at DAA initiation and at participants last visit (post-DAA response).

Segmented generalized linear mixed models, also known as multiple baseline interrupted time series, allowing for individual random intercepts were used to evaluate the impact of treatment response on HR-QoL [169,170]. The use of random effects captures natural heterogeneity across individuals. Individual-specific intercepts are estimated efficiently by assuming they arise from a normal distribution [209] and by borrowing strength from individuals with many data points to learn about individuals with fewer measurements. This model is particularly useful in settings where repeated measurements are made on the same individuals. Time zero was defined at DAA treatment initiation (or using data from the closest cohort visit prior to initiating DAA treatment). The pre-treatment period included all observations from cohort entry to DAA initiation (while participants were HCV RNA-positive). The post-treatment period included all observations from the date treatment response was ascertained until the administrative censoring date (October 2017). As our objective was to evaluate the impact of the response to DAA therapy (SVR or non-response) as opposed to the treatment itself, we censored observations between treatment

initiation and ascertainment of treatment response. By design, since the same individual is observed before and after exposure, patients act as their own controls, meaning that both known (e.g. sex, ethnicity, socioeconomic status) and unknown/unmeasured (e.g. genetics, motivation, determination) time-invariant confounders are accounted for[170]. The model was parameterized to include an intercept (baseline level of HR-QoL at treatment initiation), a pre-treatment slope (change in HR-QoL/year), an indicator to reflect the immediate change in HR-QoL between treatment initiation and treatment response, and a post-treatment slope (change in HR-QoL /year). The pre-treatment trends in the outcomes act as the counterfactuals for the post-treatment trends, so that the impact of the exposure can be estimated as any change in the level of the outcome at the beginning of the post-treatment period and any change in slope in the post-treatment period.

Predictors of HR-QoL at DAA initiation were estimated using multivariate generalized linear mixed models. Models included the following fixed covariates at DAA initiation; age (centered at mean), sex, advanced fibrosis (measured as an AST to Platelet Ratio (APRI) score ≥1.5), prior HCV treatment exposure, and time varying covariates which included: undetectable HIV RNA (<50 copies/mL), diagnosis of a psychiatric disorder, income (dichotomized by greater/less than $1500 CAD/month), and recent injection drug use (in the last 6 months). Because of the limited number of individuals who did not respond to DAA therapy, we did not evaluate predictors of HR-QoL among this group of people.

RESULTS:

Between 2014 and 2017, 363 participants initiated oral DAAs. After excluding participants who

accessed DAAs through clinical trials (n=44), those for whom treatment response was missing (n=29), and those who did not participate in at least 1 visit before and 1 visit after DAA treatment (n=63), 227 participants were included in the analysis. Baseline characteristics of excluded participants did not differ appreciably from those included suggesting that no selection bias was introduced by our inclusion criteria (data not shown). From the 227 participants, 1761 observations, contributed to the pre-treatment time-period (median follow-up, 2.8 years (IQR 1.1, 5.2). The post-treatment time-period included 516 observations (median follow-up, 0.6 years (IQR 0.2, 1.1). Two-hundred and ten (93%) participants achieved SVR.

The most commonly prescribed DAA therapy was ledipasvir/sofosbuvir, which 156 (69%) patients initiated. The next most commonly prescribed therapies were sofosbuvir/ribavirin (25 patients, 11%), simeprevir/sofosbuvir (17 patients, 7%), ombitasvir/paritaprevir/ritonavir/dasabuvir (14 patients, 6%), elbasvir/grazoprevir (9 patients, 4%), sofosbuvir/daclatasvir (4 patients, 2%), and sofosbuvir/velpatasvir (2 patients, 1%). At the time of initiating DAAs, the median age was 52 years (IQR 48, 56). The majority of the patients were male (75%), had well-controlled HIV infections (88% had an HIV viral load <50 copies/mL and the median CD4+ T-cell count was 510 cells/mL (IQR 300, 705)). Twenty-eight percent of the participants had evidence of liver fibrosis (based on an APRI score of greater than 1.5) (Table 8.1). The median current health state (EQ VAS) was 70 (IQR 60, 80) and the utility score was 0.8 (IQR 0.7, 1.0). Of the 5 health states, moderate to extreme anxiety/depression and pain/discomfort were most prevalent at treatment initiation (45% and 60%, respectively) (Supplemental Table 8.1).

Health states and utility scores were both constant over the pre-treatment period in patients who responded to treatment (SVR) and in those with treatment failure (NR, no response) (Figure 8.1). In contrast, the post-treatment period, slopes changed noticeably in all groups, except for the utility score among patients who achieved SVR (Figure 8.1, panel C), where after an initial improvement, the slope plateaued similar to the pre-treatment period. Table 8.2 quantifies results from Figure 8.1. The immediate effect of SVR on patients' health state (that is from pre-treatment initiation to ascertainment of SVR) was a 2.3-unit increase (95% CI, -0.1, 4.7). Health state continued to increase post-SVR by 1.4 units/year (95% CI, -0.9, 3.7), controlling for the immediate change and the pre-treatment trends (Table 8.2). Predictors of lower health state were income of less than $1500 CAD/month. Men who have sex with men (MSM) and people with an undetectable HIV viral load both reported higher health states at baseline, respectively (Table 8.1). The immediate effect of SVR on utility score was a 1.9 percentage-point increase (95% CI, -0.4, 4.3). However post-SVR trends in utility scores plateaued, when controlling for the immediate change and the pre-treatment trends (Table 8.2). Predictors of utility scores were similar to those that predicted health state with the addition of a recent injection drug use as a being a significant predictor of lower utility scores.

Only 17 people from our analytic sample did not respond to treatment. Among non-responders to DAA treatment there was no immediate statistical change in patients' health state following ascertainment of treatment response. However, health state and the utility index did decrease significantly post-treatment, controlling for the immediate and the pre-treatment trends (Supplemental Table 8.2).

DISCUSSION:

We report the impact of SVR following oral DAA therapy on HR-QoL in a real-world setting in individuals co-infected with HIV-HCV. Since HCV is a chronic infection it is important to distinguish the immediate effect of treatment which may reflect the patients' positive perceptions or "feelings" from being cured as opposed to long-term impacts of successful treatment on health which may be "biological" in nature due to eliminating the virus [249]. Using the minimal clinical important difference criteria (MCID) for PROs (3-5%) [250,251], we found SVR to have no benefit on the self-perceived health state immediately after ascertainment of treatment response. Health state trends increased in the years following SVR, but this benefit was not statistically significant. Similarly, there was a modest immediate improvement in utility scores however, trends post-treatment plateaued. In contrast, among individuals who failed DAA treatment, there was no immediate impact on health state however, there was a significant decline in utility scores over time, that met the MCID.

There are a limited number of studies that have evaluated HR-QoL in co-infected individuals following DAA treatment. Compared to previously published clinical trials, results from this study are less pronounced. The ION-4 trial evaluated changes of PROs from baseline to 4 weeks post-EOT for participants taking sofosbuvir-ledipasvir. General health, as measured using the SF-36 instrument, improved by 5% [124]. The same investigators evaluated the sofosbuvir-velpatasvir regimen from the ASTRAL-5 clinical trial and found that SVR was associated with significant improvements in 19/26 PRO domains, resulting in improvements ranging from 3.2% to 13.3% [122]. Changes in PROs following other DAA regimens such as ombitasvir/paritaprevir/ritonavir/dasabuvir and sofosbuvir-daclatasvir have been studied less in

individuals co-infected with HIV-HCV[249]. Among individuals with HCV mono-infection, investigators of the MALACHITE I and II trials, evaluating the impact of ombitasvir/paritaprevir/ritonavir/dasabuvir and found minimal improvements in PROs after treatment (ranging from a 2-unit decrease (SD 10.1) to a 3-unit increase (SD 6.4)) using the SF-36 physical and mental component summary score [252]. Two groups presented data on the impact of grazoprevir/elbasvir regimens on HR-QoL from the C-EDGE CO-INFXN and C-EDGE CO-STAR trials and found improvements in different components of the (MOS) 36-Item Short-Form Health Survey (SF-36) compared to placebo, but the results have not yet been published [249]. We attribute the difference between our study and published clinical trials to (1) the heterogeneity of our cohort, reflecting a real-world population and (2) when PROs were measured post-treatment. Firstly, our study population, unlike clinical trial populations, included people with many competing issues such as low socio-economic status, active injection drug and/or other substance use within 6 months of initiating treatment, and mental health disorders – all factors that were associated with lower HR-QoL. Secondly, similar to the clinical trials we observed an immediate impact of HCV treatment response, from baseline to response; albeit not as strong. However, assessing changes in PRO only up to the date the patient is informed of their treatment response may lead to overly optimistic conclusions about effect of HCV treatment on HR-QoL as results are most likely to reflect the initial euphoria of having obtained an HCV cure. Such approaches provide little evidence that observed improvements in HR-QoL will continue or even be maintained.

The strength of our study was we leveraged longitudinal data on a generalizable HIV-HCV co-infected population with quasi-experimental methodology. We used repeated measurements of

HR-QoL over a substantial pre-treatment period to construct a counterfactual extension of how HR-QoL would have continued in the absence of treatment and subsequent response to DAA therapy. Changes in HR-QoL before treatment are consistent with a previous report from a US national representative sample [253]. However, to make causal conclusions of the role of HCV viral cure on HR-QoL we made the assumption that no other exogenous factors other than the treatment had an impact on HR-QoL; an assumption that cannot be verified. Our study has other limitations. We only analyzed HR-QoL as measured by the EQ-5D instrument, while most clinical trials use multiple instruments. Instruments include generic instrument such as the SF-36, disease-specific instruments like the Chronic Liver Disease Questionnaire (CLDQ-HCV), and instruments designed to measure fatigue (FACIT-F) and work productivity (WPAI: SHP). Although the EQ-5D is a single generic measure of HR-QoL, a systematic review of PRO showed that this instrument was responsive to changes between groups and/or over time in patients living with HIV [254]. The EQ-5D has been noted to have problems with ceiling effects and therefore the use of the scale in individuals with early asymptomatic HIV infection is not recommended [255]. The concern of a ceiling effect may also extend to people with asymptomatic HCV infections and maybe a reason why the improvement in health state post-treatment based on the VAS did not translate to improvements of utility scores [256,257]. Stratifying by fibrosis severity may address this concern however this was not possible given the limited sample size. Finally, only 17 people failed treatment. There were no appreciable differences in clinical characteristic of the 17 people who failed compared to those who achieved SVR. However, power was limited to make inference on the clinical factors associated with of failing DAA therapy on HR-QoL. This will continue to be an issue given the era of highly effective

treatments, however this population should not be neglected, as our results do suggest substantial reductions in HR-QoL.

CONCLUSION:

Treatment uptake of these curative therapies has expanded to broader populations then what was published in clinical trials. Marginalized populations such as those co-infected with HIV face many competing issues that impacts HR-QoL and these are likely to remain even after viral clearance. In a real-world population of HIV-HCV co-infected individuals we observed modest improvements in HR-QoL following SVR with oral-DAA therapy, compared to previously published clinical trials. Longer follow up is required to examine if this impact is sustained or returns to pre-treatment levels.

Table 8.1 Characteristics of Canadian HIV-HCV Cohort participants at DAA initiation

	Median (IQR) or No. (%) N=227
Age, years	52 (48, 56)
Women	57 (25%)
Indigenous people	22 (10%)
Men who have sex with men (MSM)	80 (35%)
Single	157 (70%)
Education (>high school diploma)	78 (34%)
Gross annual income †, <$18,000 CAD	162 (72%)
Psychiatric diagnosis	16 (7%)
Living in shelter or homeless	21 (10%)
History of IDU	168 (74%)
Active PWID ‡	44 (20%)
Alcohol use	118 (53%)
Tobacco smokers	182 (80%)
Time since HIV diagnosis, years	18 (12, 24)
Undetectable HIV RNA	192 (88%)
CD4 T-cell count, cells/mm^3	510 (300, 705)
On cART	218 (96%)
Duration HCV Infection, years	25 (14, 31)
HCV Genotype, No. (%)	
1	187 (82%)
2	10 (4%)
3	24 (11%)
4	6 (3%)
Prior HCV treatment experience	40 (18%)
APRI >1.5^	64 (28%)
ESLD diagnosis	26 (12%)

Footnotes:
†-Single person low income is considered annual income of less than $18,421/yr CAD [166]
‡-Active PWID: Use of any injection drugs within 6 months of last cohort visit (self-reported)
^- APRI>1.5 indicates significant liver fibrosis

Abbreviations: Undetectable HIV RNA (RNA<50 copies/mL) HCV- Hepatitis C Virus; IDU- Injection drug use; PWID-Person who injects drugs; cART- combined antiretroviral therapy HCV-Hepatitis C Virus; APRI- AST to **P**latelet **R**atio Index, ESLD- End Stage Liver Disease

Table 8.2 Health State (Beta Coefficients) as measured by the EQ-5D VAS and EQ-5D Utility Scores among people who achieved SVR

	EQ VAS	EQ VAS[#]	EQ-5D Utility Score	EQ-5D Utility Score[#]
Baseline level (units)	68.4 (66.4, 70.4)	67.2 (62.9, 71.5)	0.763 (0.740, 0.786)	0.763 (0.717, 0.809)
Pre-treatment (change in HR-QoL/year)	0.0 (-0.3, 0.4)	-0.3 (-0.7, 0.1)	-0.006 (-0.009, -0.003)	-0.007 (-0.011, -0.003)
Immediate change (between DAA initiation and response)	2.3 (-0.1, 4.7)	2.5 (0.0, 5.0)	0.022 (-0.000, 0.045)	0.019 (-0.004, 0.043)
Impact post-DAA treatment (change in HR-QoL/year)	1.4 (-0.9, 3.7)	1.3 (-1.0, 3.6)	0.000 (-0.022, 0.022)	0.000 (-0.022, 0.022)
Age Centered (per year)		0.6 (-1.6, 2.8)		-0.003 (-0.029, 0.023)
Sex (Reference heterosexual men)				
Female		-1.7 (-6.0, 2.6)		-0.037 (0.088, 0.013)
Men who have sex with men (MSM)		4.6 (0.6, 8.5)		0.054 (0.008, 0.101)
Income <$1500/month[†]		-2.3 (-4.7, 0.0)		-0.014 (-0.037, 0.010)
Injection drug use (past 6 months)[‡]		-2.1 (-4.3, 0.3)		-0.034 (-0.056, -0.011)
Psychiatric Diagnosis		-2.1 (-4.6, 0.4)		-0.029 (-0.053, -0.005)
Undetectable HIV viral load (<50 copies/mL)		2.4 (0.1, 4.6)		0.016 (-0.006, 0.037)
Fibrosis (APRI>1.5)[^]		-0.1 (-2.2, 2.0)		-0.002 (-0.023, 0.018)
Previous exposure to HCV treatment		-1.9 (-6.4, 2.7)		-0.008 (-0.062, 0.045)

Footnotes:
Sample size (n=210) results summarized as Generalized Linear Mixed Models (#) indicates adjusted models. Range of EQ-5D VAS is 0 to 100; range of EQ-5D Utility Scores is 0 to 1
[†]Single person low income is considered annual income of less than $18,421/yr CAD [166]
[‡]Use of any injection drugs (self-reported)
[^]APRI- AST to Platelet Ratio Index >1.5 indicates significant liver fibrosis
To be consistent with the HR-QoL literature this table reports beta coefficients obtained from the regression models for both EQ 5D VAS and the EQ-5D utility scores. For ease of interpretation, in the manuscript we refer to the beta coefficients of the EQ-5D utility as changes in percentage-points by multiplying beta coefficients by 100

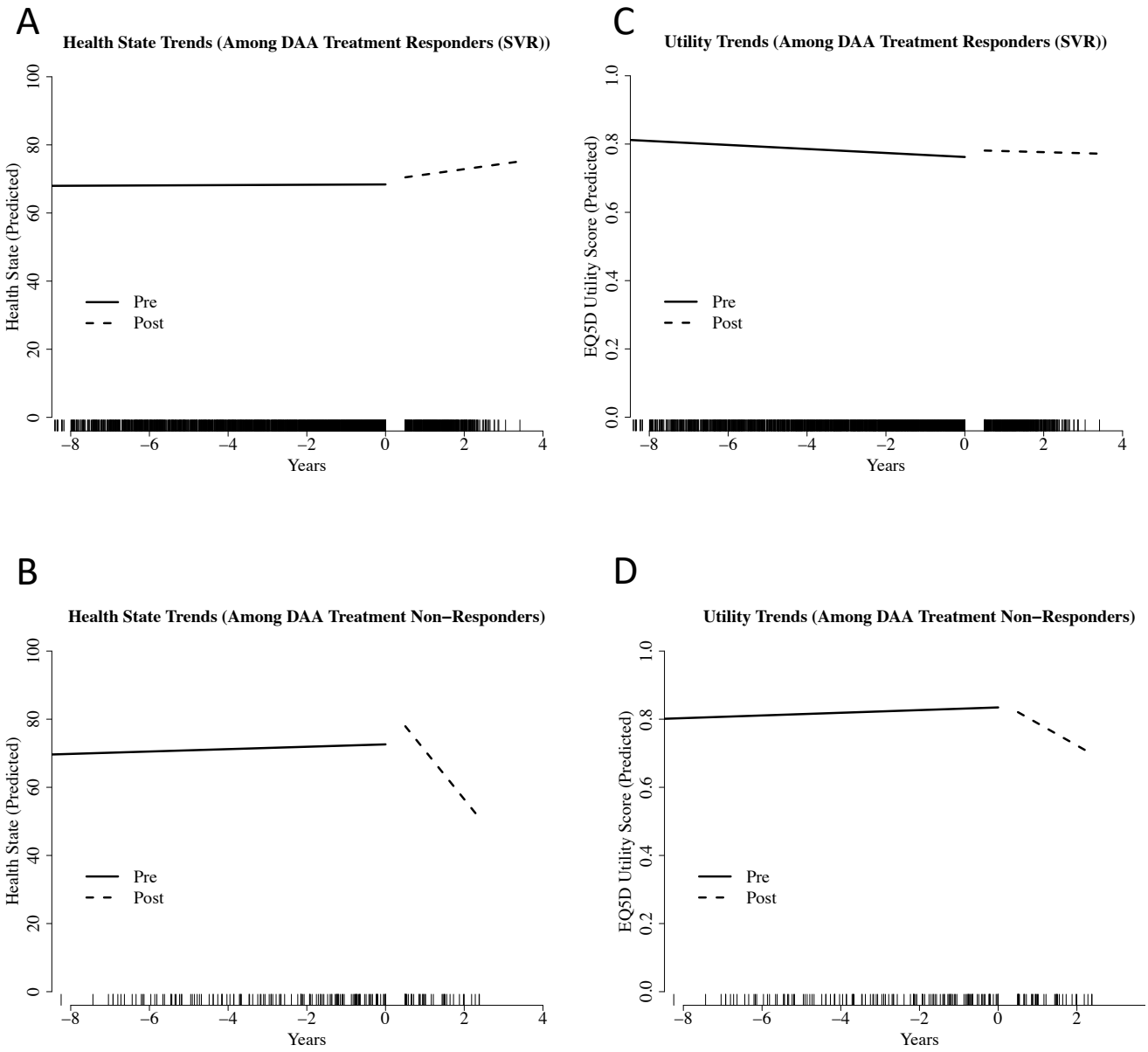

Figure 8.1 Trends in health state (EQ VAS) and EQ-5D utility scores, pre- and post- DAA therapy, stratified by treatment response
(SVR, panels A and C & Treatment Failure (panels B and D) The gap in the x-axis segregates the pre-treatment phase (years leading to treatment initiation (solid black line) and post-treatment period (years after ascertainment of DAA response (dashed black line). The vertical lines on the x-axis are individual data points at particular periods of time (denser areas include more data points).

8.3 Appendix to Manuscript 4

Supplement Table 8.1 Components of EQ-5D at Cohort Baseline, at DAA initiation and at last visit among people who achieved SVR

	At Cohort Baseline	**At DAA Initiation**	**At last visit**
VAS, range 0 to 100 (IQR)	70 (53, 80)	70 (55, 80)	75 (60, 83)
EQ-5D, range 0 to 1 (IQR)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 0.8)
Mobility			
No problems	134 (73%)	140 (66%)	142 (68%)
Some problems	49 (27%)	72 (33%)	67 (32%)
Confined to bed	1 (<1%)	2 (<1%)	
Self-care			
No problems	173 (94%)	193 (91%)	183 (88%)
Some problems	11 (6%)	19 (9%)	25 (12%)
Unable to wash	0	0	1(<1%)
Usual Activities			
No problems	128 (70%)	145 (68%)	143 (68%)
Some problems	54 (29%)	64 (30%)	64 (31%)
Unable to perform	2 (1%)	4 (2%)	2 (1%)
Pain/Discomfort			
No problems	81 (44%)	84 (39%)	77 (37%)
Moderate problems	86 (47%)	109 (51%)	107 (51%)
Extreme pain	17 (9%)	20 (9%)	25 (12%)
Anxiety/Depression			
No problems	85 (46%)	116 (55%)	116 (56%)
Moderate problems	91 (50%)	85 (40%)	81 (39%)
Extremely anxious	8 (4%)	11 (5%)	12 (6%)

Supplement Table 8.2 Health State (Beta Coefficients) of EQ VAS Range, EQ-5D Utility Scores among people who failed DAA treatment

	EQ VAS	**EQ-5D Utility Score**
Baseline level (units)	72.7 (66.5, 78.8)	0.835 (0.765, 0.905)
Pre-treatment (change in HR-QOL/year)	0.3 (-0.9, 1.6)	0.004 (-0.009, 0.016)
Immediate change (between DAA initiation and response)	5.3 (-3.4, 14.1)	-0.014 (-0.100, 0.072)
Impact post-DAA treatment (change in HR-QOL/year)	-14.6 (-23.2, -6.0)	-0.069 (-0.152, -0.014)

Footnote: Sample size (n=17) results of Generalized Linear Mixed Models. To be consistent with the HR-QoL literature this table reports beta coefficients obtained from the regression models for both EQ-5D VAS and the EQ-5D utility scores. For ease of interpretation, in the manuscript we refer to the beta coefficients of the EQ-5D utility as changes in percentage-points by multiplying beta coefficients by 100

CHAPTER 9: CONCLUSION

9.1 Summary of Results and Implications

While the development of DAAs was nothing short of revolutionary, challenges to treatment uptake remained. DAAs were fast-tracked through clinical trials, based on near perfect efficacy but licensed with an unprecedented low-level of patient exposure. Marginalized populations were largely excluded from clinical trials; paradoxically, modeling studies revealed that treatment uptake in this exact patient population was absolutely necessary to make significant strides to achieving elimination targets. Therefore, a tremendous need for real-world research on treatment uptake, and DAA effectiveness remained. This body of research presented in this thesis answered pertinent and timely research questions, with the use of innovative study designs and transdisciplinary methods to increase the confidence of the results. I addressed fundamental issues regarding the need for real-world studies on newly marketed treatments, the identification and quantification of barriers to DAA treatment initiation, and the impact of curing HCV on health-related quality of life among people living with HIV in Canada.

Well-designed and conducted randomized clinical trials provide internally valid results, hence they are vital for evaluating the efficacy of new treatments. However, to make inferences to a heterogenous population, the external validity of trials also needs to be questioned. The results from Manuscript 1 illustrated that the majority of HIV-HCV co-infected individuals engaged in healthcare would not have been eligible to participate in the DAA trials, therefore results may have limited generalizability. While restriction into clinical trials for the purpose of protecting

the safety of participants is legitimate, we found the majority of exclusionary criteria were not related to safety but instead appear to be aimed at maximizing treatment response rates.

There are broad consequences of restricting trial eligibility. First, excluding subgroups such as people who inject drugs (PWID) may reinforce biases that this population is non-adherent. Since Manuscript 1 was published, there have been several post-marketing trials that have demonstrated that sustained virologic response (SVR) rates among PWID were just as high as people who do not use illicit drugs[142,258-261] including results from Manuscript 2[246]. However, similar efficacy does not mean the generalizability of clinical trials is not a concern. Simply, that DAA treatments are so well-tolerated and efficacious that SVR rates remained consistently high even in real world settings. The generalizability of trial populations may still impact other health outcomes as evident by Manuscript 4. Second, creating homogeneous trial populations may also lead to narrow indications for medications, which can then be used by insurers to limit access to treatments. Evaluating the generalizability of DAA clinical trials was only possible because of the well characterized cohort of HIV-HCV co-infected people available to me, but such cohorts are not available for all therapeutic areas. This work supports the utility of prospective cohorts in other patient populations, so that the external validity and the real-world impact of other marketed pharmaceuticals can be assessed.

Manuscript 2 evaluated the real-world uptake and effectiveness of DAAs among HIV-HCV co-infected individuals. Here we found among a population engaged in clinical care, HCV treatment initiation rates increased by three-fold after DAAs were available. But even in a country with no overt policies restricting access to DAAs based on socioeconomic or lifestyle criteria, treatment initiation disparities existed among key populations, including PWIDs and more generally people

of lower socioeconomic status. At the time Manuscript 2 was published, the reimbursement of DAAs in Canada were mostly restricted to people with significant liver fibrosis. But progressively this restriction was removed. In Manuscript 3, we took advantage of this variation in policy change, by time and geography, to estimate the causal impact of removing this system-level barrier on treatment uptake. Here we found HCV treatment rates increased by nearly two-fold after removing fibrosis stage restrictions, accounting for temporal trends and time-invariant differences between provinces. Among PWID the impact appeared to be even stronger. However, we also found evidence to support that unrestricted access to treatment only led to a temporary increase in treatment uptake. This was empirical evidence of the "warehousing effect"–that is, physicians identified their pre-existing patients eligible for treatment and treated them as soon as access was expanded. But after that warehoused pool of patients was exhausted, treatment rates drop considerably. As treatment access continues to broaden worldwide, these results reinforce that unrestricted access to DAAs is not the all-encompassing answer to elimination. Concerted efforts are needed to treat at least the WHO's suggested 7% of the infected population each year in a sustained manner.

The underlying principle of the WHO's response to viral hepatitis is the promotion of healthcare equity[228]. Addressing health disparities is a central component of equity. "Equity" is distinct from "equality" as equality refers to treating everyone in the same way, while equity ensures outcomes are fair between populations[262]. Such health outcomes include access to- and quality of care. The results from manuscript 2 and 3, raise concerns of inequalities even in a setting of "universal" healthcare such as Canada's. Uniformly, treatment initiations among marginalized populations were low. Low treatment initiation rates by key populations cannot be justified given

the high SVR that can be obtained across sub-groups. While Canada does not have the same restrictive policies that deny access to DAAs to people who inject drugs or continue to drink alcohol, restrictions such as requiring significant liver fibrosis may unintentionally cause barriers to accessing treatment among younger and newly infected individuals. Following universal access to DAAs, PWID were almost four times more likely to initiate treatments. But this surge in treatment uptake was not sufficient to achieve health equity. Active injection drug use and Indigenous ethnicity remained significant negative predictors of treatment uptake (Manuscript 3). But this study was not designed to understand why PWID hadn't received treatment. Recent qualitative research suggests individual-level barriers to DAA treatment among PWID include poor venous access, the fragmented healthcare system, and having to manage multiple health and social priorities that interfere with keeping medical appointments such as childcare and poor access to transport services[263]. Researchers and affected populations also raise concerns that more effort needs to be made at reducing stigma and discrimination towards PWID to minimize residual barriers to DAAs[263]. If systematic patient-level barriers are not addressed, even in countries with universal access to DAAs, we will fail to make headway in reaching WHO HCV elimination targets by 2030.

The ultimate goal of eliminating HCV is to reduce morbidity and mortality associated with this disease. While viral clearance has been shown to reduce liver-related outcomes and all-cause mortality in the long term, the impact may not be immediately obvious for an individual patient. In Manuscript 4, in contrast to clinical trials that observed significant improvements in health-related quality of life (HR-QoL), we report only modest improvements following SVR with oral-DAA therapy. We attribute the difference in the results due to the generalizability of trial

populations (Manuscript 1) and the timing of when HR-QoL was measured/ assessed during the clinical trials. The results from manuscript 4 have implications to patients and providers that changes in HR-QoL may be short-lived and competing issues such as low socio-economic status, active injection drug and/or other substance use and mental health disorders are likely to remain post-treatment. While successful treatment leads to many long-term health benefits, if not intervened on, competing risks may ultimately diminish benefits of treatments. Given the global investment in HCV elimination it may be worthwhile to use the opportunity while patients are engaged in treatment to address other modifiable and risky behaviours and expand care for mental health and addictions.

9.2 Strengths and Limitations

The quality of the data from the Canadian Coinfection Cohort is one of the principal strengths of this thesis. Participants were recruited from 18 sites across Canada with the intention of capturing a representative cohort of HIV-HCV co-infected population in care. The detailed information includes sociodemographic, lifestyles choices, illicit drug use, clinical results and validated clinical outcomes that are not routinely collected through administrative data sources nor in clinical care cohorts. The real-world diversity of the cohort also represents the HIV-HCV epidemic in Canada by including active and former injection drug users, men who have sex with men, people of Indigenous ethnicities and women. Without this well characterized target population, the assessment of the generalizability of DAA trials would not have been possible (Manuscript 1). The longitudinal nature of the cohort was instrumental at evaluating treatment uptake over time (Manuscript 2 & Manuscript 3); allowed us to carry out and evaluate the assumptions of the difference-in-difference analysis used to evaluate the impact of removing

fibrosis stage restrictions on treatment uptake (Manuscripts 3); and to use a segmented mixed effects model to evaluate changes in HR-QoL following a SVR (Manuscript 4). But of course, using data from the CCC, means that the results from this thesis are only generalizable to co-infected populations similar to a Canadian context (i.e. high income, universal access to health care, and broad access to harm reduction services).

Manuscript 1 is not without limitations, though none that compromised the final conclusions. Firstly, I focused on eligibility criteria listed in trial protocols. Additional factors such as overall willingness and motivation to participate in clinical trials were not assessed and may have further reduced the proportion of co-infected participants eligible. Also, not all eligibility criteria from the trial protocols were routinely collected as part of the CCC. As such I assumed, they were met, thus this could have led to an overestimation of the generalizability of the trials.

The strength of Manuscript 2 is the identification of key populations based on prospective self-reported questions as opposed to secondary data extractions from billing codes (a common limitation of other studies evaluating access to HCV treatment) [29,154]. It directly addressed a call from the literature to report SVR rates among active PWID in real world settings [5,101,232,248] Finally, unlike the multi-payer system in the United States where there is considerable variation in DAA reimbursement, in regards to active substance use; in Canada there are no such "overt" system-level restrictions. This allowed us to evaluate these patient-level barriers independent of policy restrictions.

The results from Manuscript 2 can be defined as exploratory and should not be interpreted causally. It was not possible to identify reasons why individuals belonging to the key populations did not access treatment. Overlapping patient-level barriers make it difficult to identify factors independently associated with treatment uptake. Due to the limited sample size, it was not informative to explore formal statistical tests to identify synergistic relationships between the main exposures of interest (Indigenous ethnicity, PWID and biological sex). Therefore, the results from the multivariate analysis and figures assume that the relationship between each of the risk factors is independent and exactly multiplicative. We were not able to account for an individual's proximity to healthcare and center's human resource limitations; which could influence treatment uptake (residual confounders). Limited resources may also lead to an inherent bias towards physicians treating more "stable" patients, as opposed to simply treating everyone. If this is true SVR rates in sub-populations maybe over-estimated and will need to be interpreted with this limitation in mind. Finally, we focused on a population already in care - that is, at the end of the cascade of care. To evaluate the population level impact of DAAs, it will be important to evaluate each step of the care continuum, including on-going surveillance of reinfections.

The strengths of Manuscript 3 were capitalizing on a natural experiment and using quasi-experimental methodology to answer the research question. The changes in DAA reimbursement policies within provinces allowed us to make plausibly causal conclusions on the impact of removing fibrosis stage restrictions on treatment uptake among people living with HIV, given assumptions, which we verified by several sensitivity analyses.

This study also has limitations. Results were based on participation in the Canadian Co-Infection Cohort Study. While the cohort strives to recruit inclusively, it does not reflect those who have yet to be linked into healthcare– which may represent up to 15% of the total co-infected population in Canada[136]. This unengaged population most likely represents people who are more marginalized and vulnerable. While our secondary analysis provides insight as to who remains eligible for treatment, this latter analysis was not designed to attribute causality. Further research is needed to elucidate the individual-level barriers to accessing DAA treatment. In addition, our study, and specifically the exposure of interest coincides with the fentanyl epidemic. While the epidemic is widespread across North America, in Canada, the province of British Columbia has been the hardest hit. In 2017 there were 29.8 opioid-related deaths per 100,000 British Columbians up from 20.3 per 100,000 in 2016. In comparison Ontario's opioid-related death rates were 7.8 per 100,000 people in 2017 compared to 5.2 per 100,000 in 2016; and in Quebec 1.5 per 100,000 people in 2017 compared to 1.6 per 100,000 in 2016[247]. While this crisis did not directly impact death rates in our study population during the period analyzed, it is possible that health care resources in British Columbia were reprioritized, making HCV treatment a less pressing issue. Physicians may also have been more hesitant to treat active PWID if they believed overdose was inevitable. Finally, loss-to-follow-up rates were high, although non-differential between the provinces. If participants who disengaged from care were less likely to have initiated treatment, censoring could be informative, which would lead to an overestimation of our results. In contrast, it is also possible that people who lost-to follow-up may have been treated outside of the CCC, which in turn could underestimate our results.

Combining longitudinal data on a generalizable HIV-HCV co-infected population with quasi-experimental methodology was also a strength of Manuscript 4. Here we used repeated measurements of HR-QoL over a substantial pre-treatment period to construct a counterfactual estimate of how HR-QoL would have continued in the absence of treatment and subsequent response to DAA therapy. We also report changes in HR-QoL over a longer follow up period compared to the clinical trials. However, to make causal conclusions on the role of HCV viral cure on HR-QoL, we made the assumption that nothing other than the exposure is changing over time that would have an impact on HR-QoL; an assumption that cannot be verified. Also, we analyzed HR-QoL as measured by the EQ-5D instrument, which is a generic measure of HR-QoL compared to the many instruments that were used in the clinical trials. A systematic review of patient reported outcomes did show that this instrument was responsive to changes between groups and/or over time in patients living with HIV [254]. The EQ-5D has been noted to have problems with ceiling effects and therefore the use of the scale in individuals with early asymptomatic HIV infection is not recommended [255]. The concern of a ceiling effect may also extend to people with asymptomatic HCV infections and maybe a reason why the improvement in health state post-treatment based on the VAS did not translate to improvements of utility scores [256,257]. Stratifying by fibrosis severity may address this concern, however this was not possible given the limited sample size.

9.3 Future Directions

The research summarized in this thesis contributes to a growing body of epidemiological studies, identifying patient, provider and system level barriers to accessing DAA treatments. This work was a necessary first step to identify disparities in treatment uptake among vulnerable co-

infected populations. But pressing questions still remain: **why** haven't vulnerable populations accessed treatment? **How** do we scale up access to treatment and eliminate HCV as a public health threat?

While the cost of DAAs was a significant barrier to treatment and used as a reason why disparities existed, this argument has become outdated. Market forces have reduced the cost of DAA treatments to a fraction of their original price. The actual cost of DAAs –that insurers pay in Canada is confidential, but it is estimated treatments now cost between $15,000- $20,0000 CAD. Nevertheless, treatments remain expensive, and in many parts of the world will remain a barrier to accessing treatment. Currently in Canada, we are in the era of "universal access" where the costs of treatments are covered by the provincial health plans with very few restrictions.

Future work will need to focus on finding innovative ways of implementing strategies to increase treatment uptake. While treating all chronically infected individuals may seem like a daunting task, experts encourage a more pragmatic "micro-elimination" approach. That is to apply elimination goals to smaller and well-characterized subpopulations. By tailoring interventions to specific subpopulations, treatments can be delivered more quickly and effectively. Micro-populations that have been identified as priority populations for elimination of HCV are patients with advanced liver disease, patients with hemophilia, patients who are co-infected with HIV, incarcerated individuals, children, migrant communities, PWID in networks, MSM, generational cohorts and geographically defined areas. It will remain important to take an implementation science approach to designing interventions. That is, to engage community, policy makers and other stakeholders coupled with comprehensive epidemiological data to monitor outcomes

(preferably in real time). To achieve micro-elimination, it will require action at each step of the HCV care cascade. Successful programs need to start with country or provincial level action plans including: a) broad access to harm reduction; b) targeted communication campaigns directed at key populations; c) screening strategies in "at risk-groups" to find undiagnosed persons with HCV; d) projects to track previously diagnosed patients but who are lost to follow-up; e) integrated healthcare including primary care, addiction care and liver care; f) solid epidemiologic data on HCV care cascade in all HCV risk groups through registries; and g) and ongoing surveillance for reinfections and other associated health outcomes[264].

The focus of this thesis was access to HCV treatment, but it is important to acknowledge the many factors that lead to HCV infections and which can then subsequently lead to reinfections if not addressed.

Harm Reduction:

The cornerstone of public health is prevention and in the absence of a vaccine the only viable strategy of preventing HCV infections and reinfections is harm reduction. Combined substance use treatments and safe injection sites have been proven efficacious, cost-effective, and cost-saving at preventing HCV transmission[265-268]. Lessons can be learned from strong public health initiatives such as those in Vancouver, British Columbia. A dramatic decline in syringe sharing and borrowing practices were observed from 20% of users in 1998 to under 10% in 2003, by shifting the focus from syringe exchange to distribution[269]. A later study reported use of safe injection facilities was independently associated with a 70% reduction in syringe sharing[270]. Multipronged approaches are most effective. The "Georgia Model" is based on success in a

small Eurasian country that was the first to set national HCV elimination targets. Their national plan included low threshold mobile harm reduction for remote areas and on-site addictions support and point of care screening and treatment in urban cities. While harm reduction is mostly widespread in urban cities it remains a limitation in rural areas in Canada and needs to be addressed. In the United States the Cherokee Nation is another example of an elimination program with a focus on harm reduction. As of 2017, almost half the Cherokee tribe (80,000 people) had been screened and around one quarter infected have already been cured. Scaled up of opioid substitution programs in Oklahoma state (where the Cherokee Nation mostly resides) was also incorporated into their elimination project, although needle exchanges remain illegal in the state. Finally, 15 years ago in Portugal health authorities tackled a growing HIV epidemic by decriminalizing drugs[271,272], an action that reduced rates of HIV, HCV and overdoses. Multipronged widespread harm reduction will remain a vital and essential step at eliminating HCV as a public health threat.

Social determinants of health:

Even among high-income countries like Canada, where universal health care and social assistance are available, social disparities plague vulnerable populations, which in turn propagates' the spread of infectious diseases. Upstream to the risky behaviors, testing, diagnosis, treatment and overall medicalization it is also important to understand where these marginalized populations are coming from. There are no genetic markers that predispose someone to be living with HIV or HCV; however social determinants are strongly associated with both infections. Therefore, if elimination is the goal, then we need to stop the vicious cycle of despair. Poverty leads to a downward spiral of food/shelter insecurities. Physical and sexual abuse increases the risk of mental illness and

addictions. In Canada, Indigenous populations face unique distal determinants such as colonialism and racism that cannot be ignored. Broad social interventions also need to be designed to address these determinants of health inequalities as preventative measures to eliminating HCV and HIV.

9.4 Conclusions

The last four years have truly been revolutionary. More than half of the participants of the CCC have been successfully cured of HCV, a triumph unimaginable just 10 years ago. The studies presented in this dissertation sought to track this revolution, providing stakeholders with data on barriers and facilitators of DAA initiation. It also brought awareness to issues regarding the generalizability of clinical trials and the importance of continuing to monitor outcomes in real world settings. In the process of addressing two objectives in the thesis, two tutorials were also developed to help public health officials and epidemiologists understand two study designs that have broad applications to evaluating policies and acute-individual level exposures such as curing HCV. Together these thematically linked studies represent an original body of high impact clinical and policy-relevant research.

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