

**Injection drug use and food insecurity among HIV-hepatitis C virus co-infected
individuals: associations, mechanisms, and interventions**

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November 2017

A thesis submitted to McGill University

in partial fulfillment of the requirements of the degree of Doctor of Philosophy (PhD)

in Epidemiology

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Abstract

Background: In Canada, 20% of individuals living with HIV are estimated to be co-infected with hepatitis C virus (HCV). In addition to the high prevalence of injection drug use (IDU), the characteristics of individuals living with HIV-HCV co-infection reflect socioeconomic and sociodemographic vulnerability. Central to the concept of food insecurity (FI), a social determinant of health, is the focus on uncertain or inadequate food access due to limited financial resources. The existing evidence has documented high prevalences of FI, particularly severe FI, among individuals living with HIV. Furthermore, FI is associated with lower CD4 cell counts, incomplete HIV viral load suppression, and sub-optimal HIV treatment adherence. These consequences of FI motivate studies that focus on identifying modifiable risk factors for FI with the goal of informing interventions to reduce FI. However, given the differences between those living with HIV mono-infection and HIV-HCV co-infection and the context-specific nature of FI risk factors, the generalizability of findings from HIV-related studies that do not consider HCV co-infection is unclear. Therefore, novel research is needed to further our understanding of the relationship between IDU, a highly prevalent behaviour in this vulnerable subset of the HIV-positive population, and FI.

Objectives: The overall aim of this doctoral thesis was to examine associations, mechanisms, and interventions related to IDU and FI, particularly severe FI, in a population of HIV-HCV co-infected individuals in Canada. Specifically, this dissertation addressed the following objectives using longitudinal cohort data from individuals living with HIV-HCV co-infection:

1. To examine the relationship between IDU and FI.
2. To examine whether unemployment is a mediator in the mechanism linking IDU and severe FI.

3. To examine whether a substance use intervention, methadone maintenance treatment, is associated with a lower risk of severe FI.

Methods and Results: All research objectives were completed using biannual data from the Food Security and HIV-HCV Study of the Canadian Co-infection Cohort, an open prospective cohort of HIV-HCV co-infected individuals from 17 clinics in six provinces (November 2012 to October 2015). The exposure variables, IDU (in the past six months), IDU frequency (non-weekly/weekly in the past month), and methadone treatment for opioid dependence (in the past six months) were self-reported. The outcome variables, FI (in the past six months) and FI severity (marginal FI, moderate FI, and severe FI), were measured using the ten-item adult scale of Health Canada's Household Food Security Survey Module. In Objective 1, generalized estimating equations were used to quantify the associations between IDU, IDU frequency, and FI using Poisson regression. The associations between IDU, IDU frequency, and FI severity were estimated using multinomial regression. In Objective 2, an overall association between IDU and severe FI, as well as a controlled direct effect when treating unemployment as the mediator, were estimated using marginal structural log-linear models. In Objective 3, propensity score matching was used to estimate an average treatment effect on the treated, which quantified the association between methadone treatment and severe FI.

Longitudinal cohort analysis of associations (Objective 1): IDU and FI, particularly severe FI, are common in this HIV-HCV co-infected population. Moreover, there is an association between IDU and FI, particularly weekly IDU and severe FI, independent of socioeconomic, sociodemographic, behavioural, and clinical confounders.

Mediation analysis of mechanisms (Objective 2): After adjustment for time-varying confounders affected by prior exposure and addressing selection bias, there is evidence of an

overall association between IDU and severe FI. Furthermore, an overall association and a controlled direct effect that are similar in magnitude suggests that the potential impact of IDU on unemployment is not the primary mechanism linking IDU and severe FI.

Propensity score matching analysis of interventions (Objective 3): Methadone maintenance treatment, a substance use intervention, is associated with a lower likelihood of severe FI.

Specifically, the average risk of experiencing severe FI is lower among individuals receiving methadone treatment, compared to those who are not receiving treatment, after adjustment for confounders.

Conclusions: The estimated associations between IDU and FI, particularly weekly IDU and severe FI, indicate that reductions in IDU may mitigate FI, especially severe FI, among individuals living with HIV-HCV co-infection. While further research is required to understand the mechanisms linking IDU and severe FI, the association between IDU and severe FI is primarily through pathways that are not mediated by unemployment. In addition, methadone treatment for opioid dependence may reduce the likelihood of severe FI. Therefore, the research undertaken in this thesis indicates that IDU is a risk factor for FI and that there is a substance use intervention which has the potential to decrease the risk of co-infected individuals experiencing severe FI. Findings from this dissertation are relevant to researchers and clinical care providers involved with HIV-HCV co-infected individuals who are engaged in IDU.

Résumé

Contexte: Au Canada, on estime que 20% des personnes vivant avec le VIH sont co-infectées par le virus de l'hépatite C (VHC). En plus d'une forte prévalence de consommation de drogues injectables, on retrouve chez les personnes co-infectées par le VIH et le VHC des caractéristiques reflétant d'importantes vulnérabilités socioéconomiques et sociodémographiques. L'accès incertain ou inadéquat à la nourriture en raison de ressources financières limitées est central au concept d'insécurité alimentaire (IA), un déterminant social de la santé. Des données probantes démontrent des prévalences élevées d'IA et plus particulièrement un degré grave (ou sévère) d'IA chez les personnes vivant avec le VIH. En plus, l'IA est associée à une diminution du nombre de cellules CD4, à une suppression incomplète de la charge virale du VIH et à une observance sous-optimale du traitement anti-VIH. Ces conséquences ont mené à des études sur l'identification des facteurs de risque modifiables de l'IA afin d'éclairer le travail d'intervention visant à réduire l'IA. Toutefois, étant donné les différences entre les personnes vivant avec la mono-infection par le VIH et celles vivant avec la co-infection VIH-VHC, et la nature contextuelle des facteurs de risque de l'IA, la généralisabilité des résultats des études liées au VIH qui ne tiennent pas compte de la co-infection par le VHC n'est pas claire. Par conséquent, une recherche innovante est nécessaire pour mieux comprendre la relation entre la consommation des drogues injectables, un comportement très répandu dans ce sous-ensemble vulnérable de la population séropositive, et l'IA.

Objectifs: L'objectif global de cette thèse de doctorat était d'examiner les associations, les mécanismes et les interventions liés à la consommation de drogues injectables et à l'IA, plus particulièrement l'IA sévère, dans une population de personnes co-infectées par le VIH et le VHC au Canada. Plus précisément, cette thèse, qui se fonde sur des données de cohortes

longitudinales provenant de personnes vivant avec une co-infection VIH-VHC, porte sur les objectifs suivants:

1. Examiner la relation entre la consommation de drogues injectables et l'IA.
2. Examiner si le chômage est un médiateur du mécanisme liant la consommation de drogues injectables à l'IA sévère.
3. Examiner si un programme de traitement à la méthadone est associé à un moindre risque de l'IA sévère.

Méthodes et Résultats: Les objectifs de recherche ont été complétés à l'aide de données semestrielles de l'étude sur la sécurité alimentaire et le VIH-VHC de la cohorte canadienne de co-infection, une cohorte prospective ouverte de personnes co-infectées par le VIH-VHC provenant de 17 cliniques réparties dans six provinces (novembre 2012 à octobre 2015). Les variables d'exposition, la consommation de drogues injectables (au cours des six derniers mois), la fréquence de consommation (non hebdomadaire/hebdomadaire au cours du dernier mois) et le traitement à la méthadone pour la dépendance aux opioïdes (au cours des six derniers mois), ont été rapportées par les répondants. Les variables de résultat, l'IA (au cours des six derniers mois) et le degré d'IA (faible, modéré, sévère), ont été mesurées à l'aide d'une échelle de dix items du module de l'Enquête sur la sécurité alimentaire des ménages de Santé Canada. Dans l'Objectif 1, des équations d'estimation généralisées ont été utilisées pour quantifier les associations entre la consommation de drogues injectables, la fréquence de consommation de drogues injectables et l'IA en utilisant le modèle de régression de Poisson. Les associations entre la consommation de drogues injectables, la fréquence de consommation de drogues injectables et la sévérité de l'IA ont été estimées à l'aide de régressions multinomiales. Dans l'Objectif 2, une association globale entre la consommation de drogues injectables et l'IA sévère, ainsi qu'un effet direct contrôlé par

le chômage en tant que médiateur, a été estimée à l'aide de modèles log-linéaires structuraux marginaux. Dans l'Objectif 3, l'appariement des scores de propension a été utilisé pour estimer un effet moyen du traitement sur les personnes traitées, afin de quantifier l'association entre le traitement par la méthadone et l'IA sévère.

Analyse de cohorte longitudinale des associations (Objectif 1): La consommation de drogues injectables et l'IA, particulièrement l'IA sévère, sont fréquentes dans cette population co-infectée par le VIH et le VHC. De plus, il existe une association entre la consommation de drogues injectables et l'IA, particulièrement la consommation hebdomadaire et l'IA sévère, indépendamment des facteurs de confusion socioéconomiques, sociodémographiques, comportementaux et cliniques.

Analyse de médiation des mécanismes (Objectif 2): Après ajustement pour les facteurs de confusion variant avec le temps qui sont affectés par une exposition antérieure, et la prise en compte d'un biais potentiel de sélection, il y a des preuves d'une association globale entre la consommation de drogues injectables et l'IA sévère. De plus, une association globale et un effet direct contrôlé d'une ampleur similaire suggèrent que l'impact potentiel de l'injection de drogues sur le chômage n'est pas le principal mécanisme liant la consommation de drogues injectables et l'IA sévère.

Analyse de l'appariement du score de propension des interventions (Objectif 3): Le traitement à la méthadone, une intervention liée à la consommation de substances, est associé à une plus faible probabilité d'IA sévère. Plus précisément, le risque moyen de subir une IA sévère était plus faible chez les personnes recevant un traitement à la méthadone, comparativement à celles ne recevant pas de traitement, après ajustement en fonction des facteurs de confusion.

Conclusions: Les associations estimées entre la consommation de drogues injectables et l'IA, et plus particulièrement entre la consommation hebdomadaire de drogues injectables et l'IA sévère, indiquent que les réductions de consommation de drogues injectables peuvent atténuer l'IA, en particulier l'IA sévère, chez les personnes vivant avec la co-infection VIH-VHC. Bien que d'autres recherches soient nécessaires pour comprendre les divers mécanismes qui associent la consommation de drogues injectables et l'IA sévère, l'association entre la consommation de drogues injectables et l'IA sévère se fait principalement par des voies non médiées par le chômage. De plus, le traitement à la méthadone pour la dépendance aux opioïdes peut réduire la probabilité d'une IA sévère. Par conséquent, la recherche entreprise dans cette thèse indique que l'injection de drogues est un facteur de risque de l'IA et qu'il existe une intervention sur l'utilisation de substances qui pourrait diminuer le risque d'IA sévère pour les personnes co-infectées. Les résultats de cette thèse sont pertinents pour les chercheurs et les prestataires de soins cliniques travaillant avec des personnes co-infectées par le VIH et le VHC qui consomment des drogues injectables.

Acknowledgements

I must express my deepest appreciation to my co-supervisors, Drs. Joseph Cox and Erica Moodie, for their encouragement, guidance, and research mentorship. I often describe the serendipitous arrangement of my mentorship team as “hitting the jackpot.” The support of Joe and Erica, a clinician-scientist and biostatistician, was complementary and unwavering. I feel that the best manner to summarize my doctoral experience is to say that anyone who gets to work with them, particularly students, are truly fortunate. Whenever I felt discouraged, I took comfort in the fact that I had compassionate mentors who were invested in my success. On more than one occasion, I have said that “I could compile a textbook with Erica’s e-mail responses” to my statistical questions. I hope to emulate Joe and Erica’s elegant and thorough mentorship styles as I progress in my own career.

I would also like to thank my committee members, Drs. Anne-Marie Hamelin and Sam Harper, for their feedback. Anne-Marie has also presented me with opportunities to become more involved in research coordination and data management; these are skills that will prove valuable moving forward. Also, I extend my appreciation to the professors and staff who have shaped my experience at Purvis Hall, with a specific mention of Dr. Madhu Pai, Andrew Griffin, Katherine Hayden, Deirdre Lavery, and André Yves Gagnon. To my fellow PhD students: Catherine, Carmine, Abebula, and Hiroshi, thank you for your close friendships. I must also acknowledge Dr. Marina Klein, the Canadian Co-infection Cohort research staff (Chantal Burelle, Leo Wong, Jennifer Kocilowicz, and Costas Pexos), Emilie Maurais, as well as Dr. Robert Hogg and the staff at the CANOC Centre in Vancouver.

Of course, I express my gratitude to my parents, Jill and Mike, and my sister Karley. While the journey of post-secondary education was foreign to our family, my upbringing allowed

me to realize the value of an education. From a young age, my parents created and maintained a home environment that facilitated my academic pursuits. I do not doubt that the countless walks, discussions, and phone calls with my mom have allowed me to overcome many personal and research-related hurdles. Overall, the positive impact of my family's life-long love and support is something that cannot be quantified. Finally, I must acknowledge my partner, Karina, and her family. Karina is the reason why I was able to find balance and enjoy the wonderful city of Montreal while completing my PhD. Given the distance from my family and friends, Karina's empathy and eagerness to explore my new surroundings were paramount to my happiness. To those closest to me: I will never forget your patience and reassurance during my time at McGill.

Statement of financial support

I acknowledge and express my thanks for the financial support that I have received during my doctoral studies. Stipend funding was provided to me by the CANOC Centre and the CIHR Canadian HIV Trials Network (2015-2017), McGill University's Faculty of Medicine (2014-2015), as well as by Drs. Joseph Cox, Anne-Marie Hamelin, and the Department of Epidemiology, Biostatistics and Occupational Health (2013-2014). I also received conference travel awards from the CANOC Centre (2016-2017), the Department of Epidemiology, Biostatistics and Occupational Health (2016), the Ontario HIV Treatment Network (2016), and the CIHR's HIV/AIDS Research Initiative (2016).

Contributions of authors

Manuscript 1: Injection drug use, food insecurity, and HIV-HCV co-infection: a longitudinal cohort analysis

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TM, EEMM, AMH, MBK, and JC participated in the design of the study. TM managed the data, carried out the statistical methodology, interpreted the results, and drafted the manuscript. MBK and JC were involved in data collection. TM, EEMM, SH, AMH, AA, WA, MBK, and JC reviewed and contributed to drafts of the manuscript. All authors approved the final version of the manuscript.

Manuscript 2: Injection drug use, unemployment, and severe food insecurity among HIV-HCV co-infected individuals: a mediation analysis

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Manuscript 3: Methadone treatment, severe food insecurity, and HIV-HCV co-infection: a propensity score matching analysis

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TM, EEMM, AMH, MBK, and JC participated in the design of the study. TM managed the data, carried out the statistical methodology, interpreted the results, and drafted the manuscript. CC, MBK, and JC were involved in data collection. TM, EEMM, AMH, SH, CR, SLW, SBR, CC, MBK, and JC reviewed and contributed to drafts of the manuscript. All authors approved the final version of the manuscript.

Statement of originality

The work contained in this thesis represents an original contribution to the field of epidemiology with respect to injection drug use (IDU) and food insecurity (FI) in an HIV-hepatitis C virus (HCV) co-infected population. The three manuscripts included in this thesis build on each other to better understand associations, mechanisms, and interventions related to IDU and FI.

Manuscript 1 was the first study to explore a dose-response relationship between IDU frequency and FI while also examining the impact of IDU on FI severity among individuals living with HIV-HCV co-infection. This longitudinal cohort analysis indicated that there is an association between IDU and FI, particularly, weekly IDU and severe FI. This suggests that reductions in IDU may mitigate FI, especially severe FI, in this vulnerable subset of the HIV-positive population.

Manuscript 2 built upon the findings of Manuscript 1 and it was the first study to quantitatively examine a potential mechanism through which IDU is associated with severe FI. This mediation analysis indicated that there is an overall association between IDU and severe FI and provided evidence that the association is primarily through pathways that are not mediated by unemployment. Specifically, the potential impact of IDU on unemployment is not the primary mechanism linking IDU and severe FI. While further research is required to understand the various pathways between IDU and severe FI, the strong overall association, estimated after adjustment for time-varying confounders affected by prior exposure and addressing selection bias, provided further evidence that reductions in IDU may mitigate severe FI.

Manuscript 3 was motivated by the findings in Manuscripts 1 and 2 which suggest that substance use interventions aimed at IDU may reduce the likelihood of FI, particularly severe FI,

in this population. While the previous manuscripts focused on IDU and the use of any drug type, the injection of opioids is known to be common among co-infected individuals. I hypothesized that opioid injection is responsible, in part, for the associations between IDU and severe FI. As such, Manuscript 3 examined whether methadone treatment for opioid dependence is associated with a lower likelihood of severe FI. This propensity score matching analysis indicated that methadone treatment is associated with a lower risk of severe FI. While I examined the impact of a treatment that is only applicable to a subset of those who are engaged in IDU, this was the first study to examine whether a substance use intervention is associated with a lower likelihood of severe FI in this population.

While I have received guidance from my co-supervisors, thesis committee members, and several co-authors regarding the methodological, statistical, and substantive aspects of this thesis, I declare that the conception, execution, and drafting of this thesis was my own.

List of abbreviations

AIDS	Acquired immunodeficiency syndrome
ATE	Average treatment effect
ATT	Average treatment effect on the treated
CCC	Canadian Co-infection Cohort
CCHS	Canadian Community Health Survey
CDE	Controlled direct effect
CI	Confidence interval
ELISA	Enzyme-linked immunosorbent assay
FI	Food insecurity
FS Study	Food Security and HIV-HCV Study
HCV	Hepatitis C virus
HFSSM	Household Food Security Survey Module
HIV	Human immunodeficiency virus
HR	Hazard ratio
IDU	Injection drug use
IPW	Inverse probability weights
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple imputation
MNAR	Missing not at random
OR	Odds ratio
PO	Potential outcome
PSM	Propensity score matching
RD	Risk difference
RR	Risk ratio
RRR	Relative-risk ratio
SMD	Standardized mean difference

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Chapter 1: Introduction

Human immunodeficiency virus (HIV), hepatitis C virus (HCV), and HIV-HCV co-infection are highly prevalent globally and within Canada.¹⁻⁷ An estimated 2.3 million individuals living with HIV are co-infected with HCV worldwide.⁵ In Canada, 20% of HIV-positive individuals are estimated to be HCV co-infected, representing approximately 13,000 individuals.^{6,7} Each blood-borne viral infection has important clinical implications, such as HIV-related immune dysfunction and HCV-related liver disease,^{8,9} and the presence of both infections is particularly deleterious.^{10,11} In addition, given the relatively low risk of HCV transmission through sexual contact,^{3,9} most individuals who are HIV-HCV co-infected most likely contracted both blood-borne viruses through injection drug use (IDU)¹²; among co-infected individuals, the prevalence of IDU is alarmingly high.¹³

Given the clinical characteristics of this population^{10,11} and the prevalence of IDU,¹³ several studies have compared HIV mono-infected and HIV-HCV co-infected populations to characterize those living with both viral illnesses. In North American studies, the characteristics of individuals living with co-infection reflect socioeconomic and sociodemographic vulnerability.¹⁴⁻¹⁶ For example, in Ontario, Canada, co-infected individuals are more often unemployed, less educated, experiencing unstable housing, and earning a lower income than those living with HIV mono-infection.¹⁶ This suggests that individuals living with HIV-HCV co-infection represent a vulnerable subset of the HIV-positive population.

According to the Universal Declaration of Human Rights,¹⁷ access to adequate food is considered a basic human right. An intrinsic precursor to this right is food security. Lack of food security, known as food insecurity (FI), exists “whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is

limited or uncertain.”¹⁸ Central to the concept of FI, as commonly measured in published research and in this thesis, is the focus on uncertain or inadequate food access due to limited financial resources.¹⁹ FI, a social determinant of health,²⁰ is a dimension of nutritional vulnerability.²¹ Therefore, the deprivation that underlies the experience of FI suggests that this condition is a public health issue and a matter for social action.²²⁻²⁴ The measurement of FI facilitates the identification of population sub-groups, such as individuals living with HIV-HCV co-infection, whose health is potentially compromised because of FI.¹⁹ Once sub-groups are identified, specific consequences of FI can be investigated.^{25,26} Such enquiries may also motivate the investigation of FI risk factors that may inform interventions to reduce FI.

In the HIV context, the body of FI-related literature is diverse, with studies in a variety of settings focused on estimating FI prevalence, describing consequences of FI, and examining risk factors for FI in HIV-positive populations. It is clear that there are consistently high prevalences of FI, particularly severe FI, among HIV-positive individuals²⁶⁻²⁸; FI prevalence estimates in HIV-positive populations are substantially higher than those found in comparable general populations.²⁹⁻³¹ Moreover, the literature related to consequences of FI, specifically FI’s associations with poor clinical outcomes such as lower CD4 cell counts,^{32,33} incomplete HIV viral load suppression,^{33,34} and sub-optimal HIV treatment adherence,³⁵ is rigorous and diverse. Such works have motivated studies that identify risk factors for FI which are relevant to the HIV and HIV-HCV co-infection contexts.²⁵

Similar to studies that are not restricted to individuals living with HIV,³⁶ HIV-related studies have identified socioeconomic and sociodemographic factors, such as income, employment status, housing situation, and age as independent risk factors for FI.³⁷⁻³⁹ Several studies in HIV-positive populations have also quantified independent associations between

behavioural risk factors, such as illicit^{38,40,41} and IDU,³⁷ and FI. Given the high prevalence of IDU in co-infected populations,¹³ further examination of this behaviour as a prevalent and modifiable risk factor for FI is of particular interest.⁴² Acknowledging that actions cannot be taken against non-modifiable factors (e.g., age) and that it is potentially difficult to intervene on socioeconomic and sociodemographic factors (e.g., income, employment, and housing situation),^{43,44} substance use interventions on IDU to reduce FI may be more feasible in the short-term.⁴⁵⁻⁴⁷

While there is an existing evidence-base related to FI among HIV-positive individuals, I am not aware of any published studies outside of our research group that have focused on individuals living with HIV-HCV co-infection. While it is plausible that a proportion of the participants in the existing HIV-related literature are also co-infected with HCV, these studies did not consider HCV co-infection in their analyses or interpretations. Given the differences between those living with HIV mono-infection and HIV-HCV co-infection¹⁴⁻¹⁶ and the context-specific nature of FI risk factors,^{25,26} the generalizability of findings from HIV-related studies that do not consider HCV co-infection is unclear. To date, IDU, a behaviour concomitant with co-infection,¹³ has only been examined as a risk factor for FI in two Canadian studies; one study was cross-sectional³⁷ and the other was an exploratory or hypothesis-generating analysis completed by our research group.⁴⁸ Therefore, additional research is needed to further our understanding of associations, mechanisms, and interventions related to IDU and FI in the HIV-HCV co-infection context.

1.1 Thesis aim and research objectives

The overall aim of this doctoral thesis is to examine associations, mechanisms, and interventions related to IDU and FI, particularly severe FI, in a population of HIV-HCV co-infected individuals in Canada. Specifically, this dissertation addresses the following objectives using longitudinal cohort data from individuals living with HIV-HCV co-infection:

1. To examine the relationship between IDU and FI.
2. To examine whether unemployment is a mediator in the mechanism linking IDU and severe FI.
3. To examine whether a substance use intervention, methadone maintenance treatment, is associated with a lower risk of severe FI.

1.2 Format of the thesis

This is a manuscript-based thesis. It includes three manuscripts that each address one of the three research objectives. These manuscripts are presented in their own chapters that begin with a preface outlining the rationale and relation to the corresponding objective. Additional chapters are included to complement these three manuscripts to form a cohesive dissertation. Chapter 2 includes a literature review. Subsequently, Chapter 3 provides an overview of the data sources, the Canadian Co-infection Cohort and the Food Security and HIV-HCV Study, as well as a rationale for the chosen methodologies in each manuscript. Chapter 4 contains Manuscript 1, a longitudinal cohort analysis that quantifies the association between IDU and FI among HIV-HCV co-infected individuals in Canada. Chapter 5 contains Manuscript 2, a mediation analysis that examines a potential mechanism through which IDU is associated with severe FI. Chapter 6 contains Manuscript 3, a propensity score matching analysis that quantifies the association between methadone treatment, a substance use intervention for individuals who are dependent on

opioids, and severe FI. Chapter 7 contains a discussion of the findings from this thesis, directions for future research, and concluding remarks. The references to the publications or other sources cited in this work, including those cited in the manuscripts, are provided in the References section at the end of the thesis.

Chapter 2: Literature review

2.1 Natural history and epidemiology of HIV

HIV is a retrovirus that infects cells in the immune system, specifically CD4+ T cells, which are a type of lymphocyte that have a central role in cell-mediated immunity.^{8,49} HIV is transmitted through bodily fluids, such as blood, semen, vaginal fluids, or breast milk. Once infected, HIV leads to lower CD4 cell counts through a variety of mechanisms, such as pyroptosis and apoptosis, which are two forms of programmed cell death.⁵⁰ When CD4 cell counts decline below a critical level, cell-mediated immunity is lost. Over time, uncontrolled HIV infection can lead to acquired immunodeficiency syndrome, AIDS, representing an advanced stage of HIV infection.^{8,49} In Canada, the presence of an AIDS-defining condition (e.g., *Pneumocystis jiroveci* pneumonia) concurrent with positive HIV serology are used to define AIDS.⁵¹

In 2016, the World Health Organization estimated that 36.7 million individuals were living with HIV worldwide and that one million individuals died of HIV-related illnesses in that year.¹ In Canada, approximately 75,500 individuals were living with HIV in 2014 and 2570 new infections were acquired.² Since the advent of highly active antiretroviral HIV therapies, a combination of treatments that are taken for the remainder of one's life to maintain HIV viral suppression, substantial reductions in HIV-related morbidity and mortality have been achieved.^{52,53} While HIV infection is now a chronic and manageable condition in Canada,⁵¹ new infections continue to occur.² This suggests that the prevalence of HIV will continue to increase, requiring increased demand for long-term HIV treatment and care in Canada.⁵¹

2.2 Natural history and epidemiology of HCV

HCV is a single-stranded RNA virus.⁵⁴ HCV is the cause of hepatitis C, which is an infectious disease of the liver,³ a vital organ with a range of functions including detoxification, protein synthesis, and the production of bio-chemicals for digestion.⁵⁵ HCV infection leads to liver disease primarily through immune-mediated mechanisms, such as inflammation and fibrogenesis.⁵⁶ HCV is primarily a blood-borne virus with a low risk of sexual or vertical transmission.^{3,9} Therefore, the major risk factors for HCV infection are IDU, and historically, receipt of contaminated blood products. Prior to effective and routine screening of blood for HCV in Canada (1992), HCV infection was common from blood transfusions; this is no longer the case in developed countries.^{57,58}

The initial or acute phase of HCV infection is often asymptomatic.^{3,9} Some individuals may spontaneously clear HCV within six months of infection, but the majority of HCV mono-infected individuals will develop a chronic infection (75-85%).⁹ A chronic infection is defined as having detectable HCV RNA six months after an anti-HCV antibody is detectable, or six months after seroconversion. Over time, a chronic infection can lead to advanced liver diseases, such as cirrhosis, and further complications such as liver failure and liver cancer (e.g., hepatocellular carcinoma).^{3,9,57}

In 2015, approximately 71 million people were living with a chronic HCV infection globally.³ It is estimated that approximately 399,000 individuals die each year from HCV, primarily due to complications from cirrhosis and hepatocellular carcinoma.³ In 2011, an estimated 332,414 individuals in Canada were seropositive for HCV, indicating either a current or past infection with the virus. Individuals currently or formerly engaged in IDU comprised 43% of all antibody-positive HCV cases and those born outside of Canada comprised an

additional 35% of all antibody-positive cases.⁴ While there are new, effective, and more tolerable treatments for HCV, known as direct-acting antivirals,⁵⁹ these treatments are currently prohibitively expensive and limited to patients with advanced fibrosis.⁶⁰ Furthermore, re-infection with HCV is possible, particularly among individuals engaged in IDU.⁶¹

2.3 Epidemiology of HIV-HCV co-infection

HIV and HCV are blood-borne viruses that share common routes of transmission through exposure to contaminated blood.^{3,49} While sexual transmission is the primary risk factor for HIV,² IDU is the primary risk factor for becoming co-infected with HIV and HCV¹²; unlike HIV, HCV transmission is rare through sexual contact.^{3,9} Most individuals who engage in IDU administer their drugs intravenously.⁶² However, subcutaneous and intramuscular injections may also occur. Regardless, exposure to contaminated blood through the sharing of needles or other injection materials (e.g., drug solution and filters) may facilitate both HIV⁸ and HCV transmission.⁹ Globally, an estimated 2.3 million HIV-positive individuals are co-infected with HCV.⁵ Of these, more than half are currently or were previously engaged in IDU. In addition to the small proportion of HCV infections that are due to sexual transmission, the remaining infections are primarily attributable to the receipt of contaminated blood products in developing countries.⁵⁸ In studies of co-infected populations, there is a high prevalence of IDU.¹³ While other routes of drug administration include sniffing, smoking, eating, drinking, and transdermal administration,⁶³ research has indicated that IDU often occurs after an individual builds a tolerance to, and becomes dependent on, an addictive substance.⁶³⁻⁶⁵ Therefore, it is reasonable to suggest that those who use illicit drugs by injection are more entrenched in this behaviour and may have a substance use disorder.^{66,67}

Clinically, HIV is known to advance the natural history of HCV infection. As noted, progression to a chronic HCV infection following the acute phase occurs in approximately 75-85% of HCV mono-infected individuals.⁹ However, more than 90% of HIV-HCV co-infected individuals are estimated to progress to a chronic HCV infection¹⁰; the proportion of individuals who will spontaneously clear their HCV infection is lower among those who are co-infected with HIV. HIV-HCV co-infected individuals have also been shown to progress to cirrhosis and hepatocellular carcinoma at a faster rate than HCV mono-infected individuals.¹¹ In many settings, end-stage liver disease now represents the leading cause of death after AIDS among individuals living with HIV.¹³ Furthermore, the risk of hospitalization (adjusted risk ratio [RR] = 1.80, 95% confidence interval [CI] = 1.30-2.50), emergency department visits (adjusted RR = 1.70, 95% CI = 1.40-2.10), and disability days (adjusted RR = 1.60, 95% CI = 1.30-1.90) was higher among HIV-HCV co-infected individuals compared to those living with HIV mono-infection.⁶⁸ With respect to clinical outcomes, HIV-HCV co-infected individuals represent a vulnerable subset of the HIV-positive population.

2.3.1 Characteristics of HIV-HCV co-infected populations

HIV, HCV, and HIV-HCV co-infection are highly prevalent globally and within Canada.¹⁻⁷ In Canada, one in five individuals living with HIV is estimated to be co-infected with HCV.^{6,7} Each blood-borne viral infection has important clinical implications (e.g., immune dysfunction, AIDS-defining illnesses, and liver-related diseases)^{8,9} and the presence of both infections is particularly deleterious.^{10,11} Furthermore, given the low risk of HCV transmission through sexual contact,^{3,9} individuals who are HIV-HCV co-infected most likely contracted both blood-borne viruses through IDU.¹² In the Canadian Co-infection Cohort, a cohort of co-infected individuals who contributed the data for this thesis, over 80% of participants reported a history of

IDU.⁷ Given the clinical effects of HIV and HCV^{8,9} and the prevalence of IDU,¹³ several studies have compared HIV or HCV mono-infected and HIV-HCV co-infected populations to characterize the vulnerability that is concomitant with co-infection.

A study comparing HIV mono-infected and HIV-HCV co-infected individuals in British Columbia, Canada, indicated that co-infected individuals report more symptoms consistent with depression, fatigue, and a lower quality of life.¹⁴ After further examination, the authors determined that the impact of HIV-HCV co-infection on these symptoms was better explained by the sociodemographic and behavioural characteristics of the participants, specifically poverty and IDU, rather than the HCV infection itself. Similar conclusions were drawn from a study comparing HCV mono-infected and co-infected individuals in the United States, where co-infected participants experienced more depressive symptoms, less social support, and had lower self-esteem than participants living with HCV alone.¹⁵ These authors also argued that their findings were explained, in part, by differences in sociodemographic characteristics; compared to the HIV-HCV co-infected individuals, those living with HCV mono-infection were more commonly white, heterosexual, highly educated, and employed.

This theme was further explored in a study comparing various socioeconomic and sociodemographic factors of HIV-HCV co-infected and HIV mono-infected adults in Ontario, Canada.¹⁶ When compared with the HIV mono-infected participants, those who were co-infected were more likely to be Aboriginal, less educated, unemployed, and earning $\leq$ \$1,200 Canadian dollars per month. Co-infected participants were also more likely to have reported a history of homelessness and to have moved two or more times in the past year. Therefore, while it is known that IDU is highly prevalent¹³ and that living with both HIV and HCV increases an

individual's risk of experiencing negative clinical outcomes,^{10,11} the socioeconomic and sociodemographic profiles of co-infected individuals also reflect vulnerability.

It must be noted that the works comparing mono- and co-infected populations were cross-sectional in design.¹⁴⁻¹⁶ As such, it is difficult to determine whether co-infection leads to subsequent socioeconomic or sociodemographic disadvantage, or whether such disadvantage predisposes one to high risk behaviours, like IDU, which then leads to co-infection; it was not the objective of these studies to answer this question. While the directionality of these associations is unclear, it is known that HIV-HCV co-infection is concomitant with the aforementioned socioeconomic and sociodemographic characteristics.

2.4 Food insecurity

According to Article 25 of the United Nations' Universal Declaration of Human Rights,¹⁷ access to adequate food is considered a basic human right. A precursor to this right is food security. Lack of food security, known as FI, exists "whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain."¹⁸ Implicit in this definition is the notion that food insecure individuals may experience one or more of the following: a preoccupation with continuity in access to enough food, a shortage of food, the unsuitability of both food and diet, and a lack of control over one's food situation. This may push an individual to acquire food in socially unacceptable manners, including by begging, relying on charity, scrounging, stealing, exchanging sex for food, and/or other illicit activities.⁶⁹ It is critical to understand that central to the concept of FI, as commonly measured in published research and in this thesis, is the focus on uncertain or inadequate food access due to limited financial resources.¹⁹ Therefore, it is logical to examine this phenomenon

among individuals who experience socioeconomic and sociodemographic vulnerability, such as those who are living with HIV-HCV co-infection.¹⁴⁻¹⁶

Historically, FI is a concept that has been defined and measured in numerous ways. Several terms have been used in discussions of FI and this has resulted in difficulties describing what is being measured.⁷⁰ Briefly, “hunger” is often conflated with FI, perhaps due to the emotive strength of the concept.⁷¹ However, hunger, or the uneasy or painful sensation caused by a lack of food, may only be experienced by a subset of individuals experiencing severe FI (see Table 2.2 for a definition of each FI severity category).²¹ Similarly, “food insufficiency,” or an inadequate amount of food intake due to a lack of money or resources, may be best described as a synonym for severe FI.⁷² “Undernourishment,” which describes a state when caloric intake is below the minimum dietary energy requirement, is also considered to be a severe form of FI.⁷⁰ Overall, hunger, food insufficiency, and undernourishment characterize the most severe forms of FI. This is important because FI is a broader concept that is best understood by reviewing the items within a given FI measurement tool (see Table 2.1).

2.4.1 Measurement of food insecurity

FI, a social determinant of health,²⁰ is a dimension of nutritional vulnerability.²¹ There have been a number of studies quantifying the relationship between measures of FI and poor dietary intake,⁷³ including studies among Canadian adults and adolescents,⁷⁴ low income adults in the United States,⁷⁵ women with children in New York State,⁷⁶ elderly individuals in the United States,⁷⁷ Korean children from low-income families,⁷⁸ and students at a Canadian university.⁷⁹ Dietary intakes of adult women in Toronto, Canada have also been shown to vary systematically with FI severity.⁸⁰ With these considerations in mind, FI is hypothesized to affect health outcomes in which nutrition is implicated. For example, outside of the HIV context, FI has

been associated with obesity,⁸¹ diabetes,⁸² hypertension,⁸³ and cardiovascular disease.⁸⁴

Therefore, the deprivation that underlies the experience of FI and the potential consequences of this condition suggest that FI is a matter for social action and a public health issue.²²⁻²⁴

The measurement of FI facilitates the identification of population sub-groups whose health and well-being is potentially compromised because of uncertain or inadequate food access.¹⁹ In order to identify potential consequences of FI, FI can be treated as a risk factor or predictor of health and clinical outcomes. Subsequently, context-specific risk factors for FI can be examined and this information can be used to inform interventions to reduce FI.^{25,26} Several projects during the 1980s and early 1990s developed the concept of FI in a North American context, elucidating the complex and multi-dimensional nature of this experience.²¹ This work was largely qualitative in nature and focused primarily on low-income families. The conceptual work that was based on interviews with low-income women in New York was of significance.^{85,86} These women were asked “if they had ever gone hungry or had been close to going hungry” and then were asked to describe their situation with respect to food access. From these data, the quantitative, qualitative, psychological, and normative dimensions of FI were first identified.^{85,87,88} These data were used to create the Radimer/Cornell instrument, a questionnaire-based tool that initially comprised 12 items which could be used to measure FI status and severity.⁸⁷ This 12-item instrument was developed through factor and cluster analyses as well as reliability testing of a larger set of thirty items that had been derived from the qualitative interview data.^{85,86}

In 1995, the United States Census Bureau incorporated the first “Food Security Supplement” into the Current Population Survey.⁸⁹ This was an undertaking of several government agencies, including the United States Department of Agriculture. The FI

measurement tool used in the Current Population Survey, which later became known as the United States Household Food Security Survey Module, was grounded in the items initially represented in the Radimer/Cornell instrument.⁸⁷ In Canada, FI is primarily measured using Health Canada's Household Food Security Survey Module (HFSSM).¹⁹ The HFSSM is also a questionnaire-based tool that was adapted from the aforementioned FI measurement tools developed in the United States.

The HFSSM, which was first administered in Canada in 2004, focuses on self-reports of uncertain or inadequate food access due to limited financial resources.¹⁹ Similar to its antecedents,^{87,89} the HFSSM is not designed to capture other possible reasons for compromised food consumption, such as voluntary dieting or fasting. The focus on limited financial resources reflects the recognition that while financial resources are one of a range of factors that operate to determine individuals' food consumption patterns, financial resources are the primary determinant of FI in Canada.²¹ The HFSSM contains 18 questions regarding food access over the previous twelve months. Ten of the 18 items are specific to the experiences of adults, while eight are specific to the experiences of children under the age of 18. Each item specifies a lack of money or the inability to afford food as the reason for the condition or behaviour.¹⁹ Given that all participants included in the data sources analyzed in this thesis are adults (see Section 3.2), only the ten items from the adult scale of the HFSSM will be described.

Table 2.1 The ten-item adult scale of Health Canada’s Household Food Security Survey Module (HFSSM).

HFSSM Item		Responses ^a
1	You and your household worried that food would run out before you got money to buy more. Was this often true, sometimes true, or never true in the past six months?	Often true Sometimes true Never true
2	The food that you and your household bought just didn’t last and there wasn’t any money to get more. Was this often true, sometimes true, or never true in the past six months?	Often true Sometimes true Never true
3	You and your household couldn’t afford to eat balanced meals. Was this often true, sometimes true, or never true in the past six months?	Often true Sometimes true Never true
4	In the past six months, did you ever cut the size of your meals or skip meals because there wasn’t enough money for food?	Yes No
5	How often did this happen? (<i>Referring to Item 4</i>)	Every month Some months but not every month Only 1 or 2 months Not applicable (“No” to Item 4)
6	In the past six months, did you ever eat less than you felt you should because there wasn’t enough money to buy food?	Yes No
7	In the past six months, were you ever hungry but didn’t eat because you couldn’t afford enough food?	Yes No
8	In the past six months, did you lose weight because you didn’t have enough money for food?	Yes No
9	In the past six months, did you ever not eat for a whole day because there wasn’t enough money for food?	Yes No
10	How often did this happen? (<i>Referring to Item 9</i>)	Every month Some months but not every month Only 1 or 2 months Not applicable (“No” to Item 9)

^a Responses in **bold** are the “affirmative responses” to each item. Health Canada categorizes a respondent’s FI according to the number of affirmative responses on the HFSSM. Each item can only count as one affirmative response. All ten items, regardless of the severity of FI, are treated equally. Furthermore, the responses “often true” and “sometimes true” are treated equally, as are “every month” and “some months but not every month.”

A characteristic of FI measurement tools, including the HFSSM, is that the items comprising the tools vary across a range of severity.^{19,21} The range of severity identified by the items is evident from inspection. For example, not eating for a whole day (Item 9) is a more severe manifestation of FI than cutting the size of meals or skipping meals (Item 4). In turn, cutting the size of meals or skipping meals indicates a more severe level of FI than does worrying about whether food will run out (Item 1). FI, including the severity of the FI experience, is determined by the number of “affirmative responses” reported on the HFSSM.¹⁹ A HFSSM respondent can be categorized as food secure vs. food insecure or categorized as experiencing a particular severity of FI by the number of questions that the individual answers affirmatively (see Tables 2.1 and 2.2). Depending on the question, a response is considered affirmative if the individual indicates: “Often true,” “Sometimes true,” “Yes,” “Every month,” or “Some months but not every month” in a pre-defined reference period. To reflect the data collection schedule of the data sources described in Sections 3.1 and 3.2, the reference period of the FI assessment in all analyses described in this thesis refers to the past six months. Modification of the HFSSM from 12 to six months, a shorter reference period, has been justified in previous literature.⁹⁰

In the first analyses of HFSSM-measured FI by Health Canada in 2004 (see Section 2.4.2),¹⁹ 0-1 affirmative responses were indicative of food security. In this categorization, ≥ 2 affirmative responses were indicative of FI (food secure vs. moderate FI or severe FI). Within the category of “any FI,” 2-5 affirmative responses indicated moderate FI and ≥ 6 affirmative responses indicated severe FI. Recently, researchers have suggested that the FI threshold of ≥ 2 affirmative responses may be too strict; it has been shown that even one affirmative response on the HFSSM is indicative of FI.⁹¹ The change to a less conservative threshold, from ≥ 2 to ≥ 1

affirmative responses as being the FI cut-off, was made by researchers after taking into consideration both the cognitive content of the items and findings on health and nutrition among food insecure individuals.⁹² This resulted in the creation of an additional FI category, known as “marginal” FI, which exists when one affirmative response on the HFSSM is provided.²² All manuscripts described in this thesis include the marginal FI category and categorize FI severity at three levels (food secure vs. marginal FI, moderate FI, or severe FI). The definitions of each category are displayed in Table 2.2. Marginal and moderate FI are indicative of worrying about running out of food or compromises in the quality and/or quantity of food consumed, whereas severe FI indicates disrupted eating patterns, reduced food intake, and the physical sensation of hunger.²²

Table 2.2 Food insecurity categorizations based on the number of affirmative responses on the ten-item adult scale of Health Canada’s Household Food Security Survey Module (HFSSM).

Category	Definition	Historic cut-offs based on the number of affirmative responses on the HFSSM (excluding marginal FI) ^a	Contemporary cut-offs based on the number of affirmative responses on the HFSSM (including marginal FI) ^b
Food secure	No report of an income-related problem of food access.	0-1	0
Marginal FI	Some indication of worry or an income-related barrier to adequate and secure food access.	-	1
Moderate FI	Compromise in quality and/or quantity of food consumed due to a lack of money for food.	2-5	2-5
Severe FI	Disrupted eating patterns and reduced food intake.	≥ 6	≥ 6

^a As described in Section 2.4.1, those who would have been categorized as experiencing marginal FI using the contemporary cut-offs were historically categorized as being food secure.

^b Analyses described in this thesis included the category of marginal FI: 1 affirmative response on the HFSSM. Therefore, Participants with 1, 2-5, and ≥ 6 affirmative responses on the HFSSM were identified as experiencing marginal, moderate, or severe FI, respectively. As described in Section 2.4.2, this differs from the original HFSSM analyses that did not consider marginal FI.

Differences in the severity of the FI experience are observed in the HFSSM response patterns. It is known that the more severe items are affirmed by fewer individuals than the less severe items. Moreover, an individual who affirms an item of mid-range severity is likely to have affirmed all items that are less severe. Similarly, an individual who denies a mid-range item is likely to answer non-affirmatively to all items that are more severe.¹⁹ These response patterns are not universal, but they are predominant. Among individuals who do deviate from the typical patterns, the extent of deviation is minor. As previously described, the Rasch measurement model formalizes the severity-ordering of items and it provides statistical methods to estimate the relative severity of each item.⁹⁰ Notably, all ten items, regardless of the severity, are treated equally in the counting of affirmative responses and each item can only count as one affirmative response. The total number of affirmative responses cannot exceed ten. Lastly, within individual

questions, the affirmative responses of “Often true” and “Sometimes true” as well as “Every month” and “Some months but not every month” are treated equally.⁸⁷

It is important to understand that I used the HFSSM to assess FI at the individual-level among HIV-HCV co-infected study participants in this thesis. As noted, within the HFSSM, there are two sets of items. One set measures FI among adults within a household and the other measures FI among children within a household.¹⁹ With respect to the national estimates described in Section 2.4.2, the number of questions in the HFSSM that the adult and/or child answers affirmatively, in each of the adult and child scales, first determines the FI status at the adult- and child-levels. Once the FI status of the adults and children are known, the FI status of the household can be determined. Notably, I did not determine household FI status as we did not administer the child scale to children who may have been living with the adult participants. As described in a report published by Health Canada,²¹ the HFSSM yields individual-level measures of FI under such a scenario.

An additional clarification is necessary when using the HFSSM to measure FI among adults at the individual-level. Given that the HFSSM was designed to report FI at the household-level, the first three items of the HFSSM’s adult scale references the respondent (“you”) and “your household” (Table 2.1). The remaining questions (Items 4-10) refer to the adult respondent directly.¹⁹ If the respondent lives alone, individual-level FI is reflective of household-level FI. Furthermore, if there are no children living in a household, the mention of “your household” reflects the fact that only one (adult) respondent is necessary to measure the FI status of the entire household. The implications of this are such that if a participant experiences FI at the individual-level, and this participant does not live with children, it would also be appropriate to indicate that their household, which may include other adults, is also food insecure. However,

given that some participants do in fact live with children (see Table 4.1), and the FI status of these children was not measured, I do not extrapolate our FI measures to the household-level. This was not necessary as all other measures in this thesis were specific to the level of the individual.

2.4.2 Food insecurity in Canada

In Canada, national estimates of HFSSM-measured FI were first published by Health Canada using 2004 FI data.¹⁹ Health Canada uses data from the Canadian Community Health Survey (CCHS) to ascertain the prevalence of FI. While most households had consistent access to food in 2004, the findings of Health Canada's first report identified that FI was a reality for many vulnerable individuals. Overall, 2.7 million Canadians, or 8.8% of the population, experienced FI in 2004.¹⁹ The HFSSM has been included in subsequent cycles of the CCHS, presenting opportunities to study FI on a national- and provincial-level over time. Currently, the CCHS is an annual cross-sectional survey administered by Statistics Canada that collects health-related information from approximately 65,000 domiciled Canadians.⁹³ Public access to the CCHS data has allowed researchers, like the "PROOF" research group at the University of Toronto, to publish reports on FI.^{22,30} These publications, which first reported on 2011 FI data,⁹⁴ are complementary to Health Canada's efforts and have become critical to advancing our understanding of FI in Canada.

In 2013 and 2014, the HFSSM was optional on the CCHS; the 2013 and 2014 FI data are the most recent. As noted in the PROOF report that examined 2014 FI data, not all provinces and territories chose to administer the HFSSM in their respective jurisdictions.²² However, among the provinces and territories that did measure FI, the prevalence of FI remained high. In the participating jurisdictions (Alberta, Saskatchewan, Ontario, Quebec, New Brunswick, Nova

Scotia, Prince Edward Island, the Northwest Territories, and Nunavut), 3.2 million individuals experienced FI in the previous twelve months in 2014. This estimate included approximately one million children.²² The most recent PROOF report with national FI data in all provinces and territories, prior to the opt-out option, used 2012 FI data. In 2012, four million individuals, including 1.15 million children, experienced some level of FI.³⁰ This overall prevalence is not directly comparable to the 2014 estimates that did not include all of the provinces and territories. Furthermore, one in five of the food insecure households experienced severe FI in 2012, indicating disrupted eating patterns, reduced food intake, and the physical sensation of hunger.^{21,30} Similar to the thesis analyses described herein, the PROOF reports include the marginal FI category. Therefore, while both Health Canada and the PROOF research group used the same FI measurement tool (HFSSM) and CCHS data to measure FI in the general Canadian population, the estimates from these two groups are not directly comparable (see Table 2.2). It is for this reason that I have focused my attention on the PROOF estimates.

Overall, analyses of CCHS data by Health Canada and PROOF have consistently documented high national and provincial FI prevalences.^{19,21,22} Despite the measurement and monitoring of FI since 2004,¹⁹ uncertain or inadequate food access continues to be described as a serious social and public health problem in Canada.²²⁻²⁴ This would suggest that additional evidence is needed to inform strategies to reduce FI, particularly in vulnerable sub-groups of the Canadian population. While individuals living with HIV are not a focus of these Canadian reports, I will now overview a large evidence-base which illustrates that the prevalence of FI is alarmingly high among HIV-positive populations in Canada and throughout the world.

2.5 Food insecurity in HIV-positive populations

The body of FI-related literature is diverse, with studies in a variety of contexts focusing on estimating FI prevalence, describing consequences of FI and risk factors for FI, as well as evaluating interventions to reduce FI among individuals living with HIV.²⁶⁻²⁸ As described in Sections 2.5.1-2.5.3, the majority of studies have been completed in Africa. Several studies have also been completed in multiple regions within the United States. Canadian studies are currently limited to HIV-positive populations in the provinces of British Columbia and Ontario.

The literature related to consequences of FI, specifically FI's potential associations with poor clinical outcomes such as lower CD4 cell counts,^{32,33} incomplete HIV viral load suppression,^{33,34} and sub-optimal HIV treatment adherence,³⁵ is comprehensive. Such works have motivated studies that focus on risk factors for FI with the goal of informing interventions to reduce FI. As noted, risk factors for FI are context-specific.^{26,27} For example, HIV-related stigma may be a more prevalent driver of FI in Uganda⁹⁵ or the Dominican Republic⁹⁶ than in North America, where income-related barriers are the most prominent.²¹ Similar to studies that are not restricted to individuals living with HIV,³⁶ HIV-related studies have consistently identified socioeconomic factors, such as income, employment, and housing situation as independent risk factors for FI.³⁷⁻³⁹ Several studies have also quantified independent associations between behavioural factors, such as illicit^{38,40,41} and IDU,³⁷ and FI (see Section 2.5.5). Potential interventions on such behaviours⁴⁵⁻⁴⁷ may be more feasible in the short-term than hypothetical interventions to increase income or employment.^{43,44}

These works in HIV-positive populations, excluding our own studies (see Section 2.7),^{33,48,97} do not focus on those living with HIV-HCV co-infection. While it is likely that a proportion of the participants in these studies were also infected with HCV, these researchers did

not document the prevalence of HCV infection in their study samples. As such, these samples are likely heterogeneous with respect to their co-infection status. Furthermore, while there is a large body of evidence related to FI in the context of HIV, I was not able to identify publications related to FI among individuals living with HCV mono-infection. Overall, given the differences between those living with HIV mono-infection and HIV-HCV co-infection¹⁴⁻¹⁶ and the context-specific nature of FI risk factors,^{26,27} the generalizability of findings from HIV-related studies that do not consider HCV co-infection is unclear.

2.5.1 Prevalence of food insecurity

Given the high prevalence of HIV in Africa,¹ most studies of FI have been completed among individuals living with HIV on this continent, particularly in Uganda.^{95,98} For example, in a study of 406 HIV-positive Ugandans (2007), 7.4% experienced mild or marginal FI, 30.8% experienced moderate FI, and 38.2% experienced severe FI.⁹⁹ Among 244 HIV-positive adults in Nigeria (2016), the prevalence of FI, overall, was 72%.¹⁰⁰ Prevalences of overall FI reflect estimates that do not delineate between specific FI severities. For example, 63% of the 319 HIV-positive adults receiving HIV treatment in Southwest Ethiopia experienced FI (2009).¹⁰¹ A similar FI prevalence was documented in a sample of 898 HIV-positive adults in the Democratic Republic of Congo (2012), where 57% experienced FI. In this particular study, FI severity was further examined: 1% of participants were mildly food insecure, 5.1% were moderately food insecure, and 50.9% were severely food insecure.¹⁰² In a Kenyan study (2009), all 67 HIV-positive participants were either severely (79.1%) or moderately (20.9%) food insecure.¹⁰³ Moreover, among 101 individuals living with HIV in rural Zambia (2014-2015), 93% experienced FI of whom 74% experienced severe FI.¹⁰⁴ Similar estimates were found in a sample of 95 HIV-positive participants in Senegal, where 78% of participants experienced severe FI.¹⁰⁵

While the prevalences of FI are high in these African populations, it is also striking that severe FI is the most common. Comparatively, while country-specific estimates of FI are difficult to obtain in Africa, the Food and Agriculture Organization of the United Nations released a report in 2016 describing the following prevalences of severe FI: 26% in sub-Saharan Africa, 28% in Eastern Africa, 31% in Middle Africa, 20% in Southern Africa, and 23% in Western Africa.²⁹ General population estimates of FI overall (including the marginal and moderate FI severity levels) are not available. These estimates suggest that severe FI is more prevalent among HIV-positive populations in Africa than in the regions where general population estimates are available.

Several HIV-related studies of FI have also been published in the United States. The lowest FI prevalence documented was among HIV-positive patients in the Veterans Aging Cohort. This cohort included participants from eight Veterans Affairs Medical Centers in six states. In this cohort of military veterans, 24% experienced FI (2002-2008).¹⁰⁶ The authors of these estimates highlighted that their study was conducted among patients who have accessed care through the Veterans Health Administration and are likely “ostensibly less disenfranchised”¹⁰⁶ than HIV-positive participants in other studies^{107,108}; much higher FI prevalences have been documented in other populations. In a sample of 346 HIV-positive homeless and marginally housed individuals in San Francisco (2007-2010), more than half (55%) experienced FI: 6.1% were mildly food insecure, 18.2% were moderately food insecure, and 31.2% were severely food insecure.^{107,108} Similarly, in a study of 592 individuals living with HIV in the Boston and Providence areas of Massachusetts (1995-2005), 375 participants (63%) experienced FI on one or more occasions during follow-up.¹⁰⁹ In Atlanta, Georgia, 60% of 808 HIV-positive participants experienced FI.¹¹⁰ Lastly, a cross-sectional study of 167 HIV-positive patients in Miami, Florida (2011-2012) revealed that 59% of participants experienced FI and

approximately 25% experienced severe FI.¹¹¹ Each of these estimates is substantially higher than estimates that have been described in the United States general population, where the United States Department of Agriculture has estimated that 12.3% or 15.6 million households were food insecure in 2016.³¹ Acknowledging that this is a household-level national estimate, there are notable differences in FI prevalence when comparing this general population estimate to those documented among individuals living with HIV in the United States.

In what I identify to be the first study of FI among HIV-positive individuals in Canada, 48% of 1213 individuals living with HIV in British Columbia experienced FI (1998-1999).³⁷ In a subsequent study in British Columbia (2007-2008), 71% of 457 HIV-positive individuals receiving HIV treatment experienced FI.³⁸ This prevalence estimate of 71% was assessed using the Radimer/Cornell instrument, the same FI measurement tool used in the initial study completed approximately ten years earlier. This is suggestive of an increase in FI over time among individuals living with HIV in British Columbia. More recently, a community-based research initiative, also using a British Columbia sample (2011-2012), revealed that 73% of 262 HIV-positive individuals experienced FI.³⁹ Other studies have also been completed in vulnerable subsets of the HIV-positive British Columbia population (2005-2009), where the prevalence of severe FI was 71% among 470 individuals living with HIV engaged in IDU in Vancouver.¹¹² A separate study of 254 HIV-positive individuals engaged in IDU in British Columbia revealed that 42.5% of participants experienced hunger, an experience that is concomitant with severe FI (1998-2011).¹¹³ Most recently, among 649 adults living with HIV that were recruited from community-based AIDS service organizations in Ontario, almost three-quarters of participants (70.3%) experienced FI and 31% reported experiencing hunger (2011-2013).⁴¹

Similar to comparisons of HIV-related FI studies with regional African²⁹ and national United States³¹ general population FI prevalences, FI is more common among HIV-positive individuals living in British Columbia and Ontario, compared to estimates from Canada's general population (see Section 2.4.2).²² In the 2012 PROOF report,³⁰ which included national household-level data on all provinces and territories, 3.8% of households in British Columbia experienced marginal FI, 5.7% experienced moderate FI, and 3.2% experience severe FI. This overall FI prevalence of 12.7% is equivalent to 225,600 households. In Vancouver, the prevalence of household FI was 10.4% in 2012. In Ontario, 3.4% of households experienced marginal FI, 5.5% experienced moderate FI, and 2.7% experienced severe FI. Acknowledging that these are household-level estimates, the prevalences of FI among individuals living with HIV in British Columbia,³⁷⁻³⁹ Vancouver,¹¹² and Ontario⁴¹ are substantially higher than these provincial and municipal estimates.

Studies outside of North America have also documented high prevalences of FI. Among 103 HIV-positive individuals in Brazil (2010), 71% experienced FI.¹¹⁴ Among 160 individuals living with HIV in the Dominican Republic (2012), 19% experienced mild FI, 11% experienced moderate FI, and 58% experienced severe FI.¹¹⁵ In a study of HIV-positive treatment-naïve individuals in Russia (2012-2015), FI was experienced by 52% of the 364 participants.⁹⁸ Overall, regardless of the geographical location, it is clear that there are consistently high prevalences of FI among HIV-positive individuals. Although comparability may be problematic across studies, particularly due to differences in the tools used to measure FI, the prevalence estimates of FI among individuals living with HIV have resulted in several researchers describing the relationship between FI and HIV as a “vicious cycle” as well as a syndemic that must be addressed.²⁶⁻²⁸

2.5.2 Consequences of food insecurity

In the field of HIV, a substantial evidence-base exists that treats FI as an exposure variable and examines whether FI is associated with a health or clinical outcome. A recent systematic review and meta-analysis summarized the evidence describing the relationship between FI and CD4 cell counts among individuals living with HIV.³² Given that HIV infection causes the selective loss of CD4 cells, CD4 cell counts are often used as a primary measure of HIV progression.^{8,49} It has been argued that it is clinically relevant if FI has a negative impact on CD4 cell counts among those living with HIV.³² Among the 4589 HIV-positive individuals from seven studies in the United States and one in Uganda, the pooled measure of association indicated a higher odds of having a lower CD4 cell count among individuals experiencing FI (pooled odds ratio [OR] = 1.32, 95% CI = 1.15-1.53). In addition, compared to food secure individuals, those experiencing FI had, on average, 91 fewer CD4 cells (mean difference in CD4 cell count = -91.09, 95% CI = -156.16, -26.02). I am also aware of a study among HIV treatment-naïve individuals in Russia that was published after this systematic review. This publication found no differences in CD4 cell counts between individuals experiencing marginal, moderate, or severe FI, compared to those who were food secure.¹¹⁶ While the authors cited that an absence of HIV treatment may explain their findings, they also stated that their analyses may have been under-powered to examine this association.

Another recent systematic review (2017) summarized the evidence related to the association between FI and HIV viral suppression,³⁴ a clinical outcome that is indicative of HIV treatment success⁴⁹; I was involved with this review. Eleven total studies (total N = 7562), completed between 2009 and 2015 in the United States (seven studies), Canada (two studies), Uganda (one study), and Brazil (one study), were included in this review. A meta-analysis

indicated that the odds of achieving complete HIV viral suppression is lower for those experiencing FI (pooled OR = 0.71, 95% CI = 0.61-0.82). The magnitude and direction of this association was consistent across various characteristics, including study design, study quality, and viral suppression threshold.

Along with the important clinical outcomes of CD4 cell counts³² and HIV viral suppression,³⁴ FI has also been associated with other deleterious outcomes among individuals living with HIV, including sub-optimal HIV treatment adherence.³⁵ In Atlanta, Georgia, FI was associated with a lower odds of HIV treatment adherence (adjusted OR = 0.68, 95% CI = 0.51-0.89).¹¹⁰ As expected, similar findings were also documented in Atlanta with respect to the relationship between hunger, or severe FI, and treatment adherence.¹¹⁷ FI was also associated with HIV treatment non-adherence among homeless and marginally housed individuals in San Francisco (adjusted OR = 1.48, 95% CI = 1.19-1.85).¹⁰⁸ In Uganda, qualitative interviews with 47 individuals living with HIV (2007) revealed that FI was an important barrier to adherence.¹¹⁸ A quantitative longitudinal study of HIV-positive Ugandans (2007-2010) also documented an association between FI and HIV treatment non-adherence (adjusted OR = 1.56, 95% CI = 1.10-2.20).¹¹⁹ Furthermore, an association between FI and non-adherence was documented in the Democratic Republic of Congo (adjusted OR = 2.06, CI = 1.38-3.09).¹⁰² A review on this topic argued that FI is an important barrier to adherence in both resource-rich and resource-poor settings.¹²⁰ A prominent hypothesis, with respect to a potential mechanism, is that the fear or actual experience of side effects of HIV treatments are exacerbated when experiencing FI, resulting in HIV-positive food insecure individuals not adhering to their medications.^{35,120}

Other potential consequences of FI, including an increased risk of mortality, have also been identified in HIV-related publications. For example, in a sample of individuals on HIV

treatment in Vancouver with a median follow-up time of 8.2 years, FI was identified as a risk factor for non-accidental mortality in underweight (body mass index < 18.5) individuals (adjusted hazard ratio [HR] = 1.94, 95% CI = 1.10-3.40).¹²¹ Notably, these researchers adjusted for concurrent HIV treatment adherence, CD4 cell count, and socioeconomic variables. It has also been documented that FI is associated with all-cause mortality among individuals living with HIV that are engaged in IDU in British Columbia (adjusted HR = 1.95, 95% CI = 1.07-3.53).¹¹³ This work also adjusted for age, Aboriginal ethnicity, income, year of HIV treatment initiation, and concurrent measures of CD4 cell count and HIV viral load. In my opinion, a prospective mediation analysis in this area would be valuable in determining whether FI is acting through CD4 cell counts and/or HIV viral load at a later point in time to impact mortality.

In addition to the clinical and mortality-related consequences of FI, physical consequences of this experience have also been described. Among 119 HIV-positive individuals who use drugs in Miami, Florida (2002-2003), FI was associated with HIV-related wasting or an unintentional weight loss of $\geq 10\%$ of body weight over a six month period.¹²² Conversely, in a cross-sectional study of individuals living with HIV in the Dominican Republic (2012), severe FI was associated with increased body mass index and body fat.¹¹⁵ While these findings may seem contradictory, FI has been associated with weight loss and weight gain, depending on the context and setting⁸¹; the literature continues to support theories related to the consumption of high-calorie lower cost foods of poor quality when experiencing FI.^{81,123} The choice of purchasing poor quality high-calorie foods, which may result in weight gain, as opposed to buying less food of high quality, which may result in weight loss, appears to depend on factors such as sex, age, marital status, food stamp program participation, and geographical location.

Furthermore, among individuals living with HIV in Uganda, severe FI was associated with worse physical health-related quality of life, opportunistic infections, and increased hospitalizations.⁹⁹ Associations with health care utilization were also found in a longitudinal cohort of HIV-positive homeless and marginally housed individuals in San Francisco (2007-2010), where those experiencing severe FI had a higher odds of hospitalizations (adjusted OR = 2.16, 95% CI = 1.50-3.09) and emergency department visits (adjusted OR = 1.71, 95% CI = 1.06-2.30).¹²⁴ Regarding mental health-related outcomes, in a study of HIV-positive women in Uganda, severe FI was associated with depression symptom severity.¹²⁵ Similarly, in a cross-sectional study involving 167 HIV-positive patients in Miami, Florida (2011-2012), FI was associated with poor mental well-being.¹¹¹ Among HIV-positive homeless and marginally housed individuals in San Francisco, severe FI was also associated with increased depressive symptom severity.¹⁰⁷

Several studies have also documented that FI is associated with sexual risk behaviours. Qualitative interviews with 41 individuals living with HIV in Uganda (2007) revealed that FI was associated with transactional sex, lack of condom use, and sexual violence.¹²⁶ Quantitatively, among 1100 HIV-positive participants in Atlanta (2012-2014), FI was negatively associated with daily condom use.¹²⁷ Additionally, a recent systematic review of seven studies in sub-Saharan Africa, North America, and Europe found that the current literature pointed to an association between FI and increased sexual risk. The hypothesized mechanism was that of transactional sex and an inability to negotiate safer sex among HIV-positive food insecure women.¹²⁸ In Vancouver, a longitudinal study of HIV-positive individuals engaged in IDU revealed that severe FI was independently associated with unprotected sex (adjusted OR = 2.68, 95% CI = 1.49-4.82).¹¹² FI has also been identified as a risk factor for unprotected sexual activity

and multiple sexual partners among homeless and marginally housed individuals living with HIV in San Francisco.¹²⁹

2.5.3 Risk factors for food insecurity

Another important body of evidence relates to FI as an outcome variable. This type of work, with the goal of identifying predictors or risk factors for FI, is often motivated by analyses that have treated FI as an exposure variable. Similar to the objectives of this thesis, the goal of the forthcoming studies was to use the quantified associations between particular factors and FI to further our understanding and to inform interventions to reduce FI.

In Canada, most of the published work related to risk factors for FI, excluding our studies described in Section 2.7, has been conducted in British Columbia. In a cross-sectional study among individuals living with HIV in this province (1998-1999), unstable housing, unemployment, low income, and living with children were associated with FI.³⁷ In a separate British Columbia study (2007-2008), low income, smoking of tobacco, depressive symptoms, and younger age were associated with FI among HIV-positive participants.³⁸ A more recent community-based HIV research initiative (2011-2012) documented the following risk factors for FI: procurement of food using non-traditional methods, younger age, unstable housing, household gross annual income, and symptoms of depression.³⁹ Outside of British Columbia, a single study was recently completed in Ontario (2017) using data from the aforementioned community-based HIV research initiative. In Ontario, having dependent children at home, residing in large urban areas, low annual household income (<\$40,000 Canadian dollars), difficulty meeting housing-related expenses, cigarette smoking, and depression were associated with FI.⁴¹

In the United States, a cross-sectional study of homeless and marginally housed HIV-positive individuals in San Francisco⁴⁰ revealed that those who were white had over twice the odds of experiencing FI (adjusted OR = 2.03, 95% CI = 1.11-3.71); 32% of the sample were white, 42.8% were African American, 9.2% were Latino, and 16% were of other racial or ethnic backgrounds. Also, individuals with higher physical health composite scores (adjusted OR for each 10-point increase = 0.74, 95% CI = 0.58-0.94) as well as those with higher mental health composite scores (adjusted OR for each 10-point increase = 0.68, 95% CI = 0.54-0.85) had a lower odds of experiencing FI. To the best of my knowledge, I am not aware of any other North American studies that focus explicitly on examining independent associations between risk factors and FI among individuals living with HIV.

Outside of North America, several studies have been conducted in the African setting. In a population of adults receiving HIV treatment in Southwest Ethiopia, education level and family monthly income were associated with FI.¹⁰¹ Qualitative interviews with 30 HIV-positive women in the Dominican Republic also revealed that experiences of HIV-related labour discrimination and stigma were the primary drivers of FI.⁹⁶ In a sample of HIV-positive Ugandans, social support and HIV-related stigma were independently associated with FI.⁹⁵ Moreover, in a Kenyan mixed-methods study, the following factors were identified as determinants of FI: older age, number of children, and not being married.¹⁰³ Perceived mental distress was also associated with FI in Zambia.¹⁰⁴

As can be deduced from this review of HIV-related FI literature, the evidence is diverse with studies in a variety of contexts focusing on estimating FI prevalence and describing consequences of FI. However, studies examining risk factors for FI are infrequent and investigations in the North American setting have often identified socioeconomic and

sociodemographic FI risk factors (i.e., unstable housing, unemployment, low income, living with children, and age)^{37-39,41} that may be difficult to intervene upon and modify in the short-term.^{43,44} Section 2.5.4 describes a small body of evidence that evaluates FI interventions in the HIV setting.

2.5.4 Food insecurity interventions

While there is a growing evidence-base related to FI in the context of HIV, there is little work dedicated to evaluating interventions to reduce FI in this population. For example, a recent systematic review (2017) highlighted a lack of published HIV research in the area of FI-related interventions in resource-rich countries.¹³⁰ The authors suggested that there are currently no standardized practices to intervene upon individuals living with HIV to reduce FI and concluded that there is a need for more evaluation and longitudinal research. However, among the interventional studies in HIV-positive populations that do exist, many focus on the direct provision of food. For example, in the San Francisco area, medically appropriate food assistance, such as meals and snacks designed to comprise 100% of daily energy requirements and to meet nutritional guidelines, was associated with a reduction in FI in an HIV-positive population.¹³¹

Outside of North America, a study of HIV-positive individuals in an urban Ugandan community found that the practice of agriculture was a coping strategy in the context of FI.¹³² In addition, an impressive example of food assistance was that of a program implemented in Western Kenya.¹³³ A collaborative effort, including partners such as the World Food Program and the United States Agency for International Development, provided over 50,000 HIV-positive patients and their dependents with food support through a combination of agricultural production, donations, and food purchases. While the endeavour was impressive and successful in reducing FI over a six-month period, the authors raised several concerns with respect to

program costs and sustainability. Lastly, among individuals living with HIV in central Haiti, food assistance, in the form of approximately 950 kilocalories of cereal, dried legumes, vegetable oil, corn-soya blend, and iodized salt per day, was associated with a reduction in FI.¹³⁴

Despite the aforementioned studies and targeted calls for interventions to reduce FI in HIV-positive populations by the World Health Organization¹³⁵ and the World Food Program,¹³⁶ there remains a concerning lack of research related to addressing this issue among individuals living with HIV. In addition, it has been argued that food assistance is not targeting the causes of FI, as it does not impact a risk factor or determinant of the FI experience.^{137,138} This argument is grounded in the understanding that the overarching goal of risk factor epidemiology is to identify unbiased associations, or causes of outcomes, and to intervene on such causes.^{139,140} While potential risk factors for FI have been identified (see Sections 2.5.3 and 2.5.5), the provision of food does not necessarily intervene on these determinants.

In Canada, food banks are the most visible and well-known response to FI.¹⁴¹ However, a recent study of low-income families in Toronto found that less than one-quarter of food insecure families used food banks, and when food banks were used, they were unable to protect individuals from experiencing FI.¹⁴² Similar findings were described in a recent systematic review on this topic,¹⁴³ indicating that while food banks have an important role to play in providing immediate solutions to severe food deprivation, they are limited in their capacity to reduce FI. Ultimately, while I acknowledge the role of interventions directly on outcomes (e.g., the provision of food by food banks), this thesis is grounded in the belief that the identification of context-specific FI risk factors and interventions on those risk factors may be needed to sustainably reduce FI in both the short- and long-terms. Section 2.5.5 discusses a limited

evidence-base related to illicit drug use, including IDU, as a modifiable risk factor for FI among individuals living with HIV.

2.5.5 Illicit drug use and food insecurity

According to the United Nations Office on Drugs and Crime, there were an estimated 255 million individuals engaged in illicit drug use worldwide in 2015, including an estimated 11.8 million individuals engaged in IDU.¹⁴⁴ As described in Section 2.3, because HIV and HCV are blood-borne viruses that share a common route of transmission,¹² IDU is common in both HIV-positive¹⁴⁵ and HIV-HCV co-infected populations.¹³ Therefore, it is reasonable for researchers to examine whether illicit drug use, including IDU, is having a role in driving the high prevalences of FI among individuals living with HIV.⁴² In addition to the risk factor-related research described in Section 2.5.3, this section discusses studies that have identified illicit drug use as a risk factor for FI.

In Canada, a cross-sectional study among individuals receiving HIV treatment in British Columbia indicated that illicit drug use, defined as the use of cocaine, heroin, speedball, and/or crystal methamphetamine, was associated with FI (adjusted OR = 1.85, 95% CI = 1.03-3.33).³⁸ A separate British Columbia study also found that a history of IDU was associated with FI (adjusted OR = 2.31, 95% CI = 1.56-3.43).³⁷ Moreover, in a sample of 144 individuals engaged in IDU in London, Ontario (2006-2007), where 3% of the sample were HIV-positive and 53% reported being infected with HCV, participants were between 2.5 and six times more likely to experience FI.¹⁴⁶ Most recently, among adults living with HIV who were recruited from community-based AIDS service organizations in Ontario, harmful drug use, as defined by the ten-item Drug Abuse Screening Test (DAST-10 $\geq$ 3), was associated with FI (adjusted OR = 1.68, 95% CI = 1.01-2.77).⁴¹

In a longitudinal cohort in the United States, 881 individuals living with HIV were followed from 1995-2005. In this study, FI and hunger were more prevalent among individuals who reported a history of IDU, compared to those who had never used injection drugs.¹⁴⁷ Interestingly, while FI among individuals who had engaged in IDU remained high throughout follow-up, the prevalence of FI among those who never engaged in IDU decreased over time; this study did not involve regression adjustment. Furthermore, in a cross-sectional study of homeless and marginally housed individuals living with HIV in San Francisco, crack use was independently associated with FI (adjusted OR = 2.06, 95% CI = 1.09-3.91).⁴⁰ Lastly, a single study outside of North America revealed that among 107 HIV-positive individuals engaged in IDU in Chennai, India (2007), 2% experienced mild FI, 13% experienced moderate FI, and 54% experienced severe FI.¹⁴⁸ This sample had no heterogeneity in IDU status to examine IDU as an exposure, but it revealed a high prevalence of FI, particularly severe FI, among individuals engaged in this behaviour. Overall, the evidence related to illicit drug use, IDU, and FI is limited. Given that IDU is a substantial risk factor for HIV¹⁴⁵ and HCV^{3,9} transmission, as well as the high prevalences of FI in HIV-positive populations,²⁶⁻²⁸ there is a research gap with respect to studies that quantify potential associations between IDU, a modifiable behaviour, and FI.

2.6 Substance use interventions

As described in Section 2.5.2, there is a diverse evidence-base related to potential consequences of FI, specifically FI's associations with poor clinical outcomes such as lower CD4 cell counts,^{32,33} incomplete HIV viral load suppression,^{33,34} and sub-optimal HIV treatment adherence.³⁵ Such works have motivated studies that focus on risk factors for FI with the goal of informing strategies to reduce FI. While Section 2.5.4 describes food-related interventions to address FI in the HIV context, I am not aware of studies that in fact evaluate the impact of an

intervention that is designed to reduce the occurrence of a potential FI risk factor, such as illicit or IDU (Section 2.5.5).

As noted, the goal of risk factor epidemiology is to identify unbiased exposure-outcome associations that can be used to inform interventions.^{139,140} The objectives of Manuscripts 1 and 2 (Chapters 4 and 5) are to quantify associations between a potentially modifiable behaviour, IDU, and FI. However, while information regarding associations (Manuscript 1) and mechanisms (Manuscript 2) can provide evidence that reductions in IDU may mitigate FI, there is a need to further discuss strategies that can be taken to intervene on such an exposure.

A substance use intervention is a program or service that is designed to mitigate an individual's dependence on drugs.¹⁴⁹ The terminology of “dependence” and “addiction” is used interchangeably in the medical literature, although the terms are not necessarily synonymous.¹⁵⁰ According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the key feature of a drug dependence is a cluster of cognitive, behavioural, and physiological symptoms that results in an individual continuing their use of a substance despite significant problems related to the use of that substance.¹⁵¹ There are a variety of evidence-based approaches for treating drug dependence,^{149,152} including behavioural therapy and/or pharmacological approaches. The types of treatments and whether they are used in combination will vary depending on an individual's needs and on the class of drugs that are being used (e.g., opioids and central nervous system depressants or stimulants).¹⁵³ The types of programs that exist are diverse and vary in implementation and effectiveness. For example, counseling, rehabilitation, and detoxification programs serve a variety of purposes that are designed to address the cognitive, behavioural, and physiological dimensions of drug dependence. However, studies on the nature and effectiveness of these treatments are inconsistent.^{149,152,154} Furthermore, harm

reduction programming is designed to reduce the potential consequences associated with an individual's drug use.¹⁵⁵ Needle and syringe exchange programs, for example, are effective in reducing the transmission of HIV¹⁵⁶ and HCV.¹⁵⁷ However, unlike counseling, rehabilitation, and detoxification, harm reduction programs do not have the immediate goal of reducing drug use.¹⁵⁵ While these programs and services are of paramount importance for drug dependent individuals, this section will emphasize one particular substance use intervention known as methadone maintenance treatment, a well-known and researched pharmacological approach.

Methadone treatment is the most widely used form of treatment for individuals who are dependent on opioids.⁴⁵ Opioids are a class of substances that act on opioid receptors to produce morphine-like effects. In a medical setting, opioids are primarily used for pain relief and anesthesia.¹⁵⁸ Opioids include opiates, an older term that refers to drugs derived from opium, a dried latex material obtained from the opium poppy. Opioids also include semi-synthetic and synthetic drugs (e.g., heroin, hydrocodone, oxycodone, and fentanyl), antagonist drugs (e.g., naloxone), and endogenous peptides (e.g., endorphins).^{158,159} Methadone is a synthetic opioid that works by alleviating the symptoms of withdrawal from other opioids.⁴⁵ It is known to decrease the illicit use of opioids, regardless of the route of administration.^{46,47} This pharmacological intervention is a form of substitution therapy⁴⁵; methadone is an opioid that is used as a substitute to other illicit opioids.

Methadone works by alleviating the symptoms of opioid withdrawal as soon as there is a stable and sufficient blood-level of methadone.⁴⁵ Since methadone is a longer-acting drug than some other opioids, such as heroin, a single oral dose daily prevents the onset of opioid withdrawal symptoms (i.e., anxiety, restlessness, runny nose, tearing, nausea, and vomiting) for 24 hours or longer.¹⁶⁰ Methadone also diminishes the euphoric effects of other opioids without

necessarily causing sedation or analgesia. This means that self-administered illicit opioids will not lead to euphoria, making it less likely that individuals will use illicit opioids in the short-term.⁴⁵

In Canada, there is a national regulatory framework for methadone prescription⁴⁵ and only physicians who have received an exemption under the Controlled Drugs and Substances Act are allowed to prescribe methadone. Pure methadone is a white crystalline powder that is usually dissolved in a flavoured drink and taken orally once a day.¹⁶⁰ Methadone treatment may be delivered in a variety of settings, including: substance use treatment centres, community health centres, private medical clinics, pharmacies, hospital-based clinics, HIV clinics, mental health agencies, and correctional facilities.⁴⁵ However, there is no universal definition of a methadone maintenance treatment program.^{46,47} While the common feature is the use of methadone, treatment components and policies vary within Canada. As noted by the Government of Canada,⁴⁵ a comprehensive approach to methadone treatment generally includes a number of components, such as: methadone dose, medical care, other substance use treatments, counseling, mental health support, and linkage to community supports. While the definition of “methadone treatment” may be more specific than “counseling,” “rehabilitation,” or “detoxification,” it is difficult to determine which components of the methadone treatment program are in fact causing opioid-dependent individuals to reduce their drug use. Therefore, depending on how treatment status is measured and defined in a study (e.g., Manuscript 3), a researcher cannot necessarily attribute the entire estimated impact of methadone treatment on an outcome, such as FI, to methadone itself.

The motivation for examining the impact of a substance use intervention on FI is based on the findings in Manuscripts 1 and 2, which focus on IDU as a FI risk factor. However,

methadone is only indicated for the treatment of opioid dependence and it is not restricted to the mitigation of IDU per se.^{45,160} As such, methadone treatment is only applicable to a subset of those who are engaged in IDU. This is important because the use of non-opioids, such as cocaine, is also common among HIV-HCV co-infected individuals.¹⁶¹ Given that IDU is examined as the primary exposure in Manuscripts 1 and 2, it is likely that the injection of non-opioids is also a substantial contributor to any IDU-FI relationship that is quantified. In addition, individuals receiving methadone may be using opioids by routes of administration other than injection. While the FI-related evidence in HIV-positive populations is primarily based on the injection of any drugs,^{37,48} the methadone treatment-severe FI association quantified in Manuscript 3, for example, may also be partially explained by the treatment's impact on non-injection drug use.

These statements raise the question of why such a specific treatment is being studied in Manuscript 3, one that is only applicable to a subset of those who are engaged in IDU, as opposed to a treatment that has the potential to impact the injection of any drug types. First, an earlier review has indicated that methadone maintenance treatment is the most evaluated approach in the field of substance use interventions.⁴⁷ Second, given the large evidence-base, it has become widely known that this treatment is highly effective in reducing illicit opioid use. For example, a meta-analysis of six randomized controlled trials indicated that methadone was more effective than non-pharmacological approaches (i.e., detoxification and drug-free rehabilitation) in the suppression of heroin use as measured by self-reports as well as urine and hair analyses (pooled RR = 0.66, 95% CI = 0.56-0.78).¹⁶² In a trial of incarcerated individuals in Baltimore, Maryland (2003-2005), participants receiving methadone and counseling were less likely to have had an illicit opioid-positive urine specimen, compared to those who were only receiving

counseling.¹⁶³ Another systematic review has suggested that methadone is comparable to buprenorphine for retaining individuals in treatment; buprenorphine is a synthetic opioid that is also used in substitution therapies.¹⁶⁴

There are no approved medications for the treatment of non-opioid drug dependence at this time.^{165,166} Unlike methadone and buprenorphine for opioid dependence, there are no pharmacological substitution therapies available for individuals who are dependent on central nervous system depressants (e.g., benzodiazepines) or stimulants (e.g., cocaine). In these scenarios, the substance use intervention that is commonly recommended is that of cognitive behavioural therapy and/or detoxification.¹⁶⁵ As described, it is less clear whether an association between such interventions and FI would be quantifiable, given inconsistencies in the effectiveness of such strategies.^{149,152,154}

When examining a substance use intervention-FI relationship that is based on the premise that IDU is a risk factor for FI, it is logical to focus on an intervention that is relatively well-defined and effective,^{46,47} such as methadone treatment. As with any treatment, the benefits must be considered along with other factors, such as drug safety,¹⁶⁷ the potential for the diversion of methadone,¹⁶⁸ and rates of relapse.¹⁶⁹ Furthermore, I acknowledge that methadone does not address early life stressors, trauma, or other distal risk factors that may lead an individual to develop a drug dependency.^{170,171} However, as with any sequence of experiences, a researcher must determine where in the pathway there is an opportunity to intervene. Given the focus on IDU as a proximal FI risk factor, I have concentrated on an intervention that reduces the illicit use of opioids in the short-term.⁴⁵ The examination of methadone treatment in the context of FI does not indicate that other interventions, including those that may mitigate distal risk factors for drug dependence, are inconsequential. I also acknowledge that reductions in illicit drug use, the

goal of methadone treatment,^{46,47} is not the only outcome that should be sought after. As described, harm reduction, with the goal of mitigating the potential consequences of an individual's drug use,¹⁵⁵ provides important benefits for individuals engaged in IDU.^{156,157} However, given that Manuscripts 1 and 2 quantify the independent or isolated impact of IDU as a prevalent behavioural FI risk factor,¹³ it was logical to focus on an intervention which has the immediate goal of reducing the occurrence of IDU.

2.7 Food insecurity and HIV-HCV co-infection

To my knowledge, outside of the manuscripts described in this thesis, only three FI-related studies have been published using data from HIV-HCV co-infected individuals^{33,48,97}; all of these works were recently completed by our research group. The first study was an exploratory analysis of FI risk factors that was published in November 2016.⁴⁸ In this publication, we used interim data from the Food Security and HIV-HCV Study of the Canadian Co-infection Cohort between November 2012 and June 2014 at 15 health centres (as opposed to November 2012 to October 2015 at 17 centres - see Section 3.2). Among the 525 participants, 59% experienced FI at their first study visit and the majority of the food insecure participants experienced severe FI. This work did not include the marginal FI category (see Table 2.2), which would suggest that this FI prevalence, overall, is an underestimate. While this hypothesis-generating work provides insights into potential correlates of FI, our primary objective was to suggest important variables for consideration in future hypothesis-confirming analyses, such as those included in this thesis.

The objective of this first analysis using the Food Security and HIV-HCV Study data was not to estimate the independent association between one factor and FI. Our modeling included many independent variables and the multivariable model building was informed by a

consideration of statistical significance; there were no confounders per se. This work revealed the following correlates of FI: enrolment at a Quebec study site (adjusted OR = 0.42, 95% CI = 0.27-0.67), employment (adjusted OR = 0.55, 95% CI = 0.35-0.87), and average personal monthly income (adjusted OR per \$100 increase = 0.98, 95% CI = 0.97-0.99), recent IDU (adjusted OR = 1.98, 95% CI = 1.33-2.96), trading away food (adjusted OR = 5.23, 95% CI = 2.53-10.81), and recent experiences of depressive symptoms (adjusted OR = 2.11, 95% CI = 1.48-3.01). Acknowledging the exploratory modeling approach and the fact that this work was completed with interim data, this research helped inform the selection of exposures and confounders in the forthcoming thesis manuscripts (see Chapters 4, 5, and 6). This publication also provided preliminary evidence of a IDU-FI association in this HIV-HCV co-infected population.⁴⁸

The second FI-related manuscript in an HIV-HCV co-infected population was published in October 2017.⁹⁷ Similar to the HIV-related papers in Section 2.5.2 (Consequences of food insecurity), this work treated FI as an exposure variable. We found that moderately (adjusted RR = 1.63, 95% CI = 1.44-1.86) and severely food insecure (adjusted RR = 2.01, 95% CI = 1.79-2.25) co-infected participants had a higher risk of experiencing depressive symptoms, as measured by the Center for Epidemiologic Studies Depression Scale (CES-D-10 $\geq$ 10). As noted in our hypothesis-generating analysis,⁴⁸ it has been suggested that depressive symptoms may be both a FI risk factor³⁸⁻⁴¹ as well as a potential consequence of FI.^{107,111,125}

In our third manuscript, published in November 2017,³³ we documented that both moderate FI and severe FI were associated with incomplete HIV viral load suppression and lower CD4 cell counts among co-infected individuals in Canada. Our findings corroborated the evidence in the systematic reviews and meta-analyses that summarized the previous studies

related to the negative impacts of FI on HIV viral load³⁴ and CD4 cell counts³² among individuals living with HIV; our work among HIV-HCV co-infected individuals was not included in these reviews.

2.8 Literature review summary

In Chapter 2, I described the natural history and epidemiology of HIV and HCV, the characteristics of HIV-HCV co-infected populations, and the concept, measurement, and prevalence of FI in Canada. I also summarized the previous literature related to FI in HIV-positive populations, with a specific focus on FI prevalence, consequences of FI, and risk factors for FI in this setting. Subsequently, I described a limited HIV-related evidence-base relating to illicit drug use, including IDU, and FI. This was followed by a summary of methadone treatment for opioid dependence, a substance use intervention designed to reduce the illicit use of opioids. Lastly, an overview of our previous publications in the HIV-HCV co-infection context was presented, with a particular emphasis on the findings from our exploratory analysis of FI risk factors.⁴⁸ In the next chapter, I will outline the data sources and methodologies that were used in this thesis to examine associations, mechanisms, and interventions related to IDU and FI among individuals living with HIV-HCV co-infection in Canada.

Chapter 3: Detailed methodology

3.1 Canadian Co-infection Cohort

All thesis objectives were completed using data from the Food Security and HIV-HCV Study (FS Study)⁴⁸ of the Canadian Co-infection Cohort (CCC).¹⁷² The CCC, which served as the source population, was established in 2003 and began recruitment at three university-based HIV clinics in Montreal, Quebec, Canada. As an open prospective cohort of HIV-HCV co-infected individuals, the CCC now includes 19 sites in six Canadian provinces (Quebec, British Columbia, Ontario, Saskatchewan, Alberta, and Nova Scotia).

Participating recruitment centres now include community-based clinics and outreach programs in large and small urban centres across Canada, as well as university-based HIV treatment programs.^{172,173} The five Quebec sites include: Hôpital Notre-Dame (Montreal), Clinique médicale du Quartier Latin (Montreal), the Montreal General Hospital (Montreal), the Montreal Chest Institute (Montreal), and Centre hospitalier de l'Université Laval (Quebec City). In British Columbia, recruitment occurs at four sites in Vancouver: the Oak Tree Clinic, the Pender Clinic, the BC Centre for Excellence in HIV/AIDS, and the Vancouver Native Health Centre. In Ontario, participants are recruited from six sites: the Ottawa General Hospital (Ottawa), the Toronto General Hospital (Toronto), the Sunnybrook and Women's College Health Sciences Centre (Toronto), the Sudbury Regional Hospital (Sudbury), the McMaster University Medical Centre (Hamilton), and the Windsor Regional Hospital (Windsor). In Saskatchewan, participants are recruited from the Regina General Hospital (Regina) and the Saskatoon HIV/AIDS Research Endeavour at the University of Saskatchewan (Saskatoon). The South Alberta Clinic is the recruitment site in Calgary and the Queen Elizabeth Hospital (Halifax)

contributes participants from Nova Scotia. Provinces are ordered from largest to smallest in terms of total enrolment counts.

To be included in the CCC, HIV-positive participants must show evidence of current or previous co-infection with HCV and be at least 16 or 18 years of age, according to provincial criteria. Participants are considered HIV-positive if they have a documented HIV infection measured by a positive enzyme-linked immunosorbent assay (ELISA) with western blot confirmation. Among those who are HIV-positive, individuals with serologic evidence of HCV exposure are identified by a positive ELISA with a recombinant immunoblot assay II or an enzyme immunoassay confirmation. Prior to seroconversion, HCV RNA positivity can also be used to determine inclusion.¹⁷² Given the dynamic nature of an HCV infection, the inclusion criteria allows for participants who may have spontaneously cleared their infection in the past, as well as those who are chronically infected and those who may have received HCV treatment.

Socioeconomic, sociodemographic, behavioural, and clinical information is collected at each study visit, spaced approximately six months apart (see Section 3.6). Blood samples are also collected at each visit to obtain additional clinical information. Funding for the CCC is provided by the Canadian Institutes of Health Research (CIHR), the Fonds de recherche du Québec-Santé (FRQ-S), and the CIHR Canadian HIV Trials Network (CTN).¹⁷² CCC recruitment and data collection is on-going with CIHR Foundation Grant funding until 2022.

3.2 Food Security and HIV-HCV Study

Between November 2012 and October 2015, the FS Study was implemented and biannual data collection related to FI, including the ten-item adult scale of Health Canada's HFSSM, was integrated into CCC study visits at 17 of the 19 CCC sites in six provinces.⁴⁸ The Clinique

médicale du Quartier Latin in Montreal and the Ottawa General Hospital were not involved in the FS Study.

In addition to measuring FI, supplementary socioeconomic and sociodemographic data were also collected as a part of the FS Study. While this study received separate funding from the CIHR and the CTN, it was operationalized entirely within CCC study sites. Starting in November 2012, all existing CCC participants, except for those at the two aforementioned sites, were invited to complete an additional ten-page questionnaire at each biannual CCC visit. Participants could not enrol in the FS Study unless they were enrolled in the CCC. Therefore, the FS Study included a subset of participants from the CCC who enrolled between November 2012 and October 2015; there was staggered entry into the study.

All analyses completed in this thesis used data from the subset of CCC participants who enrolled in the FS Study. This dataset was created by merging data from the CCC questionnaires and blood samples with data from the FS Study questionnaires. FS Study recruitment and data collection were completed in October 2015. Notably, the minimum age of FS Study participants was 23 years in the analytical dataset. At all visits, participants received \$15 Canadian dollars to complete the CCC questionnaire and blood sample and \$10 to complete the FS Study questionnaire. While there were qualitative interviews conducted with a small subset of the FS Study participants, this aspect is not discussed as the qualitative data were not analyzed in this thesis.

3.3 Ethical approvals and confidentiality

Both the CCC and the FS Study were approved by the McGill University Health Centre and the research ethics boards of the participating institutions.¹⁷² Prior to analyses, all participant data were de-identified by the CCC's data management team at the McGill University Health

Centre. Each of the thesis objectives addressed in Manuscripts 1-3 were also approved by the research ethics board of the McGill University Health Centre through an “amendment to an approved study” procedure (Project Number: 2013-994, 12-166, eReviews_2659).

3.4 Exposures: injection drug use and methadone treatment

In Manuscript 1 (Chapter 4), both binary IDU and categorical IDU frequency were examined as the exposure variables in separate analyses. Any IDU in the past six months was self-reported by participants on a questionnaire at each visit. IDU frequency in the past month was also self-reported at each visit and this permitted the exploration of a dose-response relationship. IDU was coded as a binary exposure variable (none vs. any IDU) and IDU frequency (none vs. non-weekly, weekly IDU) was coded as a categorical exposure variable. In Manuscript 2 (Chapter 5), IDU in the past six months was self-reported by participants on a questionnaire. The exposure was defined as a binary indicator of IDU (none vs. any IDU) at the second study visit. In Manuscript 3 (Chapter 6), methadone maintenance treatment in the past six months was self-reported by participants on a questionnaire at each visit. The primary exposure variable was a binary indicator of treatment (no treatment vs. methadone treatment).

3.5 Outcomes: food insecurity and food insecurity severity

As introduced in Section 2.4.1, the analytical outcomes of FI and FI severity were measured using the ten-item adult scale of Health Canada’s HFSSM. The HFSSM focuses on self-reports of uncertain or inadequate food access due to limited financial resources and each item specifies a lack of money as the reason for the condition or behaviour.¹⁹ The ten items that were asked to each participant at each visit are listed in Table 2.1. Briefly, FI, including the severity of the FI experience, is determined by the number of affirmative responses reported on the HFSSM. All analyses described in this thesis categorize FI severity at three levels: marginal

FI,⁹² moderate FI, or severe FI (see Table 2.2). Participants indicating 1 affirmative response were identified as experiencing marginal FI, or some indication of worry related to adequate food access. Moderate FI, indicating compromises in the quality and/or quantity of food consumed, was defined by participants indicating 2-5 affirmative responses. Severe FI, indicating disrupted eating patterns and reduced food intake, was defined by ≥ 6 affirmative responses on the HFSSM.²² Participants indicating 0 affirmative responses were identified as being food secure. To reflect the data collection schedule of the CCC,¹⁷² the reference period of the FI measurement in this thesis referred to the past six months.

In Manuscript 1 (Chapter 4), FI and FI severity were considered in separate models. First, participants reporting 1 or more affirmative response(s) were identified as experiencing any FI in the six months preceding each visit, yielding a binary outcome variable (food secure vs. any FI). Second, to examine the impact of IDU on FI severity, marginal, moderate, and severe FI were treated as separate outcome categories, with food secure as the referent category. In Manuscripts 2 and 3 (Chapters 5 and 6), participants reporting ≥ 6 affirmative responses on the HFSSM were identified as experiencing severe FI. I used this dichotomization to define a binary outcome (not experiencing severe FI vs. experiencing severe FI) and Manuscripts 2 and 3 focused exclusively on severe FI.

3.6 Missed study visits

The FS Study collected 1973 observations across five study visits from 725 participants between November 2012 and October 2015. The data collection schedule in both the CCC and FS Study is biannual, meaning that questionnaires and blood samples (in the CCC) were collected approximately every six months. Given the intended schedule, it was imperative to ensure that participants' data were collected approximately every six months. In a multi-site

cohort study, missed visits are inevitable. While there were 1973 total observations and a maximum of five study visits in the original dataset, these figures do not reflect whether the data collection occurred approximately “on schedule.” Therefore, a strategy was devised to address the issue of missed study visits.

In an ideal scenario, if a hypothetical participant enrolled early enough to complete six visits, this participant would have their data collected at enrolment and after 6, 12, 18, 24, and 30 months of follow-up. Visits that occurred in these months would be considered exactly on schedule. In this scenario, there are five whole months between visits. For example, if a second visit occurred in month 6, there should have been no visits in months 7, 8, 9, 10 or 11, with a third visit occurring in month 12. However, while attempts were made to have data collection occur every six months, it was not possible for all participants. A time-window was created to allow for the identification of what I considered an approximately on schedule second, third, fourth, fifth, and potentially sixth visit. As described, if there are approximately five whole months between on schedule visits, this would result in 2.5 months on either side of months 6, 12, 18, 24, and 30, when a visit could potentially occur. In this scenario, if a second visit occurs six months after enrolment, I deemed it reasonable that a visit which occurred 2.5 months before or 2.5 months after the sixth month would also be coded as a second visit. Similarly, month 12 ± 2.5 months was coded as a third visit, month 18 ± 2.5 months was coded as a fourth visit, month 24 ± 2.5 months was coded as a fifth visit, and month 30 ± 2.5 months was coded as a sixth visit; no participants had more than 32.5 months of follow-up in the FS Study.

After performing this exercise to identify whether visits occurred approximately every six months (± 2.5 months), eight study visits were dropped that occurred too close to the enrolment date. For these eight visits, a given participant had enrolled and subsequently completed an

additional visit within 2.5 months of enrolment. Such a visit could not be categorized as a second visit (month 6 ± 2.5 months), nor could it be categorized as a baseline visit (visit one), which had already occurred at “zero months” of follow-up. This resulted in eight visits that were deemed unusable. After this exercise, there were gaps in the visit counts for some participants, representing missed visits (± 2.5 months). For example, a participant may have had their data collected at enrolment and again approximately twelve months later, missing a second visit. Similarly, a participant may have completed visits one, two, and four, missing visit three. After tabulating all missed visits, I effectively added 150 rows to the dataset where gaps or missed visits were identified.

As described, there were 1973 observations or rows of data in the original dataset. Eight of these observations were unusable. This resulted in 1965 observations, which was then increased to 2115 observations (i.e., 1965 on schedule visits in addition to 150 missed visits). These 150 additional rows represented the 150 missed visits between November 2012 and October 2015. While time-invariant baseline data (e.g., sex) were carried forward to these missed visits, time-varying measures were missing as data were not collected approximately on schedule. Therefore, in addition to the missing data because of item non-response on the questionnaires, there were missing data due to missed visits. The numerical representations of this process are displayed in Table 3.1.

Table 3.1 Description of the analytical dataset in all thesis manuscripts after accounting for missed study visits.

Visit number	Number of observations at each study visit ^a			
	Prior to accounting for missed visits	After accounting for visit timing and dropping 8 unusable visits	Missed visits	After including missed visits
1	725	725	0	725
2	608	522	86	608
3	420	422	53	475
4	203	257	11	268
5	17	37	0	37
6	-	2	0	2
Total	1973	1965	150	2115

^a The Food Security and HIV-HCV Study collected 1973 observations across five study visits on 725 participants from November 2012 to October 2015. However, follow-up data collection was meant to occur approximately in months 6, 12, 18, 24, and 30 (every six months). Participants visit numbers were re-coded to reflect the timing of the visit (e.g., month 6 ± 2.5 months = second visit). After this process, eight visits were dropped that occurred too close to enrolment. Therefore, of the 1965 remaining visits, there were 86 missed second visits, 53 missed third visits, and 11 missed fourth visits. These visits were inserted into the dataset, yielding a total of 2115 rows of data.

The consideration of missed visits was necessary to better ensure uniform temporal-ordering in each of the longitudinal analyses performed in this thesis. This approach is based on the premise that while a given participant may have their data collected at five separate visits, the timing of these visits may not have coincided with the desired data collection schedule. This is particularly important when lagging variables (as was done in Manuscripts 1 and 3) and when mechanisms or pathways are being prospectively examined, as was done in Manuscript 2. For example, when lagging the exposure data (e.g., IDU) by one visit with respect to an outcome measure (e.g., FI), the researcher is assuming, approximately, that the exposure was uniformly ascertained in the six months preceding the outcome measure. If a given participant had completed visits one and three and I ignored the fact that a second visit did not occur, effectively coding visit three as a second visit, the exposure would not in fact reflect a measure that

represented an experience in the six months preceding the outcome measure. Ultimately, without the consideration of missed visits, uniform temporal-ordering is difficult to ensure.

While the grouping of visits using a ± 2.5 months time-window is somewhat crude, I felt that it was a fair compromise. Specifically, it was necessary to use a time-window which left no periods of follow-up time as unusable, except for the first 2.5 months of follow-up after enrolment. By using a narrower time-window (e.g., ± 1 month), I would have identified a substantial number of unusable visits; this would have required further use of multiple imputation or other methods to handle missing data. To be clear, the only visits that were unusable were the eight observations that occurred within 2.5 months of enrolment when using the ± 2.5 months approach. Every other visit was coded as a visit two, three, four, five or six using a time-window of ± 2.5 months around months 6, 12, 18, 24, and 30.

In summary, 86 visits were missing within 2.5 months of month 6. This exercise also identified 53 missed third visits and the 11 missed fourth visits. Even though there was a maximum of five visits in the original dataset, two additional sixth visits were introduced after performing this exercise; there were two visits that occurred within 2.5 months of month 30 (see Table 3.1). Overall, while time-varying measures were not available at follow-up visits that were missed, I felt that approximate uniformity in temporal-ordering was imperative to the interpretation of the analyses described in this thesis.

3.7 Multiple imputation by chained equations

Missing data are common in epidemiological studies.¹⁷⁴ Whether data are missing on exposures, outcomes, or confounding variables, various procedures have been described in the literature over several decades to address this issue.¹⁷⁵⁻¹⁷⁷ Multiple imputation (MI), which originated in the early 1970s in the context of survey non-response,¹⁷⁷ has gained in popularity

over the years.¹⁷⁸ In terms of nomenclature, an imputation represents one set of plausible values for missing data and multiple imputations represent multiple sets of plausible missing data values.¹⁷⁹ Briefly, MI is a flexible, simulation-based statistical procedure for handling missing data and the technique consists of three steps.^{174,180,181} First, a researcher-specified number of imputations or imputed (“complete”) datasets are generated under a chosen imputation model. Second, the desired statistical analyses are performed separately within each imputed dataset, which now contain complete data on all variables. Third, the results estimated within each imputed dataset, such as the estimated measure of effect and its variance, are combined or pooled into a single set of results. For example, one can specify that ten imputed datasets be generated. In the case of a regression model, an analysis in each imputed dataset would generate ten estimated coefficients (e.g., RRs) and ten variance estimates. These ten coefficients and ten variance estimates are then combined, using a procedure known as Rubin’s method,¹⁸¹ to generate a single RR and its associated variance. MI is appealing because it relies on familiar statistical methods, such as regression modeling.

Other commonly used missing data techniques include complete-case analysis and single imputation methods.^{174,180} In a setting where repeated measurements on individual participants have been completed, last-observation-carried-forward is another common approach.¹⁸⁰ Complete-case analysis discards all observations with missing data; if a given participant is missing data on one or more variables to be included in an analysis, this participant will be dropped from the sample. As such, missing observations reduce the sample size, resulting in larger standard errors, wider confidence intervals, and less statistical power. In addition, by selecting on those who have complete data on all variables, complete-case analysis may introduce selection bias into the sample.^{174,180}

Single imputation methods do not discard missing values. However, unlike MI, the imputed values are treated as being known in single imputation. This underestimates the variance of the estimates which means that the confidence intervals and significance tests are invalid.^{174,180} Alternatively, the pooling step during the MI procedure addresses this issue by accounting for between-imputation variability.¹⁸¹ In MI, the imputed values in different imputations may vary, meaning that the analyses within each imputed dataset may result in slightly different estimates. This reflects the uncertainty in the imputation process itself, as MI uses statistical models to predict or “fill in” the missing observations.

The final technique which is commonly used is that of last-observation-carried-forward.¹⁸⁰ In a repeated measures setting, this procedure replaces a participant’s missing values with the last available measurement and assumes that the participant’s responses would have been stable over time. This method suffers from the same limitations as single imputation, as the missing values are considered to be known quantities, underestimating the variance of estimates. However, unlike single imputation, last-observation-carried-forward does not use the complete information on other factors to predict missing observations for a given variable. Last-observation-carried-forward, as well as complete-case analysis and single imputation, are widely considered to be sub-optimal.¹⁸²

While MI has advantages over other techniques for handling missing data, it is not a panacea^{174,180}; assumptions about the missing data mechanisms are necessary to use this approach. To formalize these assumptions, the following terminology is important: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).¹⁷⁹ Missing data are MCAR if the probability that the data are missing is not dependent on either observed or unobserved data. Under MCAR, the missing data are a simple random

sample of all the data. In this case, any analysis that discards missing data is unbiased, albeit inefficient. Missing data are MAR if the probability that the data are missing is not dependent on unobserved data; missing data may depend on observed data. Under MAR, the unobserved data do not contain any additional information about the missing data mechanism, conditional upon the observed data. MNAR indicates that the probability that the data are missing is dependent on unobserved data. If there are no data on factors that explain the missing data mechanism, these missing data are MNAR. To use MI, it must be assumed that the data are at least MAR. This is a non-verifiable assumption because the MAR mechanism cannot be distinguished with observed data from the MNAR mechanism. Therefore, the researcher assumes that the probability that the data are missing is not dependent on unobserved data and must be confident that the variables included in the imputation models are sufficient to ensure that the data are MAR^{174,179,180}; I make this assumption in this thesis.

In all thesis manuscripts, MI by chained equations was used to impute missing observations.¹⁷⁹ In longitudinal datasets like the FS Study, it is common for missing values to be present for several variables.¹⁸³ The chained equations aspect of MI is an approach to generating imputed datasets based on a set of imputation models, where one model is used for each variable with missing values.¹⁷⁹ Initially, all missing values are filled in by simple random sampling with replacement from the observed values. The first variable with missing values (e.g., x_1) is regressed on all other variables included in the imputation models, restricted to individuals with the observed x_1 . Missing values in x_1 are replaced by simulated draws from the corresponding posterior predictive distribution of x_1 . Subsequently, the next variable with missing values (e.g., x_2) is regressed on all other variables, restricted to individuals with observed x_2 . The imputed values of x_1 are used in imputing x_2 , hence the “chained equations” terminology. Missing values

in x_2 are replaced by draws from the posterior predictive distribution of x_2 . The process is repeated for all other variables with missing values and this is known as a single iteration. To stabilize the results, the procedure is usually repeated for several iterations to produce a single imputed dataset. The entire procedure is then repeated to generate a pre-specified number of imputed datasets.¹⁷⁹

In Manuscripts 1 and 2, MI by chained equations was used to impute missing observations using 30 imputed datasets and 50 iterations. In Manuscript 3, ten imputed datasets and 100 iterations were used. The reason for the reduction in the number of imputed datasets and the increase in the number of iterations in Manuscript 3 was due to convergence issues; I required more iterations in the imputation models in Manuscript 3 for the process to converge to a stable state. However, increasing the iterations also increases the computation time; I reduced the number of imputed datasets in Manuscript 3 so that the computation time was similar to that in Manuscripts 1 and 2. All variables that were included in the main analyses were included in the imputation models. This included exposures, outcomes, and confounding variables, as well as the mediator and predictors of censoring in Manuscript 2. Additional variables that were hypothesized to predict the missing data mechanisms were also included, even if such variables were not included in the main analyses. To better acknowledge the longitudinal nature of the data, a categorical indicator for study visit was included in the imputation models. In the imputation models, continuous, binary, and categorical variables were imputed using predictive mean matching, logistic regression, and multinomial or ordered logistic regression, respectively.

3.8 Manuscript 1: Longitudinal cohort analysis

3.8.1 Analytical sample

As indicated in Table 3.1, the total sample in Manuscript 1 included 725 participants from the FS Study who contributed 2115 observations over six visits. However, as described in Section 3.7, to better acknowledge the longitudinal nature of the data, a categorical indicator for study visit was included in the imputation models. This variable included a total of two observations in the sixth visit category and this caused non-convergence of the imputation models. To use the visit indicator variable during imputation, the two sixth visits had to be dropped; this eliminated the small category causing convergence issues. This resulted in a total of 2113 observations that were included in the analytical sample.

Of the 725 FS Study participants, 608 participants completed two or more visits. Following variable lagging, which requires a minimum of two visits, 117 participants who had a single visit were dropped from the sample. Among the 608 included participants, 475, 268, and 37 participants completed a second, third, and fourth visit, respectively, for a total of 1,388 observations that were included in the analytical sample.

3.8.2 Data analysis

For the binary outcome analyses (food secure vs. any FI), generalized estimating equations with an exchangeable working correlation structure were used to estimate unadjusted and adjusted RRs from Poisson regression models with robust standard errors.^{184,185} IDU and IDU frequency were examined as the exposure variables in separate models. For the categorical outcome analyses of FI severity, unadjusted and adjusted relative-risk ratios (RRR) were estimated using multinomial regression models with robust standard errors. As with the binary outcome analyses, the IDU and IDU frequency exposure variables were examined in separate

models. In this section, I will describe the rationale for the chosen methodologies and mention alternative approaches that are commonly used to address similar research objectives.

Generalized estimating equations are an approach to estimating parameters of regression models; these equations are not themselves a model.¹⁸⁶ Generalized estimating equations are primarily used in repeated measures or longitudinal data analyses and are often introduced as an alternative to random effects modeling.¹⁸⁷ Random effects models are also referred to as multi-level models, mixed models, or hierarchical models. These models involve the specification of random intercepts and/or random slopes.¹⁸⁸ Generalized estimating equations and random effects modeling can be described as the standard regression-based approaches in the area of correlated data.¹⁸⁷ However, there are differences in the interpretation of parameters estimated by generalized estimating equations and those estimated by a random effects model. The primary reason for selecting the former approach in Manuscript 1 was because of the marginal or population-average interpretation of the parameters. In contrast, random effects models have a conditional or subject-specific interpretation.^{186,187} Given that I was interested in the effect of an exposure (e.g., IDU) in a population where everyone was exposed, compared to a population where everyone was unexposed, I chose to use generalized estimating equations.

Generalized estimating equations allow for the unbiased estimation of marginal coefficients despite possible misspecification of the correlation structure.¹⁸⁷ Given the difficulty in specifying the correct correlation structure, generalized estimating equations allow for the specification of what is known as a “working” correlation structure. This involves pre-specifying a hypothesized correlation structure, such as the exchangeable structure used in Manuscript 1, while also estimating robust standard errors. When quantifying the estimates, the idea is to make a working assumption as to the correlation structure, while also adjusting the standard errors of

those estimates for the correlation observed in the data. In plain terms, pre-specifying a correlation structure gives the model a useful starting point. An alternative to this would be the strategy employed in the categorical outcome analyses, where a multinomial regression model was fit with robust standard errors. Given that the multinomial model was not fit using generalized estimating equations, an exchangeable working correlation structure was not pre-specified. The approach in the multinomial analysis is equivalent to assuming an independence working correlation structure, as opposed to a more informative structure.^{186,187} The propensity score-based methods in Manuscripts 2 and 3 also generated marginal estimates.^{189,190} For consistency throughout the thesis, I chose to use generalized estimating equations for the binary outcome analyses in Manuscript 1 as well.

Beyond the choice to use generalized estimating equations, I also acknowledge that logistic regression is frequently used in cohort studies to estimate ORs instead of RRs. However, when the prevalence of an outcome is common (>10%), it is known that estimated ORs are further from the null, or more exaggerated, than a hypothetical RR estimate.¹⁹¹ Given the high prevalence of FI in the FS Study, I chose to quantify associations between IDU, IDU frequency, and FI using RRs estimated by Poisson regression. Interestingly, while Poisson models are typically used to model count data, it has been shown that a “modified” Poisson model,^{184,185} which is effectively a standard Poisson regression with robust standard errors, is an alternative to a log-linear regression model for binary outcomes; log-linear models directly estimate RRs. While Manuscript 2 involved the use of log-linear models to quantify several associations using RRs, these models are known to experience convergence issues.¹⁹² In practice, this typically occurs when including several variables, such as confounders, in a multivariable model. As noted, I adjusted for confounders in Manuscript 2 using weighting. A fortunate by-product of the

weighting approach to adjustment, as opposed to direct adjustment, is that confounding variables are not included in the final outcome model.¹⁸⁹ Therefore, in Manuscript 2, there were no convergence issues with the log-linear models. However, in Manuscript 1, log-linear model convergence was not achieved in the binary outcome analyses which relied on direct adjustment¹⁹²; this is the reason for selecting the modified Poisson regression approach.^{184,185}

For the categorical outcome analyses of FI severity, RRRs were estimated using multinomial regression models with robust standard errors. The IDU and IDU frequency exposure variables were examined in separate models. As described in Manuscript 2, an alternative to the multinomial model is the proportional odds model.¹⁹³ This model requires that the coefficients for all covariates in the adjusted model are equal across all cut-offs of the categorical outcome variable (i.e., FI severity); I found evidence of violations of this assumption (see Section 4.3). While a multinomial regression model is less parsimonious and does not fully exploit the ordinal nature of the outcome, I chose this model as it does not require this assumption.¹⁸⁷ Also, given that the multinomial models were estimated with robust standard errors, which is equivalent to an independence working correlation structure (as opposed to an exchangeable working correlation structure when estimating parameters using generalized estimating equations), there was a loss of efficiency. Unlike the Poisson models that used generalized estimating equations for RR estimation, software packages to fit multinomial models using generalized estimating equations are not widely available.

3.9 Manuscript 2: Mediation analysis

3.9.1 Analytical sample

Prior to MI, the total sample in Manuscript 2 was identical to that of Manuscript 1 (see Section 3.8.1). Briefly, the two sixth visits were dropped as they caused non-convergence of the

imputation models, resulting in a total of 2113 observations (see Table 3.1). However, unlike Manuscript 1, 59 of the 725 participants from the FS Study who reported being a student or retired were excluded from the mediation analysis ($N = 666$). Furthermore, this manuscript only used data from visits one, two, and three. Given that some of the 59 excluded participants had multiple visits, the total number of second and third visits dropped to 555 (from 608) and 429 (from 475), respectively.

3.9.2 Data analysis

In this section, I will describe the rationale for the chosen methodology and mention alternative approaches that are frequently used to address similar research objectives. The practice of mediation analysis has been influenced, in large part, by the work of Baron and Kenny (1986).¹⁹⁴ The earliest approaches to mediation analysis, in the regression context, are often referred to as the “Baron and Kenny approach” or more generally as the “product of coefficients method.”¹⁹⁵ This approach involves the estimation of two models. For simplicity, I will omit the mention of additional variables, such as confounders, but the same general approach can be applied with additional covariates. First, the exposure is regressed on the mediator. Second, the exposure and the mediator are regressed on the outcome. Using this approach, the direct effect is the coefficient for the exposure in the outcome model that includes the mediator as a covariate. The direct effect represents the association between the exposure and the outcome at a fixed level of the mediator. This differs from the total effect which represents the overall association between the exposure and the outcome. The indirect effect is the coefficient of the exposure, in the mediator model, multiplied by the coefficient of the mediator in the outcome model. The indirect effect represents the amount of the association between the exposure and outcome that in fact operates through the mediator.^{194,196}

While the Baron and Kenny approach is widely used in the social sciences literature,¹⁹⁷ the main criticism of this approach relates to the inadequate articulation of the confounding assumptions required to estimate these mediation effects. This approach also has limitations with respect to analyzing interactions between variables.¹⁹⁵ As described in Manuscript 2, time-varying confounders may be affected by prior exposure in a mediation analysis.^{195,198,199} Such complexities cannot be addressed using standard regression approaches, including those initially proposed by Baron and Kenny. For these reasons, a new family of mediation approaches, sometimes referred to as “counterfactual approaches,” were developed. These approaches further describe the confounding assumptions and elaborate on the definitions of direct and indirect effects.¹⁹⁸ It is common to see these mediation approaches referred to as “causal mediation analyses,” as they are most often described in the causal inference literature.¹⁹⁶ However, while the literature that describes these approaches often uses the term “causal,” I have chosen not to refer to any of my estimates as causal effects in this thesis. As an aside, I have also elected to use the terminology of “association” versus “effect,” when possible, as I believe that the latter may incorrectly imply a “cause and effect” relationship. The reasons for describing my estimates as non-causal associations are highlighted in the limitations sections of all manuscripts.

Developments in mediation methodologies are abundant in the causal inference literature.¹⁹⁶ Herein, I will exclusively focus my attention on two estimates of interest that relate to the objectives of Manuscript 2. I estimated the overall association between IDU and severe FI (through all potential pathways) and the controlled direct effect (CDE) of IDU on severe FI. The overall association is equivalent to the total effect. Furthermore, the CDE expresses how much the outcome would change, on average, if everyone was changed from unexposed to exposed and the mediator were set to a fixed level in the population.^{195,198,199} I omit the discussion of natural

effects, such as the natural direct effect and the natural indirect effect,²⁰⁰ as I do not estimate these descriptive quantities. A controlled effect, on the other hand, is prescriptive in that it characterizes what would happen if one could modify an exposure to match a policy objective (e.g., eliminate IDU in a given population).¹⁹⁸ Moreover, given that the time-varying mediator-outcome confounders may be affected by prior exposure in Manuscript 2 (see Figure 5.1), it was inappropriate to directly adjust for time-varying mediator-outcome confounders in the outcome model estimating the CDE.^{195,198,199} Therefore, a weighting approach with marginal structural log-linear models was used to estimate the overall association as well as the CDE of the exposure (IDU) on the outcome (severe FI). Specifically, weighting was used to adjust for confounding and to address selection bias due to informative censoring (formal withdrawals, deaths, losses to follow-up, and administrative censoring).¹⁸⁹ Further details on the mediation methodologies employed in this work are summarized in the appendix of Manuscript 2 (Section 5.3).

In summary, I have elected to use mediation approaches that are typically described in the causal inference literature.¹⁹⁵ While these methods can provide equivalent estimates to the earlier approaches by Baron and Kenny¹⁹⁴ in some settings, particularly in the absence of interaction, the chosen approaches explicitly define the confounding assumptions that are required for this type of work. After examining these assumptions, it becomes apparent that time-varying confounding affected by prior exposure may be present (see Figure 5.1 in Manuscript 2). In such a scenario, alternative strategies¹⁸⁹ to the Baron and Kenny approach were implemented, specifically, weighting in a marginal structural model.

3.10 Manuscript 3: Propensity score matching analysis

3.10.1 Analytical sample

Prior to MI, the total sample in Manuscript 3 was identical to that of Manuscript 1. Briefly, the two sixth visits were dropped as they caused non-convergence of the imputation models, resulting in a total of 2113 observations (see Table 3.1). As described in Manuscript 1, of the 725 participants from the FS Study, 608 participants completed two or more visits. Following variable lagging, which requires a minimum of two visits, 117 participants who had a single visit were dropped from the sample. Among the 608 included participants, 475, 268, and 37 participants completed a second, third, and fourth visit, respectively, for a total of 1,388 observations that were included in the analytical sample.

3.10.2 Data analysis

To quantify the association between methadone treatment and severe FI using observational data, I used propensity score matching (PSM).²⁰¹ Unlike standard or exact matching, which is often only feasible with a small number of binary or categorical covariates,¹⁹⁰ PSM matches on a single continuous covariate: the estimated treatment probability or propensity score. In this section, I will describe the rationale for the chosen methodology and overview alternative approaches.

PSM is often described alongside other treatment effects estimators in the causal inference literature, such as propensity score regression, propensity score stratification (within quintiles), and inverse probability weighting.^{202,203} Regardless of the estimator, treatment effects can be formalized using a potential outcomes or counterfactual framework.²⁰² For example, consider a participant that did not receive a given treatment. In such a scenario, we observe the potential outcome given no treatment (Y_0). The potential outcome for that same participant, if

they had received the treatment, would be the counterfactual outcome for that participant (Y_1). In contrast, for treated participants, we only observe the outcome under treatment (Y_1). The outcome under no treatment (Y_0) is the counterfactual outcome for participants that in fact received treatment. For any given participant, we only observe the potential outcome given the treatment that was in fact received; the counterfactual outcome under the alternative treatment is missing. The fact that the counterfactual outcomes are missing is sometimes referred to as the “fundamental problem of causal inference.”¹⁸⁷ Under certain assumptions, treatment effect estimators, including PSM, overcome the issue that we only observe Y_1 or Y_0 for a given participant.

Treatment effect estimators allow for the estimation of various parameters. The potential outcome means are the means of Y_1 and Y_0 in the population. The average treatment effect (ATE) is the mean of the difference ($Y_1 - Y_0$) and the average treatment effect on the treated (ATT) is the mean of the difference ($Y_1 - Y_0$) among the participants that in fact received the treatment²⁰⁴; the ATT is the estimate of interest in Manuscript 3. These estimates correspond to marginal associations (marginal risk differences). The ATT is not easily quantifiable in propensity score regression or propensity score stratification, but it is intuitively quantified using PSM and weighting.²⁰²⁻²⁰⁴ As demonstrated, all approaches rely on the estimation of a quantity known as the propensity score.

The propensity score is the estimated probability of receiving a given exposure or treatment. The propensity score is a balancing score in so much that individuals with similar propensity scores will have similar patterns of confounding variables.²⁰³ This suggests that an estimate which accounts for the propensity score will also adjust for measured confounders; propensity scores are used to balance confounders between the treated (exposed) and untreated

(unexposed) groups. The probability of receiving a treatment can be estimated using any appropriate regression model. In the case of a binary treatment (e.g., no treatment vs. methadone treatment in Manuscript 3), logistic regression is often used to estimate the propensity scores.²⁰⁵ The goal of the logistic propensity score model is to estimate the influence of the confounders on the probability of receiving the treatment for each individual. The treatment probability predicted by this model, which includes all relevant confounders as independent variables, is the propensity score. Independent variables that predict treatment but not the outcome, known as instrumental variables, should not be included in the propensity score model.²⁰⁶ Indeed, propensity scores were also estimated prior to generating the weights for confounding and censoring in Manuscript 2.

Regarding the parameters that can be estimated using propensity score methods, the ATT is relevant to the research objective of Manuscript 3. The ATT reflects the association between a treatment and outcome in a population with the same distribution of propensity scores as the treated individuals.²⁰⁴ The rationale for estimating an ATT is demonstrated using the example of a smoking cessation treatment. Estimating an ATT for the association between a smoking cessation treatment and an outcome (e.g., lung cancer) would require comparable untreated individuals as the control group. Intuitively, comparable untreated individuals would not include those who have never smoked or those who have never had any desire to smoke. These individuals would differ substantially from those receiving the smoking cessation treatment, particularly with respect to their smoking frequency and duration. In this case, factors related to smoking behaviour would be strong confounders of a hypothetical smoking cessation treatment-lung cancer relationship, as such factors would be strongly related to both receipt of the cessation treatment and lung cancer. In an unadjusted setting, it is plausible that those enrolled in a

smoking cessation treatment would appear to have a higher risk of lung cancer than those who are not receiving the treatment. This issue is exacerbated when the treated participants are being compared to participants who have never smoked. In other words, it is often the case that those who require a treatment or intervention, of any kind, are often those who need it most.

The importance of estimating an ATT is apparent in Manuscript 3 when acknowledging that methadone is only indicated for the treatment of opioid dependence.⁴⁵ Participants who have never used opioids, or those who have not recently used them, would have a low or potentially zero estimated probability of receiving the treatment. In this case, estimation of an ATT using PSM is important as one would not want to include individuals who do not have any indications for methadone treatment in the comparison group. Analytically, an ATT is estimated using PSM by finding matches for the treated participants only.²⁰¹ Finding matches for the untreated participants with a low or zero probability of receiving treatment is not required as we are not interested in the effect of the treatment among individuals who do not need the treatment. As such, the matched sample in Manuscript 3 includes an untreated population with a similar distribution of propensity scores as those receiving treatment; this is a key motivation for using PSM.

Notably, an ATT can also be estimated using weighting.²⁰⁴ However, given the intuition of matching, I believe that PSM may be more familiar to a general research audience.²⁰⁷ Anecdotally, it is my experience that PSM is more common than weighting in the clinical HIV literature. In this thesis, I selected PSM, in part, because I hope that this research will be disseminated to a broad clinical audience. PSM also allows for the calculation of standardized mean differences (SMDs) to assess covariate or confounder balance.²⁰⁸ To the best of my knowledge, it is not clear how one can calculate SMDs using standard regression approaches or

propensity score regression. SMDs are available, however, when stratifying on the propensity score or using weighting.

In terms of alternatives to propensity score-based matching approaches, nearest-neighbor matching determines the most similar match by using a weighted function of the covariates for each observation; often the Mahalanobis distance is used.¹⁹⁰ In this approach, the weights are based on the inverse of the covariates' variance-covariance matrix. Nearest-neighbor matching does not use a formal model for either the treatment or outcome process. However, this flexibility comes at a cost. When matching on more than one continuous covariate, the estimator must be augmented with a bias-correction term²⁰⁹; this augmentation is not necessary in PSM.

Chapter 4: Longitudinal cohort analysis of associations (Manuscript 1)

4.1 Preface to Manuscript 1

While there is an existing evidence-base related to FI among individuals living with HIV,²⁶⁻²⁸ these studies, excluding our own publications,^{33,48,97} do not focus on individuals living with HIV-HCV co-infection. Given the differences between those living with HIV mono-infection and HIV-HCV co-infection¹⁴⁻¹⁶ and the context-specific nature of FI risk factors,^{25,26} the generalizability of findings from HIV-related studies that do not consider HCV co-infection is unclear. To date, IDU, a highly prevalent behaviour among co-infected individuals,¹³ has only been examined as a risk factor for FI in two Canadian studies; one study was cross-sectional³⁷ and the other was a hypothesis-generating analysis completed by our research group (see Section 2.7).⁴⁸ As such, evidence related to IDU as a prevalent and modifiable risk factor for FI in this vulnerable subset of the HIV-positive population is limited.

Manuscript 1 was the first study to consider temporal-ordering of IDU and FI while exploring a dose-response relationship between IDU frequency and FI among individuals living with HIV-HCV co-infection. I also examined the impact of IDU on FI severity. This allowed me to determine which aspects of the FI experience were being driven by IDU, ranging from worrying about running out of food (marginal FI) to indications of disrupted eating patterns and the physical sensation of hunger (severe FI).²² Given the small evidence-base related to IDU and FI, Manuscript 1 was a fundamental step to subsequently examining mechanisms (Manuscript 2) and interventions (Manuscript 3) related to IDU and FI in the HIV-HCV co-infection context.

4.2 Manuscript 1: Injection drug use, food insecurity, and HIV-HCV co-infection: a longitudinal cohort analysis

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This manuscript was submitted for publication in July 2017.

Keywords: HIV; hepatitis C virus; injection drug use; food insecurity

Abstract: Injection drug use (IDU) and food insecurity (FI) are highly prevalent among individuals living with HIV-hepatitis C virus (HCV) co-infection. We quantified the association between IDU and FI among co-infected individuals in Canada. We used biannual data from the Canadian Co-infection Cohort (N = 608, 2012-2015). IDU (in the past six months) and IDU frequency (non-weekly/weekly in the past month) were self-reported. FI (in the past six months) and FI severity (marginal, moderate, severe) were measured using the Household Food Security Survey Module. Generalized estimating equations were used to estimate risk ratios (RR) quantifying the associations between IDU, IDU frequency, and FI using Poisson regression. The associations between IDU, IDU frequency, and FI severity were quantified by relative-risk ratios (RRR) estimated using multinomial regression. At the first time-point in the analytical sample, 54% of participants experienced FI in the past six months, 31% engaged in IDU in the past six months, and 24% injected drugs in the past month. After adjustment for confounding, IDU in the past six months (RR = 1.15, 95% CI = 1.04-1.28) as well as non-weekly (RR = 1.15, 95% CI = 1.02-1.29) and weekly IDU (RR = 1.21, 95% CI = 1.07-1.37) in the past month were associated with FI. The strongest association was between weekly IDU in the past month and severe FI (RRR = 2.68, 95% CI = 1.47-4.91). Our findings indicate that there is an association between IDU and FI, particularly weekly IDU and severe FI. This suggests that reductions in IDU may mitigate FI, especially severe FI, in this vulnerable subset of the HIV-positive population.

Introduction:

Food insecurity (FI) is highly prevalent in HIV-positive and HIV-hepatitis C virus (HCV) co-infected populations.^{28,48} By definition, FI exists “whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain.”¹⁸ In Canada, FI is usually measured using the Household Food Security Survey Module (HFSSM),¹⁹ which focuses on self-reports of uncertain or inadequate food access due to limited financial resources. FI is frequently categorized into three levels of severity based on responses to the HFSSM: marginal, moderate, and severe FI.^{19,22} Marginal and moderate FI are indicative of worrying about running out of food or compromises in the quality and/or quantity of food consumed, whereas severe FI indicates disrupted eating patterns and reduced food intake.²²

In HIV-positive populations, 20% of individuals are estimated to be living with HIV-HCV co-infection.^{6,7} In the Canadian Co-infection Cohort, a cohort of co-infected individuals who contributed the data for this study, over 80% of participants reported a history of injection drug use (IDU); IDU is the primary risk factor for HCV co-infection.⁷ In HIV-related studies, researchers have documented associations between illicit drug use,^{38,40,41} including IDU,³⁷ and FI. In our previous exploratory study of 525 HIV-HCV co-infected individuals (2012-2014), IDU in the past six months was also identified as a potential correlate of FI.⁴⁸

Given that FI is associated with sub-optimal HIV treatment adherence,³⁵ incomplete HIV viral load suppression,^{33,34} and lower CD4 cell counts,^{32,33} there is an interest in examining IDU as a potentially modifiable risk factor for FI.^{27,42} To expand upon previous exploratory work,⁴⁸ we analyzed longitudinal cohort data (2012-2015) to further examine the relationship between IDU and FI. Specifically, we temporally-ordered our data, explored a dose-response relationship

between IDU frequency and FI, and examined the impact of IDU on FI severity among individuals living with HIV-HCV co-infection in Canada.

Methods:

Study population

The Canadian Co-infection Cohort (CCC) is a prospective study of HIV-HCV co-infected individuals who receive care from HIV clinics across Canada. Details of the CCC have been described elsewhere.¹⁷² CCC participants must be at least 16 years of age with documented HIV infection and serologic evidence of HCV exposure. All eligible individuals were invited to participate and data collection occurred approximately every six months.

From November 2012 to October 2015, the Food Security and HIV-HCV Study (FS Study)⁴⁸ was implemented and biannual data collection related to FI was integrated into CCC study visits at 17 clinics in six provinces. The CCC and the FS Study were approved by the McGill University Health Centre and the research ethics boards of the participating institutions.¹⁷²

Measures

Injection drug use (exposure)

Any IDU in the past six months was self-reported by participants on a questionnaire at each visit. IDU frequency in the past month was also self-reported at each visit and this permitted the exploration of a dose-response relationship. IDU was coded as a binary exposure variable (none vs. any IDU: Models 1a/2a) and IDU frequency (none vs. non-weekly, weekly IDU: Models 1b/2b) was coded as a categorical exposure variable in a separate set of regression models.

Food insecurity (outcome)

FI in the past six months was measured by questionnaire using the ten-item adult scale of the HFSSM¹⁹ at each visit. Health Canada categorizes FI according to the number of affirmative responses on the HFSSM (see Supplementary Table 4.1). Participants indicating 0 affirmative responses were identified as being food secure (no report of problems of food access). Given that researchers have begun to stress the importance of an additional category of FI severity, known as marginal FI,⁹² participants indicating 1 affirmative response were identified as experiencing marginal FI (some indication of worry related to adequate food access). Moderate FI (compromises in the quality and/or quantity of food consumed) was defined by participants indicating 2-5 affirmative responses and severe FI (indicating disrupted eating patterns and reduced food intake) was defined by ≥ 6 affirmative responses on the HFSSM.²²

FI and FI severity were considered in separate models. First, participants reporting 1 or more affirmative response(s) were identified as experiencing any FI in the six months preceding each visit, yielding a binary outcome variable (food secure vs. any FI: Models 1a/1b). Second, to examine the impact of IDU on FI severity, marginal, moderate, and severe FI were treated as separate outcome categories, with food secure as the referent category (Models 2a/2b).

Confounding factors

All confounders were selected on substantive grounds *a priori* based on their hypothesized association with IDU and FI.^{28,42,48} Given the nature of the FI construct, we also selected factors, such as province of enrolment, which may act as proxies for unmeasured confounders. All confounders were self-reported by participants on biannual questionnaires. Given that the FI measure referred to experiences in the past six months, temporal-ordering of the exposure (IDU), confounders, and outcome (FI) was established. At each visit, the exposure

and confounders were lagged by one visit to reflect experiences prior to the FI experience, as opposed to experiences at the end of the FI period for “current” measures or experiences overlapping with the FI period for “in the past six months” or “in the past month” measures.

Socioeconomic confounders included: employment (unemployed vs. employed [part-time or full-time work]), average monthly income (before taxes; Canadian dollars [CAD]), and college or university education at enrolment (no vs. yes). Sociodemographic confounders included: province of enrolment (Quebec vs. British Columbia, Ontario, other [Alberta, Saskatchewan, Nova Scotia]), age, sex (male vs. female), ethnicity (white vs. Aboriginal [First Nations, Inuit, Métis], other [Asian, Black, Hispanic, Latino]), housing situation (homeowner, apartment/room renter, care facility vs. no fixed address or temporary situation), and living situation (alone vs. with others [no children], with children). Behavioural confounders included: non-injection drug use (none vs. use of drugs for non-medical purposes via sniffing, smoking, eating, drinking, or transdermally), cigarette use (no vs. yes), and alcohol use (no vs. yes). Clinical confounders included: self-reported anxiety or depression (no vs. yes) and self-perceived health state (visual analogue scale, 0 = worst imaginable health state to 100 = best imaginable health state) as per the EuroQol-5D instrument.²¹⁰

Data analysis

Our analyses used temporally-ordered outcome (FI) data from visits 2-3-4-5 and lagged exposure (IDU) and confounder data from visits 1-2-3-4. Summary statistics of the total sample and the FI severity-stratified prevalences were used to describe the participants at the first time-point in the analytical sample. Multiple imputation by chained equations was used to impute missing observations using 30 imputed datasets and 50 iterations. To ensure uniform timing of the lagged variables and FI, multiple imputation was also used to impute time-varying variables

at missed study visits (i.e., visits that did not occur approximately every six months). To distinguish a missed visit from censoring, a missed visit must have occurred prior to a study visit later in time.

For the binary outcome analyses (food secure vs. any FI), generalized estimating equations with an exchangeable working correlation structure were used to estimate unadjusted (see Supplementary Table 4.2) and adjusted risk ratios (RR) from Poisson regression models with robust standard errors.^{184,185} IDU (in the past six months: Model 1a) and IDU frequency (in the past month: Model 1b) were examined as the exposure variables in separate models.

For the categorical outcome analyses of FI severity, unadjusted (see Supplementary Table 4.2) and adjusted relative-risk ratios (RRR) were estimated using multinomial regression models with robust standard errors. As with the binary outcome analyses, the IDU (in the past six months: Model 2a) and IDU frequency (in the past month: Model 2b) exposure variables were examined in separate models. All models were fit to each of the 30 imputed datasets where the estimates were combined using Rubin's method.¹⁸¹ Continuous confounders were rescaled and centered at the mean. Data analyses were performed using Stata 14 (College Station, TX: StataCorp LP. 2015).

Results:

Between November 2012 and October 2015, 725 of 734 invited CCC participants enrolled in the FS Study. Of the 725 participants, 608 participants completed two or more visits. Following variable lagging, which requires a minimum of two visits, 117 participants who had a single visit were dropped from the sample. Among the 608 included participants, 475, 268, and 37 participants completed a second, third, and fourth visit, respectively, for a total of 1,388 observations during the FS Study's duration of approximately three years. During follow-up, 4

participants formally withdrew from the study, 14 died, and 3 were lost to follow-up after missing three consecutive visits. Prior to variable lagging, there were 86 missed second visits, 53 missed third visits, and 11 missed fourth visits.

As shown in Table 4.1, 54% of participants experienced FI in the six months preceding the first time-point in the analytical sample. Among the 330 participants experiencing FI, the majority experienced severe FI (47%). Regarding the exposures, 31% of participants engaged in IDU in the six months preceding the first time-point in the analytical sample, where 24% of participants injected drugs in the past month (12% injected non-weekly and 12% injected weekly).

IDU in the past six months and weekly IDU in the past month were more prevalent as FI severity increased. Similarly, several confounders typically associated with an increase in the likelihood of FI were more common as FI severity increased (e.g., no fixed address or temporary housing, non-injection drug use, and cigarette use). Conversely, known socioeconomic confounders typically associated with a decrease in the likelihood of FI were less common or had a smaller median value as FI severity increased (e.g., employment and average monthly income).

Table 4.2 displays the results of the binary outcome analyses. After adjustment for socioeconomic, sociodemographic, behavioural, and clinical confounders, both IDU (in the past six months: Model 1a) and frequency of IDU (non-weekly/weekly IDU in the past month: Model 1b) were associated with an increase in the likelihood of FI in the subsequent six months. Comparing these estimates, the association between IDU in the past six months and FI (RR = 1.15, 95% CI = 1.04-1.28) did not differ from non-weekly IDU in the past month (RR = 1.15, 95% CI = 1.02-1.29). Additionally, while weekly IDU in the past month had a slightly stronger

association with FI (RR = 1.21, 95% CI = 1.07-1.37), it was not markedly different than the non-weekly IDU estimate, providing little evidence of a dose-response relationship with binary FI.

Table 4.3 displays the results of the categorical outcome analyses. After adjustment for socioeconomic, sociodemographic, behavioural, and clinical confounders, IDU (in the past six months: Model 2a) as well as non-weekly and weekly IDU (in the past month: Model 2b) were most strongly associated with an increase in the likelihood of severe FI. The strongest association was observed between weekly IDU and severe FI (RRR = 2.68, 95% CI = 1.47-4.91). Furthermore, while the multinomial regression models provide additional detail in understanding the IDU-FI severity relationship, the magnitudes of the RRRs from Table 4.3 are not directly comparable to the RRs from Table 4.2 (see the Supplementary Material in Section 4.3).¹⁹¹

Discussion:

IDU and FI are common in this HIV-HCV co-infected population. Research which examines the relationship between IDU, a potentially modifiable behaviour, and FI can be used to inform interventions that may reduce FI.^{27,42} In addition to ensuring the temporal-ordering of exposures and outcomes, our work strengthens the evidence-base by exploring a dose-response relationship between IDU frequency and FI and by examining the impact of IDU on FI severity.

Consistent with prior work in HIV-positive populations³⁷ and in our previous exploratory analysis of FS Study data (2012-2014),⁴⁸ we found evidence of an association between IDU and FI. While there was little evidence of a dose-response relationship between IDU frequency, as defined by non-weekly or weekly IDU in the past month, and binary FI, all measures of IDU were most strongly associated with severe FI. Notably, the strongest association was between weekly IDU and severe FI. These associations were documented after variable lagging and

adjustment for a variety of socioeconomic, sociodemographic, behavioural, and clinical confounders of the IDU-FI relationship.

The importance of temporal-ordering^{139,140} is emphasized when considering findings from a recent cross-sectional analysis which indicated that FI was associated with a higher odds of illicit drug use.²¹¹ While the authors acknowledged an inability to establish temporality, other conceptual frameworks have also described the illicit drug use-FI relationship as being bi-directional.⁴² When devising interventions, the goal is often to intervene upon an antecedent exposure (in this case, IDU) to reduce a consequential outcome (in this case, FI). When generating evidence to make such an argument, it was important for us to quantify associations that were representing a prospective temporal sequence.^{139,140}

Of equal importance is the consideration of confounding bias in our observational study. In the case of an unadjusted estimate quantifying the association between IDU and FI, it is unclear as to whether it is the characteristics of those who engage in IDU that are increasing an individual's likelihood of experiencing FI, or whether it is the IDU behaviour itself. IDU is concomitant with socioeconomic and sociodemographic disadvantage,⁴² and factors such as employment, income, and education, while strong determinants of FI,^{21,22} may be difficult to modify.^{43,44} In order to determine whether it may be useful to conceptualize interventions on IDU,²⁷ it was imperative to quantify the association between IDU and FI when adjusting for such factors. After doing so, our estimates suggest that these socioeconomic and sociodemographic determinants may not be the only targets for intervention to reduce FI in this population.

We explored a dose-response relationship between IDU frequency and FI and examined the impact of IDU on FI severity. First, the association between IDU in the past six months and FI did not differ markedly from that of non-weekly or weekly IDU in the past month; the

reference period of the exposure measure (in the past six months vs. in the past month) did not appear to impact IDUs association with FI. Furthermore, weekly IDU in the past month only had a slightly stronger association with FI compared to non-weekly IDU, providing little evidence of a dose-response relationship with binary FI. This suggests that it may be equally as beneficial to target interventions on all co-infected individuals engaged in recent IDU, regardless of whether it is individuals engaged in any IDU in the past six months or non-weekly/weekly IDU in the past month. When considering FI severity (Table 4.3), all measures of IDU were most strongly associated with severe FI, particularly weekly IDU. While further research is necessary to evaluate interventions on IDU, our works suggests that reductions in IDU, particularly weekly IDU, may decrease the likelihood of the most severe form of FI; severe FI is characterized by reduced food intake and the physical sensation of hunger.^{21,22}

Regarding potential interventions, it is known that HIV-HCV co-infected individuals may interact regularly with health care and social services programs.^{7,172} While policy-level interventions are often recommended to address FI in the general Canadian population,^{43,44} drug use-related programming may be able to help reduce the likelihood of FI in this population. Specifically, our work suggests that substance use interventions aimed at IDU⁴² may reduce the risk of co-infected individuals experiencing FI, particularly severe FI. However, further research is needed to evaluate such interventions and their impact on FI.

Strengths and limitations

To our knowledge, our study is the first to consider temporal-ordering when quantifying the association between IDU and FI among individuals living with HIV-HCV co-infection. Furthermore, by examining IDU frequency and FI severity, our analyses also allowed for a more

detailed understanding of this relationship. However, our observational study design and analytical approaches had limitations.

First, because we analyzed observational data, it is possible that there were unmeasured or imperfectly measured confounders. However, given the richness of the FS Study data, particularly with respect to socioeconomic and sociodemographic factors, we are confident in our approaches to minimize confounding bias. Also, while self-reported data can result in misclassification of our exposure or outcome, a previous review has concluded that self-reports of individuals who use drugs are sufficiently reliable to provide descriptions of drug use²¹²; the HFSSM is a validated FI measurement tool as well.^{18,19} The trend in the increasing magnitudes of the associations between IDU frequency and FI severity also suggests that these measures are not greatly affected by misclassification.

Second, while we chose to use a multinomial regression model to analyze the ordinal outcome of FI severity, another intuitive choice is the proportional odds model. This model requires that the coefficients for all covariates in the adjusted model are equal across all cut-offs of FI severity¹⁹³; we found evidence of violations of this assumption (see the Supplementary Material in Section 4.3). While a multinomial regression model is less parsimonious and does not fully exploit the ordinal nature of the outcome, we chose this model as it does not require this assumption.¹⁸⁷ Also, given that the multinomial regression models were estimated with robust standard errors, which is equivalent to an independence working correlation structure, as opposed to an exchangeable working correlation structure, there was a loss of efficiency.

Third, there was a trade-off to ensuring uniform temporal-ordering by having to address larger amounts of missing data. Given that there was biannual data collection, it was imperative to ensure that participants' data were collected approximately every six months. In a multi-site

cohort study, missed visits are inevitable. For example, prior to variable lagging, there were 86 missed second visits. For these 86 participants with a missed second visit, which is now represented at the first time-point in the analytical sample for the outcome (see Table 4.1), FI data were not available and had to be imputed.

Conclusions:

Our findings indicate that there is an association between IDU and FI, particularly weekly IDU and severe FI, independent of socioeconomic, sociodemographic, behavioural, and clinical confounders, in this HIV-HCV co-infected population. While further research is necessary to evaluate interventions on IDU, the estimated associations between IDU, IDU frequency, FI, and FI severity suggest that reductions in IDU may mitigate FI, especially severe FI, in this vulnerable subset of the HIV-positive population.

Acknowledgements:

TM is supported by a CANOC Centre Doctoral Scholarship Award, a joint program of CANOC and the CIHR Canadian HIV Trials Network (CTN 242). EEMM is supported by a Chercheur-Boursier (Junior 2) Career Award from the Fonds de recherche du Quebec-Sante (FRQ-S). MBK is supported by a Chercheurs Nationaux Career Award from the FRQ-S.

The authors thank Jennifer Kocilowicz and Leo Wong for study coordination. The Canadian Co-infection Cohort investigators (CTN 222) are: Drs. Jeff Cohen (Windsor Regional Hospital Metropolitan Campus, Windsor, ON), Brian Conway (PENDER Downtown Infectious Diseases Clinic, Vancouver, BC), Curtis Cooper (The Ottawa Hospital Research Institute, Ottawa, ON), Pierre Côté (Clinique du Quartier Latin, Montreal, QC), Joseph Cox (McGill University Health Centre, Montreal, QC), John Gill (Southern Alberta HIV Clinic, Calgary, AB), Shariq Haider (McMaster University Medical Centre – SIS Clinic, Hamilton, ON), Aida Sadr (Native BC Health Center, St Paul's Hospital, Vancouver, BC), Lynn Johnston (QEII Health Science Center for Clinical Research, Halifax, NS), Mark Hull (BC Centre for Excellence in HIV/AIDS, Vancouver, BC), Julio Montaner (St Paul's Hospital, Vancouver, BC), Erica Moodie (McGill University, Montreal, QC), Neora Pick (Oak Tree Clinic, Children's and Women's Health Centre of British Columbia, University of British Columbia, Vancouver, BC), Anita Rachlis (Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON), Danielle Rouleau (Centre Hospitalier de l'Université de Montreal, Montreal, QC), Roger Sandre (Health Sciences North – The HAVEN/Hemophilia Program, Sudbury, ON), Joseph Mark Tyndall (Department of Medicine, Infectious Diseases Division, University of Ottawa, Ottawa ON), Marie-Louise Vachon (Centre Hospitalier Universitaire de Québec, Québec, QC), Steve Sanche (SHARE University of Saskatchewan, Saskatoon, SK), Stewart Skinner (Royal University

Hospital & Westside Community Clinic, University of Saskatchewan, Saskatoon, SK), and David Wong (University Health Network, Toronto, ON).

Disclosure statement: JC has received grants for investigator-initiated clinical projects and consulting fees from Gilead, ViiV Healthcare, and Merck. MBK has received grants for investigator-initiated trials from ViiV Healthcare and Merck, as well as consulting fees from Gilead, ViiV Healthcare, Merck, Bristol-Meyers Squibb, and AbbVie. The remaining authors declare that they have no conflicts of interest.

Funding: This study was funded by the Canadian Institutes of Health Research (CIHR, MOP-79529) and the CIHR Canadian HIV Trials Network (CTN 264 & CTN 222).

Table 4.1 Descriptive characteristics of 608 HIV-HCV co-infected individuals at the first time-point in the analytical sample, stratified by food insecurity severity (2012-2015).

Variables	Total N = 608	Food secure N = 192 (32%)	Food insecure ^{a,b} N = 330 (54%)			Missing ^c N = 86 (14%)
			Marginal N = 59 (18%)	Moderate N = 116 (35%)	Severe N = 155 (47%)	
Exposures	Values are the number of participants (%) ^d or median (Q1, Q3)					
Injection drug use (IDU) ^b	187 (31%)	38 (20%)	19 (32%)	41 (35%)	63 (41%)	26 (30%)
Missing ^c	31 of 608	7 of 192	4 of 59	10 of 116	6 of 155	4 of 86
Frequency of IDU (in the past month)	-	-	-	-	-	-
Non-weekly	70 (12%)	10 (5%)	9 (15%)	19 (16%)	23 (15%)	9 (10%)
Weekly	75 (12%)	13 (7%)	7 (12%)	16 (14%)	30 (19%)	9 (10%)
Missing	68 of 608	21 of 192	12 of 59	16 of 116	10 of 155	9 of 86
Socioeconomic confounders						
Employed ^e	115 (19%)	59 (31%)	10 (17%)	17 (15%)	14 (9%)	15 (17%)
Missing	45 of 608	11 of 192	4 of 59	14 of 116	9 of 155	7 of 86
Average monthly income (\$CAD) ^b	1077 (918, 1500)	1200 (927, 2500)	1100 (918, 1400)	1020 (918, 1300)	1001 (900, 1143)	1080 (918, 1450)
Missing	9 of 608	3 of 192	1 of 59	3 of 116	2 of 155	0 of 86
College or university education at enrolment	156 (26%)	71 (37%)	7 (12%)	28 (24%)	28 (18%)	22 (26%)
Missing	9 of 608	1 of 192	2 of 59	0 of 116	5 of 155	1 of 86
Sociodemographic confounders						
Province of enrolment	-	-	-	-	-	-
Quebec	258 (42%)	92 (48%)	24 (41%)	48 (41%)	60 (39%)	34 (40%)
British Columbia	192 (32%)	40 (21%)	13 (22%)	37 (32%)	68 (44%)	34 (40%)
Ontario	112 (18%)	40 (21%)	14 (24%)	23 (20%)	20 (13%)	15 (17%)
Other (AB, SK, NS) ^f	46 (8%)	20 (10%)	8 (14%)	8 (7%)	7 (5%)	3 (3%)
Age (years) ^e	48.8 (43.4, 54.0)	50.0 (43.2, 54.4)	48.5 (43.0, 54.3)	47.7 (42.9, 52.3)	48.5 (43.8, 53.1)	50.4 (45.0, 56.4)
Missing	2 of 608	0 of 192	0 of 59	0 of 116	2 of 155	0 of 86
Female	151 (25%)	45 (23%)	15 (25%)	33 (28%)	39 (25%)	19 (22%)
Missing	10 of 608	3 of 192	2 of 59	2 of 116	3 of 155	0 of 86
Ethnicity	-	-	-	-	-	-
White	455 (75%)	145 (76%)	42 (71%)	81 (70%)	115 (74%)	72 (84%)
Aboriginal	107 (18%)	31 (16%)	13 (22%)	25 (22%)	31 (20%)	7 (8%)
Asian, Black, Hispanic, Latino	37 (6%)	13 (7%)	4 (7%)	10 (9%)	5 (3%)	5 (6%)
Missing	9 of 608	3 of 192	0 of 59	0 of 116	4 of 155	2 of 86
No fixed address or temporary housing ^e	61 (10%)	12 (6%)	5 (8%)	12 (10%)	24 (15%)	8 (9%)
Living situation ^e	-	-	-	-	-	-
Alone	295 (49%)	73 (38%)	34 (58%)	70 (60%)	76 (49%)	42 (49%)
With others (no children)	266 (44%)	99 (52%)	22 (37%)	41 (35%)	64 (41%)	40 (47%)
With children	47 (8%)	20 (10%)	3 (5%)	5 (4%)	15 (10%)	4 (5%)
Behavioural confounders						
Non-injection drug use ^b	269 (44%)	65 (34%)	27 (46%)	55 (47%)	85 (55%)	37 (43%)
Missing	36 of 608	11 of 192	5 of 59	10 of 116	6 of 155	4 of 86
Cigarette use ^e	429 (71%)	125 (65%)	42 (71%)	83 (72%)	120 (77%)	59 (69%)
Missing	34 of 608	8 of 192	5 of 59	10 of 116	7 of 155	4 of 86

Alcohol use ^e	357 (59%)	107 (56%)	39 (66%)	72 (62%)	91 (59%)	48 (56%)
Missing	33 of 608	8 of 192	4 of 59	10 of 116	6 of 155	5 of 86
Clinical confounders						
Anxiety or depression ^{e,g}	282 (46%)	57 (30%)	29 (49%)	51 (44%)	101 (65%)	44 (51%)
Missing	34 of 608	7 of 192	4 of 59	11 of 116	7 of 155	5 of 86
Self-perceived health state (0-100), visual analogue scale ^{e,g}	70 (60, 80)	75 (68, 85)	70 (60, 80)	70 (60, 80)	65 (50, 75)	70 (55, 80)
Missing	35 of 608	8 of 192	4 of 59	11 of 116	6 of 155	6 of 86

^a Participants with 1, 2-5, and ≥ 6 affirmative responses on the Household Food Security Survey Module (HFSSM) were identified as experiencing marginal, moderate, or severe food insecurity, respectively.

^b Reference period: in the past six months.

^c Missing values at the first time-point in the analytical sample are due to item non-response for the exposures and confounders (as this information was taken from the first visit, which could not be missed) and missed second visits for the outcome (86 missed second visits prior to variable lagging).

^d Percentages are the number of participants divided by the number of participants listed at the top of each column (e.g., prevalence of IDU in total sample at the first time-point in the analytical sample: $187 / 608 = 31\%$). Percentages may not add to 100 due to missing data and/or rounding.

^e Reference period: currently.

^f The provinces of Alberta (AB, N = 11), Saskatchewan (SK, N = 34), and Nova Scotia (NS, N = 1) were grouped due to a small number of participants.

^g Measured as components of the EuroQol-5D instrument.²¹⁰

Table 4.2 Adjusted Poisson regression models estimated by generalized estimating equations quantifying the associations between injection drug use (Model 1a), injection drug use frequency (Model 1b), and food insecurity among 608 HIV-HCV co-infected individuals (2012-2015).

Variables	Model 1a ^a (IDU: past six months)	Model 1b ^a (Frequency of IDU: past month)
Adjusted risk ratio (RR) ^b and 95% confidence interval (CI)		
Exposures		
Injection drug use (IDU) (Model 1a) ^c	1.15 (1.04-1.28)	-
Frequency of IDU (Model 1b) ^d	-	-
None	-	Referent
Non-weekly	-	1.15 (1.02-1.29)
Weekly	-	1.21 (1.07-1.37)
Socioeconomic confounders		
Employed ^e	0.97 (0.82-1.14)	0.96 (0.82-1.13)
Average monthly income: per \$100 increase ^c	0.98 (0.97-0.99)	0.98 (0.97-0.99)
College or university education at enrolment	0.84 (0.72-0.97)	0.84 (0.73-0.97)
Sociodemographic confounders		
Province of enrolment	-	-
Quebec	Referent	Referent
British Columbia	1.33 (1.18-1.49)	1.32 (1.18-1.49)
Ontario	1.20 (1.02-1.42)	1.21 (1.03-1.44)
Other (Alberta, Sask., Nova Scotia)	1.08 (0.84-1.39)	1.09 (0.85-1.40)
Age (years): per 10-year increase	0.93 (0.87-0.99)	0.93 (0.87-1.00)
Female	0.99 (0.89-1.11)	0.99 (0.89-1.10)
Ethnicity	-	-
White	Referent	Referent
Aboriginal	0.97 (0.85-1.11)	0.97 (0.84-1.11)
Asian, Black, Hispanic, Latino	1.07 (0.86-1.33)	1.06 (0.85-1.32)
No fixed address or temporary housing ^e	1.01 (0.88-1.16)	1.01 (0.88-1.16)
Living situation ^e	-	-
Alone	Referent	Referent
With others (no children)	0.87 (0.78-0.97)	0.88 (0.79-0.98)
With children	0.91 (0.72-1.14)	0.91 (0.72-1.14)
Behavioural confounders		
Non-injection drug use ^c	1.04 (0.94-1.15)	1.04 (0.94-1.15)
Cigarette use ^e	1.13 (0.98-1.31)	1.13 (0.97-1.30)
Alcohol use ^e	1.12 (1.01-1.24)	1.13 (1.02-1.25)
Clinical confounders		
Anxiety or depression ^{e,f}	1.11 (1.01-1.23)	1.12 (1.01-1.23)
Self-perceived health state (0-100), visual analogue scale: per 10-point increase ^{e,f}	0.96 (0.94-0.99)	0.96 (0.94-0.99)
Intercept	0.42 (0.35-0.51)	0.42 (0.35-0.51)

^a Models 1a (binary exposure analysis) and 1b (categorical exposure analysis) included the same set of confounders.

^b Generalized estimating equations were used to estimate risk ratios from Poisson regression models with robust standard errors.^{184,185}

^c Reference period: in the past six months.

^d Reference period: in the past month.

^e Reference period: currently.

^f Measured as components of the EuroQol-5D instrument.²¹⁰

Table 4.3 Adjusted multinomial regression models quantifying the associations between injection drug use (Model 2a), injection drug use frequency (Model 2b), and categorical food insecurity severity among 608 HIV-HCV co-infected individuals (2012-2015).

Variables	Marginal food insecurity	Moderate food insecurity	Severe food insecurity
Adjusted relative-risk ratio (RRR) and 95% confidence interval (CI) with food secure as the referent outcome category ^{a,b}			
Exposure (Model 2a)			
Injection drug use: past six months	1.54 (0.95-2.48)	1.55 (1.02-2.35)	2.06 (1.32-3.22)
Exposure (Model 2b)			
Frequency of IDU: past month	-	-	-
None	Referent	Referent	Referent
Non-weekly	1.52 (0.78-2.97)	1.70 (0.97-2.97)	1.83 (1.05-3.22)
Weekly	2.03 (1.04-3.96)	1.85 (1.03-3.33)	2.68 (1.47-4.91)

^a Estimates were adjusted for all of the confounders listed in Tables 4.1: employment, average monthly income, college or university education at enrolment, province of enrolment, age, sex, ethnicity, housing situation, current living situation, non-injection drug use, cigarette use, alcohol use, self-reported anxiety or depression, and self-perceived health state.

^b The complete outputs (Models 2a/2b) that include the coefficients (RRRs) for the adjustment variables (confounders) are located in Supplementary Tables 4.3 and 4.4.

4.3 Appendix to Manuscript 1

Supplementary Table 4.1 The ten-item adult scale of the Household Food Security Survey Module (HFSSM).

HFSSM Item ^a	Responses ^b
1 You and your household worried that food would run out before you got money to buy more. Was that often true, sometimes true, or never true in the past six ^c months?	Often true Sometimes true Never true
2 The food that you and your household bought just didn't last, and there wasn't any money to get more. Was that often true, sometimes true, or never true in the past six months?	Often true Sometimes true Never true
3 You and your household couldn't afford to eat balanced meals. In the past six months was that often true, sometimes true, or never true?	Often true Sometimes true Never true
4 In the past six months, did you ever cut the size of your meals or skip meals because there wasn't enough money for food?	Yes No
5 How often did this happen? (<i>Referring to Item 4</i>)	Every month Some months but not every month Only 1 or 2 months Not applicable (<i>"No" to Item 4</i>)
6 In the past six months, did you ever eat less than you felt you should because there wasn't enough money to buy food?	Yes No
7 In the past six months, were you ever hungry but didn't eat because you couldn't afford enough food?	Yes No
8 In the past six months, did you lose weight because you didn't have enough money for food?	Yes No
9 In the past six months, did you ever not eat for a whole day because there wasn't enough money for food?	Yes No
10 How often did this happen? (<i>Referring to Item 9</i>)	Every month Some months but not every month Only 1 or 2 months Not applicable (<i>"No" to Item 9</i>)

^a Participants with 1, 2-5, and ≥ 6 affirmative responses on the Household Food Security Survey Module (HFSSM) were identified as experiencing marginal, moderate, and severe food insecurity, respectively.

^b Responses in **bold** are "affirmative responses" to each item. Health Canada categorizes participants' food insecurity according to the number of affirmative responses on the HFSSM. Each item can only count as one affirmative response. All ten items, regardless of the severity of food insecurity, are treated equally, where it has been shown that more severe items (i.e., Items 6-10) are less frequently affirmed than less severe items. Furthermore, the responses "Often true" and "Sometimes true" are treated equally, as are "Every month" and "Some months but not every month."

^c The HFSSM measures self-reported food insecurity in the past twelve months. Modification of the HFSSM to a shorter reference period, as done in this study (i.e., from twelve to six months), has been justified in previous literature.

Supplementary Table 4.2 Unadjusted Poisson and multinomial regression models quantifying the bivariate associations between the exposures, confounders, and food insecurity (along with food insecurity severity) among 608 HIV-HCV co-infected individuals (2012-2015).

Variables	Food insecure	Marginal FI	Moderate FI	Severe FI
	Unadjusted RR (95% CI)	Unadjusted relative-risk ratio (RRR) and 95% CI with food secure as the base outcome category		
Exposures				
Injection drug use (IDU)	1.32 (1.19-1.46)	2.20 (1.41-3.41)	2.60 (1.81-3.74)	3.70 (2.57-5.33)
Frequency of IDU	-	-	-	-
None	Referent	Referent	Referent	Referent
Non-weekly	1.29 (1.15-1.45)	2.24 (1.16-4.29)	2.91 (1.72-4.93)	3.48 (2.13-5.70)
Weekly	1.39 (1.23-1.59)	2.73 (1.47-5.07)	2.95 (1.73-5.05)	4.33 (2.56-7.34)
Socioeconomic confounders				
Employed	0.73 (0.62-0.87)	0.66 (0.38-1.14)	0.40 (0.25-0.64)	0.27 (0.17-0.42)
Average monthly income: per \$100 increase	0.97 (0.96-0.98)	0.96 (0.93-0.98)	0.94 (0.92-0.96)	0.92 (0.89-0.94)
College or university education at enrolment	0.70 (0.59-0.82)	0.42 (0.25-0.72)	0.48 (0.32-0.72)	0.40 (0.26-0.62)
Sociodemographic confounders				
Province of enrolment	-	-	-	-
Quebec	Referent	Referent	Referent	Referent
British Columbia	1.34 (1.19-1.51)	1.15 (0.67-1.95)	2.25 (1.49-3.41)	3.00 (1.97-4.56)
Ontario	0.99 (0.83-1.19)	0.92 (0.52-1.65)	1.17 (0.70-1.97)	0.92 (0.54-1.57)
Other (AB, SK, NS)	1.01 (0.79-1.30)	1.54 (0.71-3.37)	0.88 (0.42-1.87)	0.90 (0.42-1.92)
Age (years): per 10-year increase	0.91 (0.85-0.98)	0.71 (0.55-0.93)	0.70 (0.56-0.89)	0.78 (0.63-0.96)
Female	1.10 (0.98-1.24)	1.25 (0.77-2.04)	1.26 (0.84-1.91)	1.20 (0.79-1.83)
Ethnicity	-	-	-	-
White	Referent	Referent	Referent	Referent
Aboriginal	1.14 (1.00-1.30)	1.38 (0.78-2.46)	1.61 (1.01-2.58)	1.41 (0.88-2.27)
Asian, Black, Hispanic, Latino	0.98 (0.76-1.26)	0.79 (0.29-2.15)	1.13 (0.55- 2.33)	1.00 (0.46-2.18)
No fixed address or temporary housing	1.14 (0.97-1.32)	1.32 (0.66-2.67)	1.27 (0.70-2.32)	2.48 (1.49-4.14)
Living situation	-	-	-	-
Alone	Referent	Referent	Referent	Referent
With others (no children)	0.85 (0.76-0.95)	0.79 (0.51-1.23)	0.56 (0.39-0.81)	0.68 (0.48-0.97)
With children	0.78 (0.61-1.00)	0.50 (0.18-1.40)	0.51 (0.23-1.11)	0.77 (0.39-1.50)
Behavioural confounders				
Non-injection illicit drug use	1.17 (1.05-1.30)	1.74 (1.13-2.67)	1.92 (1.33-2.77)	2.67 (1.89-3.77)
Cigarette use	1.32 (1.13-1.53)	1.86 (1.16-2.98)	2.38 (1.56-3.63)	2.32 (1.51-3.59)
Alcohol use	1.12 (1.01-1.25)	1.12 (0.72-1.73)	1.78 (1.24-2.55)	1.29 (0.92-1.79)
Clinical confounders				
Anxiety or depression	1.24 (1.13-1.37)	1.60 (1.07-2.40)	1.70 (1.21-2.40)	3.99 (2.81-5.67)
Self-perceived health state (0-100), visual analogue scale; per 10-point increase	0.94 (0.92-0.97)	0.87 (0.78-0.97)	0.83 (0.76-0.92)	0.72 (0.65-0.79)

Supplementary Table 4.3 Adjusted multinomial regression model quantifying the associations between injection drug use (Model 2a) and categorical food insecurity severity among 608 HIV-HCV co-infected individuals (2012-2015).

Variables	Marginal FI	Moderate FI	Severe FI
Adjusted relative-risk ratio (RRR) and 95% CI with food secure as the base outcome category			
Exposure	<u>Model 2a</u>		
Injection drug use: past six months	1.54 (0.95-2.48)	1.55 (1.02-2.35)	2.06 (1.32-3.22)
Socioeconomic confounders			
Employed	1.45 (0.73-2.90)	0.87 (0.48-1.55)	0.85 (0.48-1.51)
Average monthly income: per \$100 increase	0.96 (0.94-0.99)	0.95 (0.92-0.98)	0.94 (0.91-0.97)
College or university education at enrolment	0.56 (0.31-1.02)	0.70 (0.44-1.12)	0.61 (0.37-1.02)
Behavioural confounders			
Province of enrolment	-	-	-
Quebec	Referent	Referent	Referent
British Columbia	1.29 (0.73-2.29)	2.61 (1.61-4.22)	3.62 (2.17-6.05)
Ontario	1.45 (0.78-2.68)	1.85 (1.02-3.35)	1.78 (0.98-3.23)
Other (AB, SK, NS)	1.86 (0.76-4.53)	1.01 (0.42-2.45)	1.44 (0.56-3.74)
Age (years): per 10-year increase	0.78 (0.59-1.03)	0.69 (0.53-0.90)	0.86 (0.67-1.11)
Female	0.99 (0.59-1.66)	0.95 (0.62-1.48)	0.83 (0.52-1.33)
Ethnicity	-	-	-
White	Referent	Referent	Referent
Aboriginal	0.84 (0.42-1.69)	0.95 (0.52-1.71)	0.75 (0.39-1.42)
Asian, Black, Hispanic, Latino	0.92 (0.34-2.49)	1.39 (0.66-2.94)	1.59 (0.71-3.55)
No fixed address or temporary housing	0.93 (0.45-1.91)	0.80 (0.42-1.54)	1.35 (0.72-2.51)
Living situation	-	-	-
Alone	Referent	Referent	Referent
With others (no children)	0.71 (0.45-1.12)	0.57 (0.38-0.87)	0.75 (0.49-1.14)
With children	0.53 (0.17-1.68)	0.67 (0.29-1.55)	1.41 (0.68-2.93)
Behavioural confounders			
Non-injection illicit drug use	1.25 (0.79-1.98)	1.16 (0.77-1.74)	1.47 (0.97-2.21)
Cigarette use	1.15 (0.69-1.93)	1.51 (0.95-2.43)	1.45 (0.88-2.41)
Alcohol use	1.17 (0.75-1.84)	2.00 (1.36-2.95)	1.30 (0.89-1.91)
Clinical confounders			
Anxiety or depression	1.19 (0.76-1.85)	1.07 (0.73-1.58)	2.39 (1.60-3.56)
Self-perceived health state (0-100), visual analogue scale: per 10-point increase	0.91 (0.81-1.02)	0.88 (0.79-0.97)	0.82 (0.74-0.91)
Intercept	0.19 (0.10-0.37)	0.23 (0.12-0.44)	0.14 (0.07-0.28)

Supplementary Table 4.4 Adjusted multinomial regression model quantifying the association between injection drug use frequency (Model 2b) and categorical food insecurity severity among 608 HIV-HCV co-infected individuals (2012-2015).

Variables	Marginal FI	Moderate FI	Severe FI
Adjusted relative-risk ratio (RRR) and 95% CI with food secure as the base outcome category			
Exposure	Model 2b		
Frequency of IDU: past month	-	-	-
None	Referent	Referent	Referent
Non-weekly	1.52 (0.78-2.97)	1.70 (0.97-2.97)	1.83 (1.05-3.22)
Weekly	2.03 (1.04-3.96)	1.85 (1.03-3.33)	2.68 (1.47-4.91)
Socioeconomic confounders			
Employed	1.46 (0.73-2.90)	0.87 (0.49-1.56)	0.84 (0.47-1.50)
Average monthly income: per \$100 increase	0.96 (0.93-0.99)	0.95 (0.92-0.98)	0.93 (0.90-0.96)
College or university education at enrolment	0.56 (0.31-1.02)	0.70 (0.44-1.13)	0.62 (0.37-1.04)
Behavioural confounders			
Province of enrolment	-	-	-
Quebec	Referent	Referent	Referent
British Columbia	1.28 (0.72-2.27)	2.59 (1.60-4.18)	3.62 (2.16-6.06)
Ontario	1.49 (0.80-2.77)	1.88 (1.03-3.41)	1.85 (1.02-3.35)
Other (AB, SK, NS)	1.91 (0.78-4.65)	1.02 (0.42-2.47)	1.50 (0.58-3.87)
Age (years): per 10-year increase	0.78 (0.59-1.04)	0.69 (0.53-0.90)	0.86 (0.67-1.11)
Female	0.99 (0.59-1.67)	0.95 (0.61-1.48)	0.81 (0.51-1.30)
Ethnicity	-	-	-
White	Referent	Referent	Referent
Aboriginal	0.84 (0.42-1.69)	0.96 (0.53-1.73)	0.74 (0.39-1.42)
Asian, Black, Hispanic, Latino	0.91 (0.34-2.47)	1.39 (0.65-2.94)	1.55 (0.70-3.43)
No fixed address or temporary housing	0.94 (0.45-1.95)	0.81 (0.42-1.56)	1.40 (0.75-2.59)
Living situation	-	-	-
Alone	Referent	Referent	Referent
With others (no children)	0.72 (0.45-1.14)	0.57 (0.38-0.87)	0.76 (0.50-1.16)
With children	0.53 (0.17-1.70)	0.67 (0.29-1.56)	1.39 (0.66-2.90)
Behavioural confounders			
Non-injection illicit drug use	1.26 (0.79-2.00)	1.16 (0.77-1.74)	1.51 (1.00-2.27)
Cigarette use	1.13 (0.68-1.90)	1.50 (0.94-2.41)	1.44 (0.87-2.38)
Alcohol use	1.19 (0.76-1.86)	2.01 (1.36-2.97)	1.34 (0.91-1.96)
Clinical confounders			
Anxiety or depression	1.20 (0.77-1.87)	1.08 (0.73-1.60)	2.40 (1.61-3.58)
Self-perceived health state (0-100), visual analogue scale: per 10-point increase	0.91 (0.81-1.03)	0.88 (0.79-0.97)	0.82 (0.74-0.91)
Intercept	0.19 (0.10-0.36)	0.23 (0.12-0.44)	0.14 (0.07-0.28)

Non-equivalence of risk ratios (Table 4.2) and relative-risk ratios (Table 4.3):

It is important to note that while multinomial regression models do not estimate odds ratios, they do use the logistic transformation. Therefore, multinomial estimates (relative-risk ratios [RRR]) are similar to odds ratios in that they are further from the null than a hypothetical risk ratio (RR) estimate, when the outcome is common (>10%) (Zhang & Yu, 1998). For example, while the RR estimated from the Poisson regression model for IDU is 1.15 (95% CI = 1.04-1.28), each of the RRRs estimated in Model 2a (across all FI severities) are substantially larger in magnitude. While the multinomial regression analyses provide additional detail in understanding the IDU-FI relationship, the RRRs from Table 4.3 are not directly comparable to the RRs from Table 4.2.

Violations of the proportional odds assumption and the use of multinomial models:

The proportional odds model requires that the coefficients for all covariates in the adjusted model are equal across all cut-offs of FI severity. This is known as the proportional odds assumption (Brant, 1990). To assess this, we fit models to a series of binary outcomes (using marginal, moderate, and severe FI as the cut-offs). The coefficients differed across models, informally indicating a violation of this assumption. However, this assumption can be relaxed by using a “partial” proportional odds model (Peterson & Harrell, 1990). We explored the use of this model by examining the proportional odds assumption for each covariate in each imputed dataset. Wald tests indicated that the assumption was violated for some covariates, including the exposure (IDU), in some of the imputed datasets. While a multinomial regression model is less parsimonious and does not fully exploit the ordinal nature of the outcome, we chose this model as it does not require this assumption (Vittinghoff, Glidden, Shiboski, & McCulloch, 2012).

Supplementary Material References:

Brant, R. (1990). Assessing Proportionality in the Proportional Odds Model for Ordinal Logistic Regression. *Biometrics*, 46(4), pp. 1171-1178.

Peterson, B., Harrell, F. E. (1990). Partial Proportional Odds Models for Ordinal Response Variables. *J Appl Stat*, 39(2):205-217.

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Zhang, J., & Yu, K. F. (1998). What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*, 18(280), pp. 1690-1691.

Chapter 5: Mediation analysis of mechanisms (Manuscript 2)

5.1 Preface to Manuscript 2

In Manuscript 1 (Chapter 4), a longitudinal cohort analysis indicated that there is an association between IDU and FI, particularly weekly IDU and severe FI, among HIV-HCV co-infected individuals. These associations were independent of socioeconomic, sociodemographic, behavioural, and clinical confounders, suggesting that reductions in IDU may mitigate FI, especially severe FI, in this population. Manuscript 2 built on the findings of Manuscript 1 and examined a potential mechanism through which IDU is associated with severe FI.

Central to the concept of FI is the focus on uncertain or inadequate food access due to limited financial resources.¹⁹ Employment, or the condition of having paid work, is one of the primary means through which an individual can acquire financial resources.²² However, there is little known about the temporal relationship between IDU, unemployment, and severe FI. Earlier works have documented that the instability associated with injecting drugs may result in absenteeism and interfere with an individuals' capacity to perform their work^{213,214}; this may result in dismissal from the workplace. If this sequence of events were to occur, increases in employment^{213,215,216} could mitigate the association between IDU and severe FI, even if there are no reductions in IDU itself. Furthermore, by examining how much of the association between IDU and severe FI was mediated by unemployment, this work provides indirect insights into other potential pathways linking these two factors. Etiologically, understanding how IDU increases the risk of severe FI is helpful in determining whether interventions on IDU may be useful in reducing severe FI (Manuscript 3).

5.2 Manuscript 2: Injection drug use, unemployment, and severe food insecurity among HIV-HCV co-infected individuals: a mediation analysis

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This manuscript was published in *AIDS and Behavior* in July 2017.²¹⁷

Keywords: HIV; hepatitis C virus; injection drug use; unemployment; severe food insecurity

Abstract: Severe food insecurity (FI), which indicates reduced food intake, is common among HIV-hepatitis C virus (HCV) co-infected individuals. Given the importance of unemployment as a proximal risk factor for FI, this mediation analysis examines a potential mechanism through which injection drug use (IDU) is associated with severe FI. We used biannual data from the Canadian Co-infection Cohort (N = 429 with three study visits, 2012-2015). IDU in the past six months (exposure) and current unemployment (mediator) were self-reported. Severe FI in the following six months (outcome) was measured using the Household Food Security Survey Module. An overall association and a controlled direct effect were estimated using marginal structural models. Among participants, 32% engaged in IDU, 78% were unemployed, and 29% experienced severe FI. After adjustment for confounding and addressing censoring through weighting, the overall association (through all potential pathways) between IDU and severe FI was: risk ratio (RR) = 1.69 (95% confidence interval [CI] = 1.15-2.48). The controlled direct effect (the association through all potential pathways except that of unemployment) was: RR = 1.65 (95% CI = 1.08-2.53). We found evidence of an overall association between IDU and severe FI and estimated a controlled direct effect that is suggestive of pathways from IDU to severe FI that are not mediated by unemployment. Specifically, an overall association and a controlled direct effect that are similar in magnitude suggests that the potential impact of IDU on unemployment is not the primary mechanism through which IDU is associated with severe FI. Therefore, while further research is required to understand the mechanisms linking IDU and severe FI, the strong overall association suggests that reductions in IDU may mitigate severe FI in this vulnerable subset of the HIV-positive population.

Introduction:

Food insecurity (FI) is highly prevalent in HIV-positive and HIV-hepatitis C virus (HCV) co-infected populations.^{28,48} By definition, FI exists “whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain.”¹⁸ In our previous study of 525 HIV-HCV co-infected individuals in Canada (2012-2014), 59% of participants experienced FI at baseline.⁴⁸ Among this group, the majority experienced severe FI, which indicates disrupted eating patterns and reduced food intake. Less severe experiences, known as marginal and moderate FI, are indicative of worrying about running out of food or compromises in the quality and/or quantity of food consumed.^{19,22}

In the HIV context, FI is associated with sub-optimal HIV treatment adherence,³⁵ incomplete HIV viral load suppression,^{33,34} and lower CD4 cell counts.^{32,33} To prevent these outcomes and identify potential targets for intervention, researchers have examined potentially modifiable risk factors for FI in HIV-positive^{37-39,41} and HIV-HCV co-infected⁴⁸ populations in Canada. In these studies, FI was measured using the Household Food Security Survey Module (HFSSM) or the Radimer/Cornell instrument.^{19,87} These instruments focus on self-reports of uncertain or inadequate food access due to limited financial resources. Therefore, when using these tools, it is important to consider the proximal role of financial resources when discussing potential mechanisms underlying the associations between risk factors and FI.

In HIV-positive populations, 20% of individuals are estimated to be living with HIV-HCV co-infection.^{6,7} In the Canadian Co-infection Cohort, a cohort of co-infected individuals who contributed the data for this study, over 80% of participants reported a history of injection drug use (IDU); IDU is the primary risk factor for HCV co-infection.⁷ In previous HIV-related studies, researchers have documented associations between this behaviour and FI,^{37,48} where IDU

was associated with FI independent of socioeconomic and sociodemographic confounders. Therefore, given that IDU is associated with FI after adjustment for factors such as concurrent income and employment status,^{37,48} there is an interest in examining mediators in pathways linking IDU and subsequent FI.⁴²

Employment, or the condition of having paid work, is one of the primary means through which an individual can acquire financial resources.²² In our previous study of co-infected individuals across Canada⁴⁸ and in studies of HIV-positive individuals in British Columbia,^{37,39} unemployment was associated with FI. However, there is little known about the temporal relationship between IDU, unemployment, and severe FI. For example, it has been documented that IDU inflicts a considerable burden on individuals, including lost productivity and social functioning.²¹⁸ In previous Canadian studies that included both HIV-positive and HIV-negative participants, IDU was associated with unemployment.^{213,218} Specifically, earlier works have documented that the instability associated with injecting drugs may result in absenteeism and interfere with an individuals' capacity to perform their work^{213,214}; this may result in dismissal from the workplace. If this sequence of events were to occur, increases in employment^{213,215,216} may mitigate the association between IDU and severe FI, even if there are no reductions in IDU itself. Furthermore, by examining how much of the association between IDU and severe FI is mediated by unemployment, our work will provide indirect insights into other potential pathways linking these two factors.

Given the role of financial resources in the FI construct¹⁹ and the importance of employment as a means of acquiring income,²² it is necessary to generate evidence that examines the temporal relationship between IDU, unemployment, and severe FI. We hypothesize that the previously identified associations between IDU and FI in HIV-positive³⁷ and HIV-HCV co-

infected⁴⁸ populations may be partially mediated by the potential impact of IDU on subsequent unemployment,^{213,218} which then goes on to increase the risk of severe FI.^{37,48} Therefore, given the high prevalence of severe FI in co-infected populations⁴⁸ and the plausibility of unemployment as one mechanism linking IDU and severe FI, we analyzed longitudinal cohort data to examine this question in a mediation analysis among individuals living with HIV-HCV co-infection in Canada.

Methods:

Study population

The Canadian Co-infection Cohort (CCC) is a prospective study of HIV-HCV co-infected individuals who receive care from HIV clinics across Canada. Details of the CCC have been described elsewhere.¹⁷² CCC participants must be at least 16 years of age with documented HIV infection and serologic evidence of HCV exposure. All eligible individuals were invited to participate and data collection occurred approximately every six months.

From November 2012 to October 2015, the Food Security and HIV-HCV Study (FS Study)⁴⁸ was implemented and biannual data collection related to FI was integrated into CCC study visits at 17 clinics in six provinces. All CCC participants were invited to enrol in the FS Study. The CCC and the FS Study were approved by the McGill University Health Centre and the research ethics boards of the participating institutions.¹⁷²

Measures

To ensure temporal-ordering of the exposure, mediator, outcome, and confounders from each participant i at visit j , biannual data from three separate study visits was used (Figure 5.1). Information on the time-invariant confounders (denoted V_{i1}) was taken from the first visit. The time-varying confounders (denoted L_{i1} and L_{i2}) were measured at the first and second visits. The

exposure and mediator were measured at the second visit, denoted A_{i2} and M_{i2} , respectively. The outcome, Y_{i3} , was measured at the third visit.

Injection drug use (exposure) and unemployment (mediator)

At the second visit, IDU in the past six months (A_{i2}) was self-reported by participants on a questionnaire. We defined the exposure as a binary indicator of IDU (none vs. any IDU). Current employment status (M_{i2}) was also self-reported at the second visit. We defined the mediator as a binary indicator of being unemployed (employed [part-time or full-time work] vs. unemployed). Given our focus on unemployment, participants who reported being a student or retired were excluded from the analyses ($N = 59$).

Severe food insecurity (outcome)

At the third visit, severe FI in the past six months (Y_{i3}) was measured using the ten-item adult scale of Health Canada's Household Food Security Survey Module (HFSSM).¹⁹ Participants with ≥ 6 affirmative responses on the HFSSM were identified as experiencing severe FI. We used this dichotomization to define a binary outcome (not experiencing severe FI vs. experiencing severe FI). To assess the internal consistency of the HFSSM, a Cronbach's alpha was calculated. Details of the HFSSM have been described in a previous FS Study publication.⁴⁸

Confounding factors

All confounders were selected on substantive grounds *a priori* based on their hypothesized association with IDU (in the exposure-outcome relationship), unemployment (in the mediator-outcome relationship), and severe FI.^{28,42,48} Given the nature of the FI construct, we selected factors (e.g., age, sex, province of enrolment, and self-perceived health state) that may also act as proxies for unmeasured confounders. All confounders were self-reported by participants on biannual questionnaires.

The time-invariant confounders (V_{i1}) included: education at enrolment (elementary school or less vs. high school vs. college or university), sex (female vs. male), ethnicity (white vs. Aboriginal [First Nations, Inuit, Métis] vs. other [Asian, Black, Hispanic, Latino]), and province of enrolment (Quebec vs. British Columbia vs. Ontario vs. other [Alberta, Saskatchewan, Nova Scotia]).

Time-varying confounders of the exposure-outcome (L_{i1}) and mediator-outcome (L_{i2}) relationships were measured at the first and second visits (details on the reference period are provided in the footnotes of Table 5.1, often referring to “current” experiences or experiences “in the past six months”). Time-varying confounders (L_{i1}, L_{i2}) included: age, housing situation (not having a fixed address, temporary situation, care facility vs. homeowner or apartment/room renter), living situation (living with others vs. living alone), non-injection drug use (none vs. use of drugs for non-medical purposes via sniffing, smoking, eating, drinking, or transdermally), cigarette use (no vs. yes), alcohol use (no vs. yes), as well as self-reported anxiety or depression (no vs. yes) and self-perceived health state (visual analogue scale, 0 = worst imaginable health state to 100 = best imaginable health state) as per the EuroQol-5D instrument.²¹⁰ Also, average monthly income (before taxes; \$ Canadian dollars [CAD]) and employment status (employed vs. unemployed), measured at the first visit, were included as exposure-outcome confounders (in addition to V_{i1} and L_{i1}).

Predictors of censoring

For each participant i at visits $j = 2$ and 3 , time-invariant and time-varying factors (listed in the Supplementary Material in Section 5.3) were used in estimating a participant’s probability of being censored due to a formal withdrawal, death, loss to follow-up (defined as missing three consecutive visits), or administrative censoring at the FS Study’s completion in October 2015

(Figure 5.2). Loss to follow-up indicates that a participant enrolled early enough to have the potential for three consecutive missed visits (between November 2012 and October 2015), whereas administrative censoring indicates that a participant enrolled later in the study and did not have the potential for three consecutive missed visits prior to October 2015.

Data analysis

Our analytic objectives were to estimate the overall association between IDU and severe FI (through all potential pathways) and the controlled direct effect (CDE) of IDU on severe FI.^{195,198,199} The CDE expresses how much the outcome would change, on average, if everyone was changed from unexposed to exposed and the mediator were set to a fixed level in the population. In our study, the CDE of IDU on severe FI compares a hypothetical population in which everyone is exposed to IDU in the six months preceding visit two to a conditionally exchangeable population in which no one is exposed, where in both populations, all individuals are employed at visit two. Therefore, the CDE provides information on the extent to which the overall association between IDU (A_{i2}) and severe FI (Y_{i3}) is mediated by unemployment (M_{i2}), after adjusting for time-invariant (V_{i1}) and time-varying confounders of the exposure-outcome (L_{i1} as well as average monthly income and employment status at visit one) and the mediator-outcome relationships (L_{i2}).

Given that the time-varying mediator-outcome confounders (L_{i2}) may be affected by prior exposure (A_{i2}), it was inappropriate to directly adjust for factors in L_{i2} in the outcome model estimating the CDE.^{195,198,199} Therefore, a weighting approach with a marginal structural log-linear model was used to estimate the CDE of IDU on severe FI. Specifically, weighting was used to adjust for confounding and to address selection bias due to informative censoring (formal withdrawals, deaths, losses to follow-up, and administrative censoring).¹⁸⁹ We also tested for an

interaction between A_{i2} and M_{i2} in the model estimating the CDE by including a product term. For details on the models, weighting approaches, and their identifiability assumptions (consistency, conditional exchangeability, and positivity), refer to the Supplementary Material in Section 5.3.

Summary statistics were used to describe the participants at each visit. Additionally, multiple imputation by chained equations was used to impute missing observations using 30 imputed datasets and 50 iterations. Continuous, binary, and categorical variables were imputed using predictive mean matching, logistic regression, and multinomial or ordered logistic regression, respectively. To maintain a uniform temporal-ordering of L_{i1} , A_{i2} , L_{i2} , M_{i2} , and Y_{i3} , multiple imputation was also used to impute time-varying variables at missed study visits (i.e., visits that did not occur approximately every six months). To distinguish a missed visit from censoring, a missed visit must have occurred prior to a study visit later in time.

For all parameters, robust standard errors were calculated. Also, continuous confounders were modeled using splines. All models were fit to each of the 30 imputed datasets and the resulting estimates were combined using Rubin's method.¹⁸¹ All data analyses were performed using Stata 14 (College Station, TX: StataCorp LP. 2015).

Results:

Among the 666 FS Study participants that enrolled between November 2012 and October 2015 (which excluded 59 students and retirees), 555 completed a second visit and 429 completed a third visit (Figure 5.2). Additionally, there were 75 missed second visits and 47 missed third visits. As shown in Table 5.1, 32% of participants injected drugs in the six months preceding visit two, 78% were currently unemployed at visit two, and 29% experienced severe FI in the six

months preceding visit three. The internal consistency of the HFSSM was acceptable in this sample as Cronbach's alpha exceeded 0.90.²¹⁹

As shown in Table 5.2, unadjusted analyses that addressed selection bias due to informative censoring indicated that IDU in the past six months is associated with an increase in the likelihood of unemployment and an increase in the likelihood of severe FI in the following six months. Also, unemployment is associated with an increase in the likelihood of severe FI in the following six months. After adjustment for confounding through weighting, the overall association between IDU in the past six months and severe FI in the following six months (through all potential pathways: $A_{i2} \rightarrow Y_{i3}$, $A_{i2} \rightarrow L_{i2} \rightarrow Y_{i3}$, $A_{i2} \rightarrow M_{i2} \rightarrow Y_{i3}$, and $A_{i2} \rightarrow L_{i2} \rightarrow M_{i2} \rightarrow Y_{i3}$) was: risk ratio (RR) = 1.69 (95% confidence interval [CI] = 1.15-2.48).

Conceptually, the CDE reflects an estimate that “excludes” the association between IDU and severe FI that is mediated by unemployment. As such, the CDE, which represents the association through all potential pathways except that of unemployment ($A_{i2} \rightarrow Y_{i3}$ and $A_{i2} \rightarrow L_{i2} \rightarrow Y_{i3}$) was: RR = 1.65 (95% CI = 1.08-2.53). Given that there was no evidence of an interaction between A_{i2} and M_{i2} in the model estimating the CDE ($p > 0.05$ for the product term), the CDE was quantified using a model where the interaction was omitted. Notably, through the use of censoring weights, all estimates (the unadjusted associations, the overall association, and the CDE) are applicable to a full-population with no censoring during follow-up.

The estimates of the overall association and the CDE are similar in magnitude (RR = 1.69 and 1.65). Thus, under the model assumptions, “excluding” the association that is mediated by unemployment did not result in a substantial attenuation or reduction in the overall association. This comparison is suggestive of other pathways from IDU to severe FI that are not mediated by unemployment immediately after the IDU reference period.

Discussion:

IDU and severe FI are highly prevalent in this HIV-HCV co-infected population. Research that examines a potential mechanism through which IDU is associated with severe FI can be used to conceptualize interventions to possibly reduce severe FI.^{27,42} Consistent with HIV-related studies of FI,^{37,48} we found evidence of an overall association between IDU and the most severe form of FI. Also, while IDU may be associated with unemployment^{213,218} and unemployment may be associated with FI,^{37,48} our work is suggestive of other pathways, beyond the role of unemployment, in the temporal relationship between IDU and subsequent severe FI.

As described, the CDE represents the association between IDU and severe FI while “excluding” the association between IDU and severe FI that is mediated by unemployment. Therefore, the structure of the data permitted us to ask and answer the following question: “Is IDU in the past six months associated with severe FI in the following six months, if employment status (immediately after the IDU reference period) could remain unaffected by IDU?” In answering this question, there were several analytical issues that were addressed.

As shown in Figure 5.1, there are measured factors (L_{i2}) that may mediate the association between IDU (exposure) and severe FI (outcome) while also confounding the association between unemployment (mediator) and severe FI. The use of weighting in a marginal structural model allowed us to adjust for mediator-outcome confounders without blocking the association between IDU and severe FI that may act through factors in L_{i2} .^{195,198,199} Specifically, while the overall association between IDU and severe FI includes all pathways (including unemployment), weighting allowed us to estimate a CDE that represents the association via all pathways except that of unemployment ($A_{i2} \rightarrow Y_{i3}$ and $A_{i2} \rightarrow L_{i2} \rightarrow Y_{i3}$).

Our theoretical framework is represented by a directed acyclic graph (Figure 5.1).²²⁰ As described, the $A_{i2} \rightarrow L_{i2} \rightarrow Y_{i3}$ pathway represents the association through other measured mediators that may also be acting as mediator-outcome confounders, excluding that of unemployment (M_{i2}). For example, IDU may be associated with experiences of anxiety or depression²²¹ which may go on to increase the likelihood of severe FI.⁴⁸ However, our analyses do not quantify the magnitude of the association that may act through mental health or other factors in L_{i2} . Therefore, the finding that the overall association is similar to the CDE indicates that, in addition to the direct $A_{i2} \rightarrow Y_{i3}$ pathway, an unknown amount of the association is possibly through other factors in L_{i2} (e.g., housing situation, living situation, non-injection drug use, cigarette use, alcohol use, anxiety or depression, and/or self-perceived health state).

The $A_{i2} \rightarrow Y_{i3}$ pathway can be conceptualized as the “direct” effect. This pathway is not to be confused with the CDE, which quantifies the association through the direct $A_{i2} \rightarrow Y_{i3}$ pathway and the $A_{i2} \rightarrow L_{i2} \rightarrow Y_{i3}$ pathway. The CDE encompasses all pathways excluding those mediated by M_{i2} and not just the direct pathway of $A_{i2} \rightarrow Y_{i3}$. In a study of HFSSM-measured FI, the role of financial resources as the proximal determinant is explicit.¹⁹ We have chosen not to conceptualize the $A_{i2} \rightarrow Y_{i3}$ pathway as being direct in a biological sense, as this would contradict the definition of severe FI, which indicates disrupted eating patterns and reduced food intake due to limited financial resources.^{19,22} In our study, the $A_{i2} \rightarrow Y_{i3}$ pathway can be conceptualized as the association through unmeasured factors that were not included in L_{i2} .

Given that the association between IDU and severe FI does not appear to be mediated, in large part, by unemployment, other potential mechanisms must be discussed. One compelling mechanism is that of competing demands on financial resources and the prioritization of the purchase of drugs instead of food.^{42,146,222} In a study of individuals who injected drugs in

Vancouver, Canada, participants reported purchasing drugs instead of food even when they were hungry.²²² Therefore, purchases of injection drugs may compete with food to an extent that results in severe FI; this pathway could be conceptualized as a more “direct” ($A_{i2} \rightarrow Y_{i3}$) impact of IDU on severe FI. This is an intriguing hypothesis when considering that employment income and what one does with their financial resources are not equivalent concepts. While being employed is a proxy for stable income, the use of financial resources for food represents one aspect of income utilization.⁴² Unfortunately, we do not have data on such expenditures. As such, it is possible that the $A_{i2} \rightarrow Y_{i3}$ pathway is representing, in part, competing demands on financial resources, which is a mechanism that we could not investigate in our study.

It is also important to note that 78% of participants were unemployed at their second visit. Therefore, while employment is one of the primary means through which an individual can acquire income,²² this may not be the case in the HIV-HCV co-infection context. For example, two previous studies describing the income-generating activities of individuals who engaged in illicit drug use in Vancouver indicated that over 80% of participants generated income through social assistance.^{223,224} Income generation through drug dealing and sex work were also common. It may be reasonable to suggest that with such high levels of unemployment, many of the individuals who inject drugs in our sample may also be reliant on non-employment sources of income. While our work suggests that IDU is not primarily acting through unemployment to increase the likelihood of severe FI, we did not examine whether IDU is having an impact on the ability of co-infected individuals to acquire financial resources through other means.

While this mediation analysis in the HIV-HCV co-infection context raises additional questions regarding mechanisms, our findings indicate that IDU is associated with severe FI independent of socioeconomic, sociodemographic, behavioural, and clinical confounders. This is

important because IDU is a potentially modifiable risk factor and severe FI is characterized by reduced food intake and the physical sensation of hunger.^{21,22} Furthermore, the CDE provides evidence that even if it were possible to intervene to ensure that everyone in the population was employed at visit two, this may not substantially mitigate the overall association between IDU and severe FI. This suggests that IDU is associated with severe FI primarily through pathways other than unemployment. Therefore, increasing employment (e.g., through employment supports)^{213,215,216} may not meaningfully reduce the association between IDU and severe FI in this population. However, the strong overall association suggests that substance use interventions aimed at IDU⁴² may reduce the likelihood of severe FI; further research is needed to evaluate such interventions.

Strengths and limitations

To our knowledge, our study is the first to quantitatively examine a potential mechanism through which IDU is associated with severe FI in a co-infected population. Using prospective longitudinal data, we employed methodologies that allowed us to adjust for time-varying confounders affected by prior exposure and to address selection bias due to informative censoring. While this work overcomes methodological complexities, our approaches required several assumptions that preclude us from claiming causality.^{195,198}

First, given a relatively small sample size, we were unable to model a more informed measure of the IDU exposure that considered frequency, duration, or drug type. By using a binary indicator (none vs. any IDU), we could not examine whether these drug-related characteristics impacted IDUs association with unemployment and subsequently, severe FI. Similarly, given the small proportion of employed participants overall, we were not able to delineate between types of employment (e.g., part-time and full-time work). Furthermore, given

our focus on disrupted eating patterns and reduced food intake, we did not explore alternative FI cut-offs (i.e., experiencing any FI or marginal/moderate FI). Also, while there was no evidence of an interaction between A_{i2} and M_{i2} in our study, we suspect that there may have been limited power to conclusively test for this heterogeneity; future studies with larger sample sizes could consider these aspects.

Second, although this analysis suggests that the association between IDU and severe FI may be primarily through pathways other than unemployment, we do not examine how much of the association is through other measured mediators. While the consideration of multiple mediators is an extension of this work,²²⁵ it should be noted that confounders of each mediator-outcome relationship must be measured and that the study sample must be sufficiently large to allow for analytical adjustment. Also, while we hypothesize that the $A_{i2} \rightarrow Y_{i3}$ pathway may represent, in part, a phenomenon of competing demands on financial resources,^{42,146,222} we did not have the data to investigate this mechanism in our study.

Third, in a mediation analysis, the timing of the biannual measurements is critical to the interpretation of our findings and the association between IDU and severe FI that may operate through unemployment at other points in time could not be quantified. For example, it is possible that while the association between IDU (in the six months preceding visit two) and severe FI (in the six months preceding visit three) is not primarily mediated by current unemployment at visit two, it may be mediated by unemployment between visits two and three. However, the proportion of unemployed participants at visit three was 79% (similar to that observed at visit two: 78% in Table 5.1). We also examined the unadjusted association between IDU in the six months preceding visit two and unemployment at visit three (instead of visit two). The estimated RR (RR = 1.20, 95% CI = 1.09-1.33) was similar to that listed in Table 5.2 for the $A_{i2} \rightarrow M_{i2}$

relationship. These consistencies suggest that unmeasured changes in employment status between visits two and three would not change our conclusions. Additionally, although we were able to use visit one confounders (L_{i1}) in estimating the exposure-outcome weights, we were required to use visit two confounders (L_{i2}) in the mediator-outcome weights. This is because we examined IDU's association, in the past six months, with subsequent unemployment at the end of those six months; there may be a reciprocal relationship between unemployment at visit two and the mediator-outcome confounders measured at the same visit.

Fourth, there was a trade-off to ensuring uniform temporal-ordering by having to address larger amounts of missing data. Given that there was biannual data collection, it was imperative to ensure that participants' data were collected approximately every six months. In a multi-site cohort study, missed visits are inevitable. There were 75 missed second visits and 47 missed third visits. For these 75 second visits, exposure, mediator, and time-varying confounder data were not available. For example, 80 participants did not have IDU data at visit two ($N = 475$ of 555). Therefore, 75 of those 80 missing data points were due to missed visits and the remaining five missing data points were due to item non-response on questionnaires. Similarly, 47 participants did not have FI data at visit three ($N = 382$ of 429) and all 47 of those missing data points were due to missed visits. To ensure uniform temporal-ordering, these data had to be imputed.

Lastly, the assumption of no unmeasured or imperfectly measured confounders may be violated in observational research that does not involve randomization of both the exposure and the mediator. While we are confident in our selection and measurement of confounders, there is the possibility that residual confounding resulted in a violation of the conditional exchangeability assumption. Also, by using weighting with a relatively small sample size, positivity violations

were more likely to occur. However, the mean and ranges of the estimated weights did not indicate such a violation. Also, while self-reported data can result in misclassification of our exposure or outcome, a previous review has concluded that self-reports of individuals who use drugs are sufficiently reliable to provide descriptions of drug use.²¹² Furthermore, the HFSSM is a validated and widely used FI measurement tool.^{18,19}

Conclusions:

Our findings indicate that there is an overall association between IDU and severe FI, independent of socioeconomic, sociodemographic, behavioural, and clinical confounders. Also, we provide evidence that the association between IDU and severe FI is primarily through pathways that are not mediated by unemployment. Specifically, an overall association and a controlled direct effect that are similar in magnitude suggests that the potential impact of IDU on unemployment is not the primary mechanism through which IDU is associated with severe FI. While further research is required to understand the mechanisms linking IDU and severe FI, the strong overall association suggests that reductions in IDU may mitigate severe FI in this vulnerable subset of the HIV-positive population.

Acknowledgements:

TM is supported by a CANOC Centre Doctoral Scholarship Award, a joint program of CANOC and the CIHR Canadian HIV Trials Network (CTN 242). EEMM is supported by a Chercheur-Boursier (Junior 2) Career Award from the Fonds de recherche du Québec-Santé (FRQ-S). MBK is supported by a Chercheurs Nationaux Career Award from the FRQ-S.

The authors thank Jennifer Kocilowicz and Leo Wong for study coordination. The Canadian Co-infection Cohort investigators (CTN 222) are: Drs. Jeff Cohen (Windsor Regional Hospital Metropolitan Campus, Windsor, ON), Brian Conway (PENDER Downtown Infectious Diseases Clinic, Vancouver, BC), Curtis Cooper (The Ottawa Hospital Research Institute, Ottawa, ON), Pierre Côté (Clinique du Quartier Latin, Montreal, QC), Joseph Cox (McGill University Health Centre, Montreal, QC), John Gill (Southern Alberta HIV Clinic, Calgary, AB), Shariq Haider (McMaster University Medical Centre – SIS Clinic, Hamilton, ON), Aida Sadr (Native BC Health Center, St Paul's Hospital, Vancouver, BC), Lynn Johnston (QEII Health Science Center for Clinical Research, Halifax, NS), Mark Hull (BC Centre for Excellence in HIV/AIDS, Vancouver, BC), Julio Montaner (St Paul's Hospital, Vancouver, BC), Erica Moodie (McGill University, Montreal, QC), Neora Pick (Oak Tree Clinic, Children's and Women's Health Centre of British Columbia, University of British Columbia, Vancouver, BC), Anita Rachlis (Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON), Danielle Rouleau (Centre Hospitalier de l'Université de Montreal, Montreal, QC), Roger Sandre (Health Sciences North – The HAVEN/Hemophilia Program, Sudbury, ON), Joseph Mark Tyndall (Department of Medicine, Infectious Diseases Division, University of Ottawa, Ottawa ON), Marie-Louise Vachon (Centre Hospitalier Universitaire de Québec, Québec, QC), Steve Sanche (SHARE University of Saskatchewan, Saskatoon, SK), Stewart Skinner (Royal University

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Compliance with Ethical Standards:

Funding: This study was funded by the Canadian Institutes of Health Research (CIHR, MOP-79529) and the CIHR Canadian HIV Trials Network (CTN 264 & CTN 222).

Conflicts of interest: JC has received grants for investigator-initiated clinical projects and consulting fees from Gilead, ViiV Healthcare, and Merck. MBK has received grants for investigator-initiated trials from ViiV Healthcare and Merck, as well as consulting fees from Gilead, ViiV Healthcare, Merck, Bristol-Meyers Squibb, and AbbVie. The remaining authors declare that they have no conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Table 5.1 Descriptive characteristics of the exposure, mediator, outcome, and confounder information among HIV-HCV co-infected individuals with one, two, and three study visits (2012-2015).

Variables	Study visits ^a		
	Visit 1 (N = 666)	Visit 2 (N = 555)	Visit 3 (N = 429)
Values are the number of participants / total with the factor measured ^b			
Injection drug use (IDU): exposure ^c	-	150 / 475 (32%)	-
Unemployed: mediator ^d	-	356 / 458 (78%)	-
Severe food insecurity (FI): outcome ^{c,e}	-	-	109 / 382 (29%)
Socioeconomic confounders			
Average monthly income:	1070 (918, 1400)	-	-
CAD (median [Q1, Q3]) ^c	/ 655		
Unemployed ^d	479 / 617 (78%)	-	-
Education at enrolment	-	-	-
Elementary school or less	137 / 657 (21%)	-	-
High school	354 / 657 (54%)	-	-
College or university	166 / 657 (25%)	-	-
Sociodemographic confounders			
Age: years (median [Q1, Q3]) ^d	48.5 (42.9, 53.3) / 664	48.9 (43.5, 53.9) / 478	-
Male	478 / 656 (73%)	-	-
Ethnicity	-	-	-
White	495 / 657 (75%)	-	-
Aboriginal	124 / 657 (19%)	-	-
Asian, Black, Hispanic, Latino	38 / 657 (6%)	-	-
Province of enrolment	-	-	-
Quebec	276 / 666 (41%)	-	-
British Columbia	225 / 666 (34%)	-	-
Ontario	106 / 666 (16%)	-	-
Other (Alberta, Sask., Nova Scotia) ^f	59 / 666 (9%)	-	-
Homeowner or apartment/room renter ^d	587 / 666 (88%)	428 / 480 (89%)	-
Living situation: living alone ^d	324 / 666 (49%)	224 / 479 (47%)	-
Behavioural confounders			
Non-injection drug use ^c	304 / 625 (49%)	172 / 446 (39%)	-
Cigarette use ^d	474 / 630 (75%)	355 / 475 (75%)	-
Alcohol use ^d	391 / 630 (62%)	281 / 475 (59%)	-
Clinical confounders			
Self-reported anxiety or depression ^{d,g}	324 / 628 (52%)	218 / 474 (46%)	-
Self-perceived health state (0-100): visual analogue scale (median [Q1, Q3]) ^{d,g}	70 (55, 80) / 627	70 (60, 80) / 474	-

^a Through the use of inverse probability of censoring weights, participants with fewer than three visits contributed to estimating the inverse probability of exposure and mediator weights at earlier visits (N = 555 were used in estimating the weights at visit two). However, only participants with all three visits (N = 429) were included in the

outcome model. See Table 5.2 and the Supplementary Material in Section 5.3 for further details.

^b Represents the occurrence of a variable out of the total with that factor measured (e.g., $N = 555 - 475 = 80$ missing observations for IDU at visit two). Missing values are due to item non-response and/or missed visits (75 missed second visits and 47 missed third visits).

^c Reference period: in the past six months.

^d Reference period: currently.

^e Participants with ≥ 6 affirmative responses on the Household Food Security Survey Module (HFSSM) were identified as experiencing severe food insecurity.

^f The provinces of Alberta ($N = 13$), Saskatchewan ($N = 45$), and Nova Scotia ($N = 1$) were grouped due to a small number of participants.

^g Measured as components of the EuroQol-5D instrument.²¹⁰

Table 5.2 Risk ratios quantifying the unadjusted associations, the overall association between injection drug use and severe food insecurity, and the controlled direct effect of injection drug use on severe food insecurity among HIV-HCV co-infected individuals (2012-2015).

Modeled relationship / association	Risk Ratio (95% CI) ^a	Weights for confounding and censoring ^{b,c,d}
Unadjusted IDU-unemployed ($A_{i2} \rightarrow M_{i2}$)	1.25 (1.14-1.38)	IPW_{i2}^C
Unadjusted IDU-severe FI ($A_{i2} \rightarrow Y_{i3}$)	1.85 (1.33-2.56)	$IPW_{i2}^C * IPW_{i3}^C$
Unadjusted unemployed-severe FI ($M_{i2} \rightarrow Y_{i3}$)	1.77 (1.02-3.07)	$IPW_{i2}^C * IPW_{i3}^C$
Adjusted overall IDU-severe FI ($A_{i2} \rightarrow Y_{i3}$)	1.69 (1.15-2.48)	$IPW_{i2}^A * IPW_{i2}^C * IPW_{i3}^C$
Controlled direct effect ($A_{i2} \rightarrow Y_{i3} M_{i2}$)	1.65 (1.08-2.53)	$IPW_{i2}^A * IPW_{i2}^M * IPW_{i2}^C * IPW_{i3}^C$

IDU = injection drug use, FI = food insecurity, CI = confidence interval, IPW = inverse probability weight, A_{i2} = IDU in the six months preceding visit two (N = 555), M_{i2} = current unemployment at visit two (N = 555), Y_{i3} = severe FI in the six months preceding visit three (N = 429)

^a Risk ratios were estimated using marginal structural log-linear models.

^b Unstabilized inverse probability of censoring weights at visits two and three (IPW_{i2}^C and IPW_{i3}^C), stabilized inverse probability of exposure weights at visit two (IPW_{i2}^A), stabilized inverse probability of mediator weights at visit two (IPW_{i2}^M). Asterisks (*) indicate multiplication of the weights.

^c Through the use of inverse probability of censoring weights, participants with fewer than three visits contributed to estimating the inverse probability of exposure and mediator weights at earlier visits (N = 555 were used in estimating the weights at visit two). However, only participants with all three visits (N = 429) were included in the outcome model.

^d Confounders listed in Table 5.1 were used in estimating the exposure and mediator weights. See the Supplementary Material in Section 5.3 for further details.

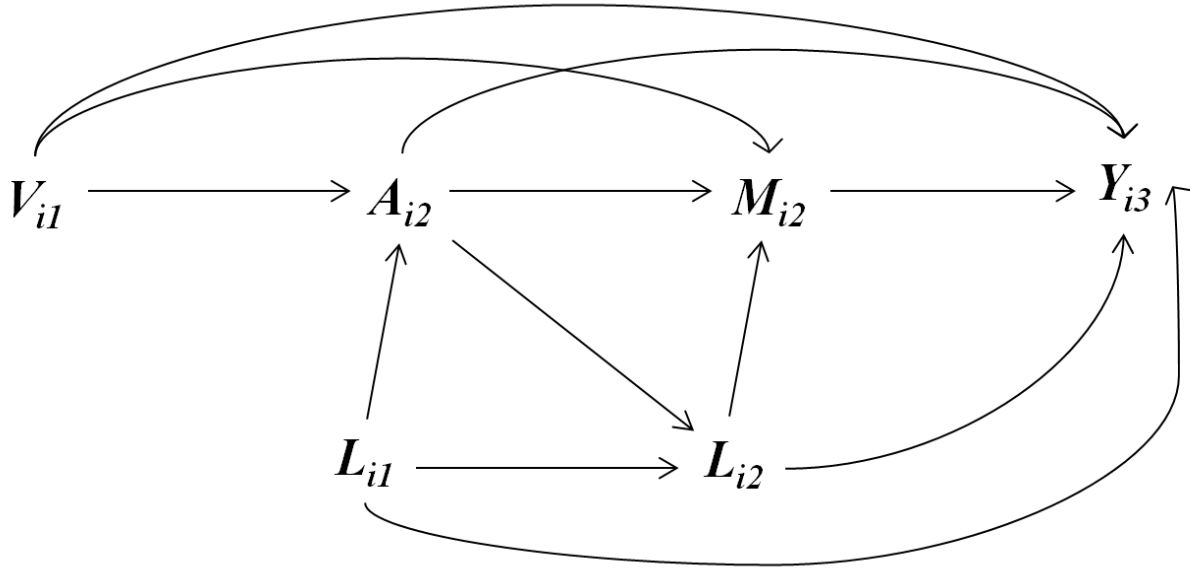


Figure 5.1 Directed acyclic graph of the hypothesized relationship between injection drug use in the six months preceding visit two (A_{i2}), current unemployment at visit two (M_{i2}), and severe food insecurity in the six months preceding visit three (Y_{i3}). V_{i1} represents time-invariant confounders (education at enrolment, sex, ethnicity, and province of enrolment) and L_{i1} and L_{i2} represent time-varying exposure-outcome and mediator-outcome confounders (age, housing situation, living situation, non-injection drug use, cigarette use, alcohol use, anxiety or depression, and self-perceived health state) measured at visits one and two, respectively. Average monthly income and employment status, measured at visit one, were also included as exposure-outcome confounders (not depicted).

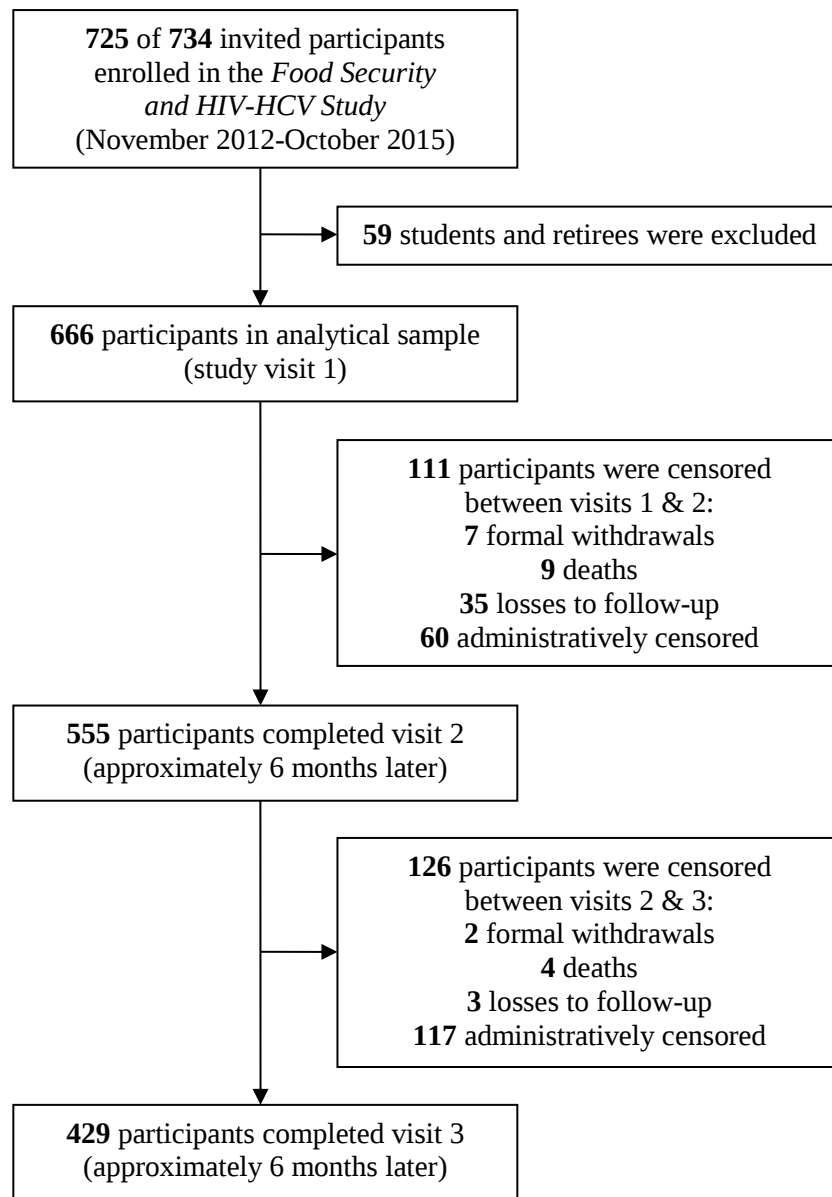


Figure 5.2 Study participant flow diagram.

5.3 Appendix to Manuscript 2

Electronic Supplementary Material: McLinden T, Moodie EEM, Hamelin A-M, et al.

Injection Drug Use, Unemployment, and Severe Food Insecurity Among HIV-HCV Co-Infected Individuals: A Mediation Analysis. AIDS Behav. Accepted July 2017.

Stabilized inverse probability of exposure weights (IPW_{i2}^A) were used to adjust for exposure-outcome confounders and stabilized inverse probability of mediator weights (IPW_{i2}^M) were used to adjust for mediator-outcome confounders for each participant i at study visit $j = 2$ [1, 2]:

$$IPW_{i2}^A = \frac{Pr(A = a_{i2} | C_{i2} = 0)}{Pr(A = a_{i2} | L = l_{i1}, V = v_{i1}, C_{i2} = 0)}$$

$$IPW_{i2}^M = \frac{Pr(M = m_{i2} | A = a_{i2}, C_{i2} = 0)}{Pr(M = m_{i2} | A = a_{i2}, L = l_{i2}, V = v_{i1}, C_{i2} = 0)}$$

The probabilities in the numerators and the denominators were estimated using logistic regression and these estimates were conditional on being observed at the second visit ($C_{i2} = 0$). IPW_{i2}^A and IPW_{i2}^M were used to create a weighted sample or pseudo-population in which A_{i2} was no longer associated with V_{i1} and L_{i1} and M_{i2} was no longer associated with V_{i1} and L_{i2} . In this scenario, there exists no confounding by these measured factors (listed in Table 5.1); this was achieved without blocking any of the controlled direct effect (CDE) of A_{i2} on Y_{i3} [1, 2]. Average monthly income and employment status, measured at the first visit, were also included as exposure-outcome confounders (in addition to V_{i1} and L_{i1}). Therefore, while L_{i1} and L_{i2} included the same set of time-varying confounders, confounders of the exposure-outcome and mediator-

outcome relationships can differ. Monthly income and employment status were not included in L_{ij} as they were not considered to be mediator-outcome confounders.

Additionally, to address potential selection bias due to informative censoring, unstabilized inverse probability of censoring weights (IPW_{i2}^C and IPW_{i3}^C) for each participant i at study visits $j = 2$ and 3 were used [3]. Specifically, the observed (uncensored) participants were up-weighted at each visit to create a pseudo-population that, when analyzed, addressed informative censoring. Predictors of censoring (X_{ij}) used in estimating the IPW_{ij}^C included: IDU in the past six months, current unemployment, education at enrolment, current age, sex, ethnicity, current housing situation, current living situation, and current self-perceived health state. These weights required estimating the probability of being observed using logistic regression:

$$IPW_{i2}^C = \frac{1}{1 - Pr(C_{i2} = 1 \mid X = x_{i1})}$$

$$IPW_{i3}^C = \frac{1}{1 - Pr(C_{i3} = 1 \mid X = x_{i2}, C_{i2} = 0)}$$

Unstabilized censoring weights were used to avoid having to directly condition on additional stabilizing factors in the outcome model. Through the use of censoring weights, participants with fewer than three visits contributed to estimating the inverse probability of exposure and mediator weights at earlier visits ($N = 555$ were used in estimating the weights at visit two). However, only participants with all three visits ($N = 429$) were included in the outcome model.

Each of the weights were multiplied together ($IPW^{A_{i2}} * IPW^{M_{i2}} * IPW^{C_{i2}} * IPW^{C_{i3}}$) to create a single IPW that was used in the outcome model to estimate a CDE of A_{i2} on Y_{i3} :

$$\log[Pr(Y_{i3} = 1 \mid A = a_{i2}, M = m_{i2}, C_{i3} = 0)] = \beta_0 + \beta_1 A + \beta_2 M$$

This is a weighted marginal structural log-linear model, where the coefficient e^{β_1} is a risk ratio (RR) estimate of the CDE of IDU on severe FI through all pathways ($A_{i2} \rightarrow Y_{i3}$ and $A_{i2} \rightarrow L_{i2} \rightarrow Y_{i3}$) except that of unemployment (M_{i2}), provided that the measured confounders used to estimate the $IPW^{A_{i2}}$ and $IPW^{M_{i2}}$ sufficed to control for confounding. In the weighted sample or pseudo-population, one can regress the outcome on the exposure and mediator using a conventional log-linear regression model that does not directly include the confounders as covariates. In this case, fitting a weighted model in the study population is equivalent to fitting a model in the pseudo-population in which there is no confounding of either the exposure-outcome or mediator-outcome relationships [3]. Lastly, through weighting by $IPW^{C_{i2}}$ and $IPW^{C_{i3}}$, this estimate is applicable to a full-population with no censoring during follow-up.

The overall association was quantified by estimating the parameters of a similar marginal structural model to that shown, in which the mediator ($\beta_2 M$) was not included and $IPW^{A_{i2}} * IPW^{C_{i2}} * IPW^{C_{i3}}$ (excluding $IPW^{M_{i2}}$) was used to adjust for exposure-outcome confounding only. Univariate marginal structural models were used to estimate the unadjusted associations between: $A_{i2} \rightarrow M_{i2}$, $A_{i2} \rightarrow Y_{i3}$, and $M_{i2} \rightarrow Y_{i3}$. Although we did not adjust for confounding in these models, we did address potential selection bias using $IPW^{C_{ij}}$ (as outlined in Table 5.2).

To estimate the parameters of the marginal structural models, three identifiability assumptions were required: consistency, conditional exchangeability, and positivity [3]. To

describe these assumptions, a potential outcomes (POs) framework is helpful. At the second visit, there were two possible exposure values for each participant: none vs. any IDU (in the past six months). At the second visit, there were also three possible mediator values for each participant: employed vs. unemployed (current). Therefore, there were four POs at the third visit, corresponding to each of the possible patterns of the exposure and the mediator. However, only one PO can be observed for a given participant and the other POs are counterfactual outcomes. Under the consistency assumption, the PO is equal to the observed outcome given the observed exposure-mediator combination. Conditional exchangeability states that the POs are independent of the exposure and the mediator, conditional on measured confounders. The positivity assumption states that there were participants who were exposed to each level of the exposure and the mediator in all of the covariate strata. The exchangeability and positivity assumptions are also required for the censoring weights. To explore potential violations of the positivity assumption, we tabulated the mean and minimum-maximum values of each of the individual and multiplied weights. Across all 30 imputed datasets, the means of the weights was approximately 1.00 and no extreme (large) weights were observed.

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1. VanderWeele TJ. Marginal structural models for the estimation of direct and indirect effects. *Epidemiology*. 2009;20(1):18-26.
2. VanderWeele TJ. *Explanation in Causal Inference: Methods for Mediation and Interaction*. Oxford University Press;2015.
3. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-64.

Chapter 6: Propensity score matching analysis of interventions (Manuscript 3)

6.1 Preface to Manuscript 3

In Manuscript 2 (Chapter 5), a mediation analysis indicated that there is an overall association between IDU and severe FI and provided evidence that the association is primarily through pathways that are not mediated by unemployment. While further research is required to understand the mechanisms linking IDU and severe FI, the strong overall association provided further evidence that reductions in IDU could mitigate severe FI.

Manuscript 3 was motivated by the findings in Manuscripts 1 and 2 which suggested that substance use interventions aimed at IDU may reduce the likelihood of FI, particularly severe FI, in this population. While the previous manuscripts focused on IDU and the use of any drug type, the injection of opioids is known to be common among co-infected individuals.^{226,227} I hypothesized that opioid injection was responsible, in part, for the associations between IDU and severe FI. As such, Manuscript 3 examined whether methadone treatment for opioid dependence is associated with a lower risk of severe FI.

The three manuscripts included in this thesis built on each other to better understand associations, mechanisms, and interventions related to IDU and FI. The examination of an IDU-FI relationship motivated the study of mechanisms. Etiologically, it helped to understand mechanisms related to IDU prior to examining the impact of interventions on IDU to reduce severe FI. In terms of informing context-specific strategies^{25,26} to reduce severe FI, Manuscript 3, related to methadone treatment, is of paramount importance in this HIV-HCV co-infected population.

6.2 Manuscript 3: Methadone treatment, severe food insecurity, and HIV-HCV co-infection: a propensity score matching analysis

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This manuscript was published in *Drug and Alcohol Dependence* in December 2017.²²⁸

Keywords: methadone treatment; severe food insecurity; HIV; hepatitis C virus; propensity score matching

Abstract:

Background: Severe food insecurity (FI) is common among individuals living with HIV-hepatitis C virus (HCV) co-infection. We hypothesize that the injection of opioids is partly responsible for the association between injection drug use and severe FI. Therefore, this analysis examines whether methadone maintenance treatment for opioid dependence is associated with a lower risk of severe FI.

Methods: We used biannual data from the Canadian Co-infection Cohort (N = 608, 2012-2015). Methadone treatment (exposure) was self-reported and severe FI (outcome) was measured using the Household Food Security Survey Module. To quantify the association between methadone treatment and severe FI, we estimated an average treatment effect on the treated (marginal risk difference [RD]) using propensity score matching.

Results: Among participants, 25% experienced severe FI in the six months preceding the first time-point in the analytical sample and 5% concurrently reported receiving methadone treatment. Injection of opioids in the six months preceding the treatment and outcome measurements was much higher among those who received methadone treatment (39% vs. 12%). Among the treated participants, 97% had injected opioids in their lifetimes. After propensity score matching, the average risk of experiencing severe FI is 12.3 percentage-points lower among those receiving methadone treatment, compared to those who are not receiving treatment (marginal RD = -0.123, 95% CI = -0.230, -0.015).

Conclusions: After adjustment for socioeconomic, sociodemographic, behavioural, and clinical confounders, methadone treatment is associated with a lower risk of severe FI. This finding suggests that methadone treatment may mitigate severe FI in this vulnerable subset of the HIV-positive population.

Introduction:

Food insecurity (FI) is highly prevalent in HIV-hepatitis C virus (HCV) co-infected populations.⁴⁸ FI is measured by self-reports of uncertain or inadequate food access due to limited financial resources¹⁹ and, by definition, it exists “whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain.”¹⁸ In our previous study of 525 HIV-HCV co-infected individuals in Canada (2012-2014), 59% of participants experienced FI.⁴⁸ Among this group, the majority experienced severe FI, indicating disrupted eating patterns, reduced food intake, and the physical sensation of hunger.^{21,22}

In HIV-positive populations, 20% of individuals are estimated to be HIV-HCV co-infected^{6,7} where injection drug use (IDU) is the primary risk factor for HCV co-infection.⁷ In HIV-related studies, researchers have documented associations between illicit drug use,^{38,40,41} including IDU,³⁷ and FI. Our previous analyses have also quantified associations between IDU and FI,⁴⁸ particularly severe FI,²¹⁷ suggesting that reductions in IDU may mitigate severe FI in co-infected populations. While our previous studies have focused on IDU and the use of any drug type when quantifying associations between drug use and FI,^{48,217} the injection of opioids is known to be common among co-infected individuals.^{226,227} We hypothesize that opioid injection is responsible, in part, for the association between IDU and severe FI.²¹⁷

Given that FI is associated with sub-optimal HIV treatment adherence,³⁵ incomplete HIV viral load suppression,^{33,34} and lower CD4 cell counts,^{32,33} there is an interest in examining whether existing interventions to reduce IDU are associated with a lower risk of experiencing severe FI. Methadone maintenance treatment, a substance use intervention for individuals who are dependent on opioids, is a form of substitution therapy.⁴⁵ Methadone is a synthetic opioid

that works by alleviating the symptoms of withdrawal from other opioids (e.g., heroin, morphine, oxycodone, and fentanyl)^{45,159} and it is known to decrease the illicit use of opioids, regardless of the route of administration.^{46,47} In this study, we analyzed longitudinal cohort data to examine whether methadone treatment is associated with a lower risk of severe FI among individuals living with HIV-HCV co-infection in Canada.

Methods:

Study population

The Canadian Co-infection Cohort (CCC) is a prospective study of HIV-HCV co-infected individuals who receive care from HIV clinics across Canada. Details of the CCC have been described elsewhere.¹⁷² CCC participants must be at least 16 years of age with documented HIV infection and serologic evidence of HCV exposure. All eligible individuals were invited to participate and data collection occurred approximately every six months.

From November 2012 to October 2015, the Food Security and HIV-HCV Study (FS Study)⁴⁸ was implemented and biannual data collection related to FI was integrated into CCC study visits at 17 of the 19 CCC clinics in six provinces. There was staggered enrolment into the FS Study of the CCC and the date of enrolment dictated how many visits could potentially occur for a given participant prior to October 2015. The CCC and FS Study were approved by the McGill University Health Centre and the research ethics boards of the participating institutions.¹⁷²

Measures

Methadone treatment (exposure) and severe food insecurity (outcome)

Methadone maintenance treatment in the past six months was self-reported by all participants, regardless of their substance use, on a questionnaire at each visit. The exposure

variable was a binary indicator of methadone treatment (no treatment vs. methadone treatment). Severe FI in the past six months was measured using the ten-item adult scale of Health Canada's Household Food Security Survey Module (HFSSM).¹⁹ Participants with ≥ 6 affirmative responses on the HFSSM were identified as experiencing severe FI. We used this dichotomization to define a binary outcome (not experiencing severe FI vs. experiencing severe FI). Details of the HFSSM have been described in a previous FS Study publication.⁴⁸

Confounding factors

All confounders were selected *a priori* based on their hypothesized association with methadone treatment and severe FI^{28,42,48} and were self-reported by participants on biannual questionnaires. Given that the methadone treatment and severe FI measures referred to overlapping experiences in the six months preceding each visit, temporal-ordering of the confounders was established. At each visit, the confounders were lagged by one visit to reflect experiences prior to the concurrent treatment and outcome measures.

Socioeconomic confounders included: employment (unemployed vs. employed [part-time or full-time work]), average monthly income (before taxes; Canadian dollars [CAD]), and education at enrolment (elementary school or less vs. high school vs. college or university). Sociodemographic confounders included: age, sex (male vs. female), Aboriginal ethnicity (no vs. yes), province of enrolment (Quebec vs. British Columbia vs. Ontario vs. other [Alberta, Saskatchewan, Nova Scotia]), housing situation (homeowner, apartment/room renter, care facility vs. no fixed address or temporary situation), and living situation (alone vs. with others [no children] vs. with children). Behavioural confounders included: recent non-injection of opioids (none vs. use of opioids via sniffing, smoking, eating, drinking, or transdermally), recent injection of opioids (none vs. injection of opioids), lifetime injection of opioids (none vs.

injection of opioids), any recent use of non-opioids (none vs. non-injection/injection of non-opioids), lifetime injection of non-opioids (none vs. injection of non-opioids), frequency of IDU (none vs. non-weekly IDU vs. weekly IDU), cigarette use (no vs. yes), and alcohol use (no vs. yes). Clinical confounders included: self-reported anxiety or depression (no vs. yes) and self-perceived health state (visual analogue scale, 0 = worst imaginable health state to 100 = best imaginable health state) as per the EuroQol-5D instrument.²¹⁰

Data analysis

Our analyses used exposure and outcome data from visits 2-3-4-5 and lagged confounder data from visits 1-2-3-4. Summary statistics of the total sample and summaries stratified by methadone treatment were used to describe the participants at the first time-point in the analytical sample. Subsequently, multiple imputation by chained equations was used to impute missing observations using ten imputed datasets and 100 iterations. Multiple imputation requires the non-verifiable assumption that the data are “missing at random”¹⁷⁹; the unobserved data cannot contain any additional information about the missing data mechanism, conditional upon the observed data. We are confident that the comprehensive list of variables included in the imputation models (i.e., the exposure, outcome, all confounders, and an indicator for study visit) were sufficient to meet this assumption. To ensure uniform timing of the lagged confounders with methadone treatment and severe FI, multiple imputation was also used to impute time-varying variables at missed study visits (i.e., visits that did not occur approximately every six months). To distinguish a missed visit from censoring, a missed visit must have occurred prior to a visit later in time.

To quantify the association between methadone treatment and severe FI, we estimated an average treatment effect on the treated (ATT).^{201,229} In this study, an ATT was estimated using

propensity score matching (PSM), where PSM matches on a single continuous covariate: the estimated treatment probability or propensity score. Given the longitudinal nature of our study, we used PSM to identify five untreated participants study visits to serve as the average unobserved potential outcome for a single treated participant study visit (1:5 matching of visits with replacement). The propensity scores were estimated using logistic regression where all confounders were included as independent variables. Subsequently, the estimated within-match differences in the risk of experiencing severe FI, among those who in fact received methadone treatment, were averaged across all matches to estimate an ATT²⁰¹; the ATT corresponds to a marginal risk difference (RD). PSM was performed in each of the ten imputed datasets where the estimates were combined using Rubin's method.¹⁸¹ For the marginal RD estimate, robust Abadie-Imbens standard errors were used to account for the two-step estimation process: estimation of the propensity scores which were then used in the PSM to estimate an ATT.²⁰¹

To assess covariate balance, the average and maximum absolute standardized mean difference (SMD) for each confounder across all ten imputed datasets were calculated before and after matching. After matching, sufficient balance was defined as an average absolute SMD of less than 0.10.²⁰⁸ Data analyses were performed using Stata 14 (College Station, TX: StataCorp LP. 2015).

Results:

Between November 2012 and October 2015, 725 of 734 invited CCC participants enrolled in the FS Study. Of the 725 participants, 608 participants completed two or more visits. Following variable lagging, which requires a minimum of two consecutive visits, 117 participants who had a single visit were dropped from the sample. Among the 608 included participants, 475, 268, and 37 participants completed a second, third, and fourth visit,

respectively, for a total of 1,388 observations during the FS Study's duration of approximately three years. During follow-up, 4 participants formally withdrew from the study, 14 died, and 3 were lost to follow-up after missing three consecutive visits. Furthermore, there were 86 missed second visits, 53 missed third visits, and 11 missed fourth visits.

As shown in Table 6.1, 25% of participants experienced severe FI in the six months preceding the first time-point in the analytical sample and 5% concurrently reported receiving methadone treatment. Regarding the drug use-related confounders, which are likely the strongest confounders of the methadone treatment-severe FI relationship, the prevalence of non-injection of opioids in the six months preceding the treatment and outcome measurements was similar among the treated and untreated groups (12% vs. 13%). However, the injection of opioids was much higher among those who received treatment (39% vs. 12%). Moreover, 97% of the treated participants had injected opioids in their lifetimes. Recent and lifetime use of non-opioids was also highly prevalent, particularly among participants receiving treatment.

Across all visits, the following opioids were used by non-injection: heroin, morphine, oxycodone, meperidine, codeine in combination with acetaminophen, hydromorphone, and oxycodone in combination with acetaminophen. In addition, the following opioids were used by injection: heroin, heroin in combination with cocaine, morphine, oxycodone, hydromorphone, oxycodone in combination with acetaminophen, and fentanyl.

To assess covariate balance in the unmatched and matched samples, Supplementary Table 6.1 displays the average and maximum absolute SMDs of confounding factors before and after completing 1:5 PSM of treated and untreated study visits in each of the imputed datasets. With the exception of college or university education at enrolment (average absolute SMD =

0.115), each of the average absolute SMDs were less than 0.10 after PSM, suggesting that the measured confounders were sufficiently balanced.²⁰⁸

Table 6.2 displays the marginal RD comparing the risk of severe FI at visits where a participant received methadone treatment matched with five visits where no treatment was received. This estimate is an average of the within-match differences in the risk of experiencing severe FI at treated visits compared to visits where no treatment was received. The estimated ATT (marginal RD = -0.123, 95% CI = -0.230, -0.015) indicates that the average risk of experiencing severe FI is 12.3 percentage-points lower for those receiving methadone treatment, compared to those who are not receiving treatment.

Discussion:

HIV-related studies have documented associations between illicit drug use,^{38,40,41} including IDU,³⁷ and FI, particularly severe FI.²¹⁷ The authors of these studies, including our own research group, have concluded that reductions in IDU may mitigate FI, especially severe FI, in HIV-positive and HIV-HCV co-infected populations. Acknowledging that the injection of opioids is common among co-infected individuals,^{226,227} we hypothesized that opioid injection is responsible, in part, for the associations between IDU and severe FI.²¹⁷ Therefore, we examined whether methadone maintenance treatment, a substance use intervention for individuals who are dependent on opioids,⁴⁵ is associated with a lower risk of severe FI.

After completing a PSM analysis, we quantified an association which indicates that methadone treatment is associated with a lower likelihood of experiencing severe FI. Our work provides evidence that an existing intervention for individuals who are dependent on opioids may mitigate the most severe form of FI; this may also have benefits for HIV treatment adherence,³⁵ HIV viral load suppression,^{33,34} and CD4 cell counts.^{32,33} While acknowledging that

our observational analysis cannot rule out confounding, it seems unlikely that methadone treatment would impact severe FI if there was no link between illicit drug use, including IDU, and severe FI. Therefore, this work lends further support to the existing evidence which suggests that severe FI is a consequence of IDU.²¹⁷

This work was largely motivated by our prior study that documented an association between any IDU and severe FI.²¹⁷ However, methadone is only indicated for the treatment of opioid dependence and it is not restricted to the injection route of administration. Therefore, we have examined the impact of a treatment that is only applicable to a subset of those who are engaged in IDU. This is important because the use of non-opioids is more common than the use of opioids in our sample. Given that any IDU was the exposure in our previous analyses,^{48,217} it is likely that the injection of non-opioids is also a substantial contributor to the IDU-severe FI relationship among co-infected individuals. As such, additional interventions for non-opioid drug dependence are likely necessary to further mitigate the increased risk of severe FI associated with IDU. Furthermore, some participants receiving methadone were using opioids but not by the injection route of administration. While the FI-related evidence in HIV-HCV co-infected populations is primarily based on the injection of any drugs,^{48,217} the methadone treatment-severe FI association quantified herein may be partially explained by the treatments impact on non-injection opioid use. These comments highlight a need to further examine specific drug types and routes of administration when examining risk factors for FI and potential interventions.

The mechanisms through which IDU is associated with severe FI have not been extensively studied. Therefore, it is difficult to explain how methadone treatment may act to reduce severe FI. For example, our previous study in this co-infected population found that the association between IDU and severe FI did not appear to be mediated, in large part, by

unemployment.²¹⁷ Another compelling mechanism is that of competing demands on financial resources and the prioritization of the purchase of drugs instead of food.^{42,146,222,230} In this scenario, purchases of injection drugs, including opioids, may compete with food to an extent which results in severe FI. To our knowledge, no study has quantitatively examined such a mechanism.

In this study, we documented a small proportion of HIV-HCV co-infected individuals who were receiving methadone treatment. Given the known efficacy of methadone to decrease the illicit use of opioids,^{46,47} we suspect that many participants receiving methadone treatment were also able to reduce or stop their purchasing of opioids. As such, these individuals would have additional financial resources for purchasing food. As noted, we could not examine this mechanism as we do not have data on drug-related expenditures. However, by synthesizing the existing literature, including our mediation analysis,²¹⁷ the quantified association in this study may be explained, in part, by this pathway.

In addition to the examination of other interventions on illicit drug use (e.g., counseling) and their impacts on FI in an observational setting, we recommend that future randomized controlled trials of substance use interventions include FI as a measured outcome variable. It would be informative if a trial were able to corroborate and build upon our findings regarding methadone treatment and its association with a lower risk of severe FI among individuals living with HIV-HCV co-infection. Qualitative studies would also be helpful to further explain the sequence of events that underlie the methadone treatment-severe FI relationship.

Strengths and limitations

To our knowledge, our longitudinal study is the first to examine whether methadone treatment is associated with a lower risk of severe FI among individuals living with HIV-HCV

co-infection in Canada. Our work benefited from the use of PSM, where participants with dissimilar covariate values may nevertheless have similar propensity scores, facilitating the matching process.¹⁹⁰ In addition, PSM allowed for the estimation of an ATT.²⁰² The importance of estimating an ATT becomes apparent when acknowledging that methadone is only indicated for the treatment of opioid dependence. Participants who have never used opioids, or those who have not recently used them, would have a low or potentially zero estimated probability of receiving the treatment. Unlike the estimation of an average treatment effect, finding matches for the untreated participants with a low or zero probability of receiving treatment is not required when estimating an ATT.²⁰¹

Regarding weaknesses of our work, it is known that matching on more distant neighbours can reduce the variance of an estimator at the cost of an increase in confounding bias.²³¹ Given the small number of participants receiving methadone treatment (e.g., 5% of participants were treated at the first time-point in the analytical sample), we completed 1:5 matching. We found that matching with the five nearest propensity scores had a small impact on the SMDs in the matched sample and we did not observe any appreciable reductions in variance when using more than five matches. Furthermore, we did not enforce a caliper on our propensity score matches as we did not observe any notable imbalances without the use of a caliper; none of the within-match propensity scores differed by more than 0.24.

Despite the use of PSM, it is not possible to verify that our observational study is devoid of unmeasured or imperfectly measured confounders. Therefore, our estimate reflects an association rather than a causal effect. However, given the richness of the FS Study data, particularly with respect to socioeconomic and sociodemographic factors, we are confident in our approaches to minimize confounding bias. Furthermore, to achieve conditional

exchangeability between treated and untreated participants, we adjusted for factors (e.g., province of enrolment) that may act as proxies for unmeasured confounders.

In addition, there was a trade-off to ensuring uniform temporal-ordering by having to address larger amounts of missing data. Given that there was biannual data collection, it was imperative to ensure that participants' data were collected approximately every six months. In a multi-site cohort study, missed visits are inevitable. For example, prior to variable lagging, there were 86 missed second visits. For these 86 participants with a missed second visit, which is now represented at the first time-point in the analytical sample for the treatment and outcome (Table 6.1), methadone treatment and severe FI data were not available and had to be imputed.

It must be also noted that after lagging the confounder data by one study visit, we examined the relationship between methadone treatment and severe FI during overlapping six-month periods of time. While we are not aware of a substantive rationale or clinical guidelines suggesting that the experience of severe FI is an indication for methadone treatment, our analysis does not exclude the possibility of a bi-directional relationship, wherein some of the quantified association may be attributable to severe FI's potential impact on the receipt of treatment. Notably, we did not have sufficient follow-up to complete an analysis that involved the lagging of confounders by two visits. This temporal-ordering would have been necessary when quantifying an association between methadone treatment in the six-month period preceding the severe FI measurement.

Lastly, it is understood that there is no universal definition of a methadone maintenance treatment program.^{46,47} While the common feature is the use of methadone as a substitution therapy, treatment components and policies vary within Canada. As noted by the Government of Canada,⁴⁵ a comprehensive approach to methadone treatment generally includes a number of

components, such as: methadone dose, medical care, other substance use treatments, counseling, mental health support, and linkage to community-based supports. Given the observational nature of our study and the fact that the receipt of methadone treatment was self-reported by participants in multiple provinces, we were unable to determine what components of the treatment program were used by individual participants. Therefore, we cannot necessarily attribute the entire estimated effect of methadone treatment on severe FI to methadone itself, nor do we have information on the dose of methadone received.

Conclusions:

Our findings indicate that methadone maintenance treatment is associated with a lower likelihood of experiencing severe FI, a potential consequence of IDU,²¹⁷ in this HIV-HCV co-infected population. When estimating an ATT, the average risk of experiencing severe FI is 12.3 percentage-points lower among those receiving methadone treatment, compared to those who are not receiving treatment, after adjustment for socioeconomic, sociodemographic, behavioural, and clinical confounders through PSM. Therefore, methadone treatment may mitigate severe FI in this vulnerable subset of the HIV-positive population.

Acknowledgements:

TM is supported by a CANOC Centre Doctoral Scholarship Award, a joint program of CANOC and the CIHR Canadian HIV Trials Network (CTN 242). EEMM is supported by a Chercheur-Boursier (Junior 2) Career Award from the Fonds de recherche du Québec-Santé (FRQ-S). MBK is supported by a Chercheurs Nationaux Career Award from the FRQ-S.

The authors thank Jennifer Kocilowicz and Leo Wong for study coordination. The Canadian Co-infection Cohort investigators (CTN 222) are: Drs. Jeff Cohen (Windsor Regional Hospital Metropolitan Campus, Windsor, ON), Brian Conway (PENDER Downtown Infectious Diseases Clinic, Vancouver, BC), Curtis Cooper (The Ottawa Hospital Research Institute, Ottawa, ON), Pierre Côté (Clinique du Quartier Latin, Montreal, QC), Joseph Cox (McGill University Health Centre, Montreal, QC), John Gill (Southern Alberta HIV Clinic, Calgary, AB), Shariq Haider (McMaster University Medical Centre – SIS Clinic, Hamilton, ON), Aida Sadr (Native BC Health Center, St Paul's Hospital, Vancouver, BC), Lynn Johnston (QEII Health Science Center for Clinical Research, Halifax, NS), Mark Hull (BC Centre for Excellence in HIV/AIDS, Vancouver, BC), Julio Montaner (St Paul's Hospital, Vancouver, BC), Erica Moodie (McGill University, Montreal, QC), Neora Pick (Oak Tree Clinic, Children's and Women's Health Centre of British Columbia, University of British Columbia, Vancouver, BC), Anita Rachlis (Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON), Danielle Rouleau (Centre Hospitalier de l'Université de Montreal, Montreal, QC), Roger Sandre (Health Sciences North – The HAVEN/Hemophilia Program, Sudbury, ON), Joseph Mark Tyndall (Department of Medicine, Infectious Diseases Division, University of Ottawa, Ottawa ON), Marie-Louise Vachon (Centre Hospitalier Universitaire de Québec, Québec, QC), Steve Sanche (SHARE University of Saskatchewan, Saskatoon, SK), Stewart Skinner (Royal University

Hospital & Westside Community Clinic, University of Saskatchewan, Saskatoon, SK), and David Wong (University Health Network, Toronto, ON).

Role of Funding Source: This study was funded by the Canadian Institutes of Health Research (CIHR, MOP-79529) and the CIHR Canadian HIV Trials Network (CTN 264 & CTN 222). The funders had no role in the study design, in the collection, analysis, and interpretation of data, in the writing of the manuscript, or in the decision to submit the article for publication.

Contributors: TM, EEMM, AMH, MBK, and JC participated in the design of the study. TM managed the data, carried out the statistical methodology, interpreted the results, and drafted the manuscript. CC, MBK, and JC were involved in data collection. TM, EEMM, AMH, SH, CR, SLW, SBR, CC, MBK, and JC reviewed and contributed to drafts of the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest: JC has received grants for investigator-initiated clinical projects and consulting fees from Gilead, ViiV Healthcare, and Merck. MBK has received grants for investigator-initiated trials from ViiV Healthcare and Merck, as well as consulting fees from Gilead, ViiV Healthcare, Merck, Bristol-Meyers Squibb, and AbbVie. The remaining authors declare that they have no conflicts of interest.

Table 6.1 Descriptive characteristics of 608 HIV-HCV co-infected individuals at the first time-point in the analytical sample, stratified by methadone treatment status (2012-2015).

Variables	Total N = 608	Methadone treatment N = 33 (5%)	No treatment N = 482 (79%)	Missing ^a N = 93 (15%)
Outcome	Values are the number of participants (%) ^b or median (Q1, Q3)			
Severe food insecurity ^{c,d}	155 (25%)	8 (24%)	147 (30%)	0 (0%)
Missing	86 of 608	0 of 33	0 of 482	86 of 93
Socioeconomic confounders				
Employed ^e	115 (19%)	6 (18%)	93 (19%)	16 (17%)
Missing	45 of 608	4 of 33	33 of 482	8 of 93
Average monthly income (CAD) ^d	1077 (918, 1500)	1158 (1100, 1400)	1032 (918, 1500)	1035 (918, 1400)
Missing	9 of 608	0 of 33	9 of 482	0 of 93
Education at enrolment	-	-	-	-
Elementary school or less	116 (19%)	13 (39%)	86 (18%)	17 (18%)
High school	327 (54%)	14 (42%)	261 (54%)	52 (56%)
College or university	156 (26%)	6 (18%)	127 (26%)	23 (25%)
Missing	9 of 608	0 of 33	8 of 482	1 of 93
Sociodemographic confounders				
Age: years ^e	48.8 (43.4, 54.0)	45.2 (38.8, 50.9)	48.7 (43.8, 53.9)	50.4 (45.0, 56.4)
Missing	2 of 608	0 of 33	2 of 482	0 of 93
Female	151 (25%)	21 (64%)	109 (23%)	21 (23%)
Missing	10 of 608	1 of 33	9 of 482	0 of 93
Aboriginal	107 (18%)	13 (39%)	85 (18%)	9 (10%)
Missing	9 of 608	0 of 33	7 of 482	2 of 93
Province of enrolment	-	-	-	-
Quebec	258 (42%)	5 (15%)	217 (45%)	36 (39%)
British Columbia	192 (32%)	19 (58%)	136 (28%)	37 (40%)
Ontario	112 (18%)	6 (18%)	89 (18%)	17 (18%)
Other (AB, SK, NS) ^f	46 (8%)	3 (9%)	40 (8%)	3 (3%)
No fixed address or temporary housing ^e	61 (10%)	4 (12%)	49 (10%)	8 (9%)
Living situation ^e	-	-	-	-
Alone	295 (49%)	17 (52%)	233 (48%)	45 (48%)
With others (no children)	266 (44%)	15 (45%)	209 (43%)	42 (45%)
With children	47 (8%)	1 (3%)	40 (8%)	6 (6%)
Behavioural confounders				
Non-injection of opioids ^d	86 (14%)	4 (12%)	64 (13%)	18 (19%)
Injection of opioids ^d	83 (14%)	13 (39%)	60 (12%)	10 (11%)
Missing	32 of 608	4 of 33	23 of 482	5 of 93
Injection of opioids (lifetime)	336 (55%)	32 (97%)	255 (53%)	49 (53%)
Any use of non-opioids ^d	284 (47%)	24 (73%)	223 (46%)	37 (40%)
Missing	31 of 608	4 of 33	22 of 482	5 of 93
Injection of non-opioids (lifetime)	479 (79%)	32 (97%)	377 (78%)	70 (75%)
Frequency of injection drug use	-	-	-	-

Non-weekly (past month)	70 (12%)	7 (21%)	54 (11%)	9 (10%)
Weekly (past month)	75 (12%)	11 (33%)	54 (11%)	10 (11%)
Missing	68 of 608	5 of 33	52 of 482	11 of 93
Cigarette use ^d	429 (71%)	26 (79%)	341 (71%)	62 (67%)
Missing	34 of 608	4 of 33	24 of 482	6 of 93
Alcohol use ^d	357 (59%)	14 (42%)	292 (61%)	51 (55%)
Missing	33 of 608	4 of 33	23 of 482	6 of 93
Clinical confounders				
Anxiety or depression ^{e,g}	282 (46%)	11 (33%)	226 (47%)	45 (48%)
Missing	34 of 608	4 of 33	24 of 482	6 of 93
Self-perceived health state (0-100), visual analogue scale ^{e,g}	70 (60, 80)	70 (60, 80)	70 (55, 80)	70 (55, 80)
Missing	35 of 608	4 of 33	24 of 482	7 of 93

^a The first time-point in the analytical sample is represented at visit one for the confounders and visit two for the treatment and outcome. Therefore, missing values at the first time-point are due to item non-response for the confounders (as the first visit could not be missed) while missing data for the treatment and outcome were due to missed second visits (86 missed second visits prior to variable lagging) as well as item non-response.

^b Percentages are the number of participants divided by the number of participants listed at the top of each column (e.g., prevalence of severe food insecurity in total sample at the first time-point: 155 / 608 = 25%). Percentages may not add to 100 due to missing data and/or rounding.

^c Participants with ≥ 6 affirmative responses on the Household Food Security Survey Module (HFSSM) were identified as experiencing severe food insecurity.

^d Reference period: in the past six months.

^e Reference period: currently.

^f The provinces of Alberta (AB, N = 11), Saskatchewan (SK, N = 34), and Nova Scotia (NS, N = 1) were grouped due to a small number of participants.

^g Measured as components of the EuroQol-5D instrument.²¹⁰

Table 6.2 Marginal risk difference quantifying the association between methadone treatment and severe food insecurity after 1:5 propensity score matching.

Average treatment effect on the treated (ATT)	Marginal risk difference ^a	Robust standard error ^b	95% confidence interval
No treatment vs. methadone treatment ^c	-0.123	0.054	-0.230, -0.015

^a Corresponds to the average of the within-match differences in the risk of experiencing severe food insecurity at treated visits compared to visits where no treatment was received. These estimates were combined using Rubin's method across ten imputed datasets after propensity score matching.

^b Robust standard errors were estimated using the approaches described by Abadie and Imbens.²⁰¹

^c An ATT was estimated after 1:5 propensity score matching (with replacement) where a study visit when a participant received methadone treatment in the past six months was matched with five visits when no treatment was received.

6.3 Appendix to Manuscript 3

Supplementary Table 6.1 Average and maximum absolute standardized mean differences (SMDs) of confounding factors among HIV-HCV co-infected participant's study visits in the unmatched and matched samples across all ten imputed datasets (2012-2015).

Variables	Unmatched sample		Matched sample	
	Average	SMD	Average	SMD ^a
Socioeconomic confounders				
Employed ^b	0.076	0.149	0.046	0.143
Average monthly income (CAD) ^c	0.243	0.314	0.085	0.222
Education at enrolment	-	-	-	-
Elementary school or less	Ref.	Ref.	Ref.	Ref.
High school	0.279	0.320	0.054	0.106
College or university	0.189	0.247	0.115	0.194
Sociodemographic confounders				
Age: years ^b	0.412	0.455	0.037	0.119
Female	0.728	0.786	0.079	0.126
Aboriginal	0.392	0.435	0.036	0.110
Province of enrolment	-	-	-	-
Quebec	Ref.	Ref.	Ref.	Ref.
British Columbia	0.844	0.903	0.034	0.083
Ontario	0.126	0.166	0.062	0.110
Other (AB, SK, NS)	0.063	0.093	0.037	0.110
No fixed address or temporary housing ^b	0.059	0.121	0.062	0.130
Living situation ^b	-	-	-	-
Alone	Ref.	Ref.	Ref.	Ref.
With others (no children)	0.122	0.173	0.054	0.160
With children	0.108	0.185	0.040	0.175
Behavioural confounders				
Non-injection of opioids ^c	0.125	0.199	0.045	0.084
Injection of opioids ^c	0.600	0.715	0.050	0.128
Injection of opioids (lifetime)	1.196	1.269	0.032	0.069
Any use of non-opioids ^c	0.439	0.537	0.044	0.135
Injection of non-opioids (lifetime)	0.592	0.664	0.048	0.122
Frequency of injection drug use	-	-	-	-
Non-weekly (past month)	0.277	0.343	0.042	0.097
Weekly (past month)	0.431	0.495	0.041	0.109
Cigarette use ^c	0.566	0.659	0.044	0.109
Alcohol use ^c	0.195	0.284	0.036	0.075
Clinical confounders				
Anxiety or depression ^b	0.156	0.220	0.089	0.156
Self-perceived health state (0-100), visual analogue scale ^b	0.031	0.105	0.051	0.119

^a Sufficient balance was defined as an average absolute standardized mean difference (SMD) less than 0.10.

^b Reference period: currently.

^c Reference period: in the past six months.

Chapter 7: Discussion and conclusions

7.1 Summary of findings

Of the estimated 13,000 individuals who are living with HIV-HCV co-infection in Canada,^{6,7} most individuals contracted both blood-borne viruses through IDU.^{3,9} In addition, the characteristics of those living with co-infection reflect socioeconomic and sociodemographic vulnerability.¹⁴⁻¹⁶ Central to the concept of FI, a social determinant of health,²⁰ is the focus on uncertain or inadequate food access due to limited financial resources.¹⁹ It is clear that there are consistently high prevalences of FI, particularly severe FI, among individuals living HIV.²⁶⁻²⁸ The literature related to consequences of FI, such as lower CD4 cell counts,^{32,33} incomplete HIV viral load suppression,^{33,34} and sub-optimal HIV treatment adherence³⁵ has motivated studies that focus on identifying risk factors for FI. However, while there is an existing evidence-base related to FI among individuals living with HIV,²⁶⁻²⁸ these studies, excluding our own publications,^{33,48,97} do not focus on individuals living with HIV-HCV co-infection. Given the differences between those living with HIV mono-infection and HIV-HCV co-infection¹⁴⁻¹⁶ and the context-specific nature of FI risk factors,^{25,26} the generalizability of findings from HIV-related studies that do not consider HCV co-infection is unclear. Therefore, additional research was needed to further our understanding of associations, mechanisms, and interventions related to IDU as a prevalent and modifiable risk factor for FI in the co-infection context.

As described in Section 1.1, the overall aim of this doctoral thesis was to examine the relationship between IDU and FI, particularly severe FI, among HIV-HCV co-infected individuals in Canada. This dissertation addressed the following objectives in three manuscripts using longitudinal cohort data: 1. To examine the relationship between IDU and FI, 2. To examine whether unemployment is a mediator in the mechanism linking IDU and severe FI, and

3. To examine whether a substance use intervention, methadone treatment, is associated with a lower risk of severe FI.

Manuscript 1 expanded upon our hypothesis-generating work⁴⁸ and describes an analysis of longitudinal cohort data that examines the relationship between IDU and FI. I temporally-ordered the data, explored a dose-response relationship between IDU frequency and FI, and examined the impact of IDU on FI severity among individuals living with HIV-HCV co-infection. In Manuscript 1, I found that 54% of participants (N = 608) experienced FI in the six months preceding the first time-point in the analytical sample. Among the 330 participants experiencing FI, the majority experienced severe FI (47%). Regarding the exposures, 31% of participants engaged in IDU in the six months preceding the first time-point in the analytical sample and 24% injected drugs in the past month. IDU in the past six months and weekly IDU in the past month were more prevalent as FI severity increased. Consistent with prior studies,^{37,48} I identified an association between IDU and FI. While there was little evidence of a dose-response relationship between IDU frequency and FI, all measures of IDU were most strongly associated with severe FI. These associations were documented after variable lagging and adjustment for a variety of socioeconomic, sociodemographic, behavioural, and clinical confounders.

Given the findings in Manuscript 1 and other HIV-related works,³⁷ there was an interest in examining mediators in pathways linking IDU and subsequent severe FI.⁴² Given the role of financial resources in the FI construct¹⁹ and the importance of employment as a means of acquiring income,²² it was important to generate evidence that examined the temporal relationship between IDU, unemployment, and severe FI. Therefore, in Manuscript 2, I estimated the overall association between IDU and severe FI and the CDE of IDU on severe FI using marginal structural log-linear models.^{195,198,199} In Manuscript 2, among the 666 FS Study

participants that enrolled between November 2012 and October 2015 (which excluded 59 students and retirees), 555 completed a second visit and 429 completed a third visit. Furthermore, I found that 32% of participants injected drugs in the six months preceding visit two, 78% were currently unemployed at visit two, and 29% experienced severe FI in the six months preceding visit three. Consistent with HIV-related studies of FI^{37,48} and Manuscript 1, I found evidence of an overall association between IDU and the most severe form of FI; this association was adjusted for confounders. Moreover, the estimates of the overall association and the CDE were similar in magnitude. While IDU may be associated with unemployment^{213,218} and unemployment may be associated with FI,^{37,48} my findings suggest that the potential impact of IDU on unemployment is not the primary mechanism linking IDU and severe FI.

Manuscript 3 was motivated by the findings in Manuscripts 1 and 2 which suggested that substance use interventions aimed at mitigating IDU may reduce the likelihood of FI, particularly severe FI, in this co-infected population. While the previous manuscripts focused on IDU and the use of any drug type, the injection of opioids is known to be common among co-infected individuals.^{226,227} As such, I examined whether methadone treatment for opioid dependence is associated with a lower risk of severe FI. To quantify the association between methadone treatment and severe FI, I estimated an ATT^{202,204} using PSM. In Manuscript 3, I found that 25% of participants (N = 608) experienced severe FI in the six months preceding the first time-point in the analytical sample and 5% concurrently reported receiving methadone treatment. Given the indications for methadone treatment, the injection of opioids in the six months preceding the treatment and outcome measurements was much higher among those who received treatment (39% vs. 12%) and 97% of the treated participants had injected opioids in their lifetimes. The estimated ATT indicated that the average risk of experiencing severe FI is lower among those

receiving methadone treatment, compared to those who are not receiving treatment. This association was adjusted for socioeconomic, sociodemographic, behavioural, and clinical confounders.

In this thesis, I examined whether the behaviour of IDU was associated with an increased risk of FI while treating other potential targets for intervention (e.g., unemployment, income, and education) as confounders. However, the identification of an independent association between IDU and FI does not indicate that these factors are not potential FI risk factors themselves. Similarly, my work does not demonstrate that IDU is the only important risk factor for FI, or that substance use interventions are more (or less) effective than hypothetical interventions on other factors (e.g., employment or income) in terms of mitigating FI in this population.

7.2 Strengths and limitations

With the exception of our exploratory analysis,⁴⁸ risk factors for FI have not been studied in the HIV-HCV co-infection context. Therefore, all manuscripts included in this thesis are novel and serve as the first examinations of the research objectives. Manuscript 1 was the first study to examine IDU frequency and FI severity when quantifying the association between IDU and FI. Subsequently, Manuscript 2 was the first analysis to investigate a potential mechanism through which IDU is associated with severe FI and Manuscript 3 was the first study to examine whether methadone treatment is associated with a lower risk of severe FI. While prior studies related to illicit drug use as a risk factor for FI in HIV-positive populations are cross-sectional and suffer from inadequate confounding adjustment and small sample sizes,^{37,38,40,41} the goal of this thesis was not necessarily to replicate previous findings; there are no prior studies that examine these research objectives among HIV-HCV co-infected individuals. Given that FI risk factors have not been studied by other researchers in this context, my thesis generated evidence that can inform

strategies to reduce FI, particularly severe FI, in this vulnerable subset of the HIV-positive population. Moreover, I have chosen appropriate methodologies to analyze correlated data¹⁸⁶ and categorical outcomes (Manuscript 1), to properly adjust for time-varying confounding affected by prior exposure (Manuscript 2),¹⁸⁹ and to quantify an association, in the form of an ATT,^{202,204} with an appropriate comparison group (Manuscript 3).

A major strength of this thesis is the use of longitudinal cohort data to address the research objectives. All analyses considered temporality of exposures, outcomes, and confounders. For example, it would have been difficult to conceive a mediation analysis without the availability of longitudinal data. Furthermore, with the exception of our publications described in Section 2.7,^{33,48,97} most of the published FI-related work in HIV-positive populations in Canada has been completed in British Columbia (Section 2.5).^{37-39,112,113} This thesis also includes the first examinations of FI in a study sample of individuals from 17 sites in six Canadian provinces. In addition to the multi-province nature of the sample, the CCC participants represent a wide variety of socioeconomic, sociodemographic, behavioural, and clinical profiles,¹⁷² increasing the generalizability of my findings.

While the FS Study was operationalized entirely within CCC study sites, the FS Study benefited from additional funding awards from the CIHR and the CTN. The FS Study also had a separate team of co-investigators with expertise in the areas of FI, HIV, HCV, and substance use. Merging of the data from the CCC and FS Study also resulted in a comprehensive dataset; prospective data were collected in a consistent and comprehensive manner for research purposes. As reflected in the descriptive tables in each manuscript, the merged dataset included detailed information on characteristics such as: employment, income, education, age, sex, ethnicity, housing and living situation, illicit drug use, cigarette and alcohol use, anxiety and depression,

and self-perceived health state. It would not have been possible to confidently estimate adjusted associations between a behavioural risk factor (IDU) and a social determinant of health (FI) without this information on confounders. I am not aware of other longitudinal cohorts in the HIV-HCV co-infection setting that contain such detailed socioeconomic and sociodemographic data, as well as information on illicit drug use and FI. Overall, I believe that the FS Study was uniquely positioned to address the objectives of this dissertation. Therefore, I am confident in expressing that this thesis, which investigates associations, mechanisms, and interventions related to IDU and FI, is novel in the area of HIV-HCV co-infection research and perhaps to the field of HIV as a whole.

As described in Section 3.6, missed study visits were addressed in all analyses. This ensured uniform temporal-ordering in the longitudinal analyses performed in this thesis. This is important when lagging variables, as was done in Manuscripts 1 and 3, and when mechanisms or pathways are being prospectively examined (Manuscript 2). In my experience, timing of study visits is not commonly discussed or addressed in the longitudinal FI-related HIV literature. However, in a multi-site cohort, particularly in a study that enrolls and follows a vulnerable population, missed visits are inevitable. While my approach required imputing more missing data, I believe that uniform temporal-ordering is a strength of my analyses.

Several limitations have been described within each manuscript. This section will elaborate on limitations that I feel are important to the overall thesis. First, Manuscripts 1 and 2 relied on IDU data that was self-reported by participants on questionnaires. I acknowledge that self-reported data can result in misclassification of the exposure. Given the sensitive nature associated with revealing information about an illicit behaviour, such misclassification may manifest itself in the form of a social desirability bias.²³² However, a previous review has

concluded that self-reports of individuals who use drugs are sufficiently reliable to provide descriptions of drug use.²¹² In Manuscript 1, the trend in the increasing magnitudes of the associations between IDU frequency and FI severity also suggests that these measures are not greatly affected by misclassification. Anecdotally, the CCC study coordinators maintain positive and confidential relationships with the participants. As such, I believe there is little reason for participants to misrepresent their drug use during the data collection process. For these reasons, I do not believe that the degree of IDU misclassification to be substantial in my studies.

Regarding the outcome variable in each manuscript, I acknowledge that the HFSSM responses used to measure FI were also self-reported by participants. However, unlike the IDU exposure or methadone treatment, which could potentially be verified using toxicological screening for drug use (albeit not necessarily confirming the route of administration)²³³ and prescription records for methadone,⁴⁵ questionnaire-based tools are the most common and valid for measuring FI.¹⁹ I also assessed the internal consistency of the HFSSM by calculating a Cronbach's alpha.²¹⁹ In my study, internal consistency describes the extent to which all of the ten items of the HFSSM measure the same concept or construct; internal consistency reflects the inter-relatedness of the items. As noted in Manuscript 2, the internal consistency of the HFSSM was acceptable in the sample as Cronbach's alpha exceeded 0.90.²¹⁹ I view the use of the HFSSM, a validated and widely used FI measurement tool,^{18,19} as a strength of my work.

In addition to the self-reported nature of the exposure variables, it could be argued that the exposure definitions for IDU and methadone treatment are crude. While IDU frequency was evaluated in Manuscript 1 and confounders were based on drug type and route of administration in Manuscript 3, I was not able to capture duration of drug use in my analyses. It is plausible that the duration of IDU may have an impact on FI and such information may allow for more targeted

interventions. Previously, proxies for the duration of drug use have been derived using CCC data from multiple study visits.¹⁶¹ However, this is difficult in the FS Study as it has a shorter duration of follow-up than the CCC as a whole. Sample size may also have precluded us from examining exposure variables that included several categories, such as an IDU exposure variable that simultaneously considered drug type and duration. Similarly, details on the components of the methadone treatment program that were used by participants, such as duration and dose of treatment, would have allowed us to estimate a more granular methadone treatment-severe FI association. However, all manuscripts described in this thesis serve as the first examinations of the research objectives and the evidence-base related to IDU and FI remains small. I would encourage that future HIV-related work considers the limitations of the exposure variable definitions in my studies and attempt to examine the relationships between IDU, methadone treatment, and FI in greater detail.

Perhaps most importantly, my analyses of observational data may have been biased by unmeasured or imperfectly measured confounders. In non-experimental research that does not involve randomization of the exposures (and mediators, in the case of Manuscript 2), there is the possibility that residual confounding resulted in a violation of the conditional exchangeability assumption; all analyses relied on the non-verifiable assumption of no unmeasured or imperfectly measured confounders. This assumption is still required when using weighting (Manuscript 2) and PSM (Manuscript 3). While the literature that describes weighting¹⁸⁹ and PSM¹⁹⁰ approaches often uses the term “causal,” I have chosen not to refer to any of my estimates as causal effects. I have also elected to use the terminology of “association” versus “effect,” when possible, as I believe that the latter may incorrectly imply a “cause and effect” relationship.

Overall, given the richness of the FS Study data, I feel confident in my measurement and selection of confounders. If confounding bias does exist in my observational analyses, I believe that the strength of this bias is small. In addition, all confounders were selected *a priori* based on their hypothesized association with the exposures (IDU or methadone treatment) and outcomes (FI, FI severity, and severe FI) in each manuscript; subject-matter knowledge informed confounder selection and no model-based approaches were used. Notably, p-value or change-in-coefficient approaches were not employed in this thesis as several researchers have argued that these approaches are inadequate.²³⁴⁻²³⁶ In an attempt to achieve conditional exchangeability between exposed and unexposed participants, I also selected factors (e.g., province of enrolment) that may act as proxies for unmeasured confounders. While it is unlikely that province of enrolment is directly associated with the exposure and outcome variables, it is plausible that high-level policy differences between provinces may have impacts on IDU, methadone treatment, and FI. The prevalence of FI and severe FI does appear to differ across provinces (see Tables 4.1, 5.1, and 6.1); suggesting that province of enrolment is not acting as an instrumental variable.²⁰⁶ At the very least, adjusting for this factor may have also controlled for unmeasured differences between provinces.

7.3 Implications of findings and directions for future research

The work contained in this dissertation represents an original contribution to the field of epidemiology with respect to IDU and FI in an HIV-HCV co-infected population. The three manuscripts included in this thesis build on each other to better understand associations, mechanisms, and interventions related to IDU and FI. The examination of an IDU-FI relationship (Manuscript 1) motivated the study of mechanisms. It was then useful to understand mechanisms related to IDU (Manuscript 2) prior to examining the impact of interventions to reduce severe FI

(Manuscript 3). As described, co-infected individuals were recruited from community-based clinics and outreach programs in large and small urban centres across Canada, as well as university-based HIV treatment programs.¹⁷² Therefore, the results from Manuscripts 1-3 are most generalizable to HIV-HCV co-infected individuals who are receiving clinical care in Canada.

Consistent with prior work in HIV-positive populations³⁷ and in our previous analysis,⁴⁸ Manuscript 1 provided evidence of an association between IDU and FI. When devising interventions, the goal is often to intervene upon an antecedent exposure to reduce a consequential outcome. Therefore, it was important for me to quantify associations that were representing a prospective temporal sequence.^{139,140} Prior to this work, it was also unclear as to whether it was the characteristics of those who engaged in IDU that were increasing an individual's likelihood of experiencing FI, or whether it was the IDU behaviour itself. IDU is concomitant with socioeconomic and sociodemographic disadvantage,⁴² and factors such as income, employment, and education, while strong risk factors for FI,^{21,22} may be difficult to modify in the short-term.^{43,44} In order to determine whether it may be useful to conceptualize interventions on IDU,²⁷ it was important to quantify the relationship between IDU and FI when adjusting for such confounding factors. My findings suggest that these socioeconomic and sociodemographic determinants may not be the only targets for intervention to reduce FI in this population.

In Manuscript 1, the association between IDU in the past six months and FI did not differ markedly from that of non-weekly or weekly IDU in the past month. Therefore, the reference period of the exposure measure (in the past six months vs. in the past month) did not appear to impact IDU's association with FI. Furthermore, weekly IDU in the past month only had a

slightly stronger association with FI compared to non-weekly IDU, providing little evidence of a dose-response relationship with FI. This suggests that it may be equally as beneficial to target substance use interventions on all co-infected individuals engaged in recent IDU, regardless of whether it is individuals engaged in any IDU in the past six months or non-weekly/weekly IDU in the past month. When considering FI severity, all measures of IDU were most strongly associated with severe FI, particularly weekly IDU. This analysis suggests that reductions in IDU, particularly weekly IDU, may decrease the likelihood of the most severe form of FI.^{21,22}

Regarding potential interventions, it is known that HIV-HCV co-infected individuals may interact regularly with health care and social services programs.^{7,172} While policy-level interventions are often recommended to address FI in the general Canadian population,^{43,44} existing drug use-related programming may also be able to help reduce the occurrence of FI among co-infected individuals in the short-term. Manuscript 1 suggested that substance use interventions aimed at IDU⁴² may reduce the likelihood of FI, particularly severe FI, in this population. However, further research was needed to examine how IDU increases the risk of severe FI (Manuscript 2) and subsequently, to evaluate the impact of a substance use intervention on severe FI (Manuscript 3).

In Manuscript 2, the association between IDU and severe FI did not appear to be mediated, in large part, by unemployment. While this raises additional questions regarding mechanisms, my findings indicated that IDU is associated with severe FI independent of socioeconomic, sociodemographic, behavioural, and clinical confounders. Similar to the findings in Manuscript 1, this is important because IDU is a potentially modifiable risk factor and severe FI is characterized by the physical sensation of hunger.^{21,22} Furthermore, the CDE provided evidence that even if it were possible to intervene to ensure that everyone in the population was

employed at visit two, this may not substantially mitigate the overall association between IDU and severe FI. Therefore, increasing employment (e.g., through employment supports)^{213,215,216} may not meaningfully reduce the association between IDU and severe FI in this population.

On the contrary, if I were to have found that the CDE was substantially smaller than the overall association, this would have suggested that IDU was not having a “direct” role in increasing the risk of severe FI. This would have resulted in different recommendations for interventions, specifically, strategies that targeted unemployment as a mediator. However, given the results, I proposed other potential mechanisms that are more direct in nature. Such a mechanism may involve competing demands on financial resources and the prioritization of the purchase of drugs instead of food.^{42,146,222} This was not investigated in Manuscript 2 as I did not have data on such expenditures. Overall, while the findings of Manuscript 2 advanced our understanding of this relationship, the conclusions were largely overlapping with that of Manuscript 1, suggesting that interventions aimed at IDU may reduce the likelihood of severe FI.

HIV-related studies, including Manuscripts 1 and 2, have documented associations between illicit drug use^{38,40,41}, including IDU,^{37,48} and FI. The concluding remarks of these studies suggest that reductions in IDU may mitigate FI, especially severe FI, in HIV-HCV co-infected populations. Acknowledging that the injection of opioids is common among co-infected individuals,^{226,227} I examined whether methadone maintenance treatment⁴⁵ is associated with a lower risk of severe FI in Manuscript 3. After completing a PSM analysis, I quantified an association which indicated that methadone treatment is associated with a lower likelihood of severe FI. My work provides evidence that an existing substance use intervention for individuals who are dependent on opioids may mitigate the most severe form of FI; this may also have benefits for HIV treatment adherence,³⁵ HIV viral load suppression,^{33,34} and CD4 cell counts.^{32,33}

It is also unlikely that methadone treatment would impact severe FI if there was no link between illicit drug use, including IDU, and severe FI. Therefore, this work lends further support to the findings in Manuscripts 1 and 2.

While Manuscripts 1 and 2 were needed to provide the etiologic motivation to examine the relationship between a substance use intervention and severe FI, Manuscript 3 provides the most direct evidence with respect to informing context-specific strategies to reduce severe FI. In Manuscripts 1 and 2, my findings indicated that reductions in IDU may mitigate FI. However, stating that IDU may increase the risk of severe FI is not particularly helpful if there are no effective interventions that can in fact reduce IDU. Furthermore, it would have been conjecturing to recommend specific substance use interventions to reduce FI in Manuscripts 1 or 2, as no interventions were explicitly evaluated in these works. Identifying a risk factor for an outcome (Manuscripts 1 and 2) does not necessarily permit a researcher to then indicate that a specific intervention on that risk factor (i.e., IDU) will in fact reduce an outcome (i.e., FI). Manuscript 3 was important in taking the associational findings of Manuscript 1 and the mechanistic findings of Manuscript 2 and placing them in the context of an intervention that may reduce the likelihood of an individual experiencing FI.

Lastly, my dissertation suggests that FI is another associated harm of IDU, whereby programs that serve individuals engaged in IDU could attempt to mitigate FI through the provision of food supports within a larger harm reduction strategy.^{26,131,146,237} However, as described in Section 2.5.4, food assistance is not targeting a risk factor or determinant of the FI experience.^{137,138} It is for this reason that I reiterate the goal of risk factor epidemiology, which is to identify unbiased associations between exposures and outcomes and to intervene on such exposures.^{139,140} While I certainly do not discourage the provision of food as a form of harm

reduction,²³⁰ my thesis does not provide direct evidence that such a strategy would in fact reduce FI in this population; this is why such a recommendation is not made within Manuscripts 1-3.

Regarding directions for future research, this thesis has summarized a body of literature which demonstrates that FI is highly prevalent among HIV-positive^{26,27} and HIV-HCV co-infected individuals.⁴⁸ In addition to the deprivation that underlies the FI experience itself,²²⁻²⁴ it is also evident that the experience of FI is associated with negative health and clinical outcomes among individuals living with HIV^{32,34,35} and HIV-HCV co-infection.^{33,97} In my opinion, this field of research has moved beyond the stage of focusing exclusively on documentations of FI prevalence. The negative impacts of FI are also established. Acknowledging the complex and multi-dimensional nature of FI,²¹ I would recommend that HIV researchers shift their attention to the examination of prevalent and modifiable FI risk factors, and subsequently, to the evaluation of new and existing interventions on such factors. For example, several studies have suggested that depressive symptoms may be a prevalent clinical risk factor for FI among individuals living with HIV³⁸⁻⁴¹; it would be valuable in determining whether mental health services may have a role in mitigating FI. Subsequently, given the importance of systematic reviews and meta-analyses in the hierarchy of evidence,²³⁸ such studies should also be completed once an evidence-base accumulates with regards to specific FI risk factors. These reviews could be similar to those completed in the areas of FI and its impacts on CD4 cell counts³² and HIV viral load.³⁴

In addition to further examining interventions on illicit drug use (e.g., counseling, rehabilitation, and detoxification programs) and their associations with FI in an observational setting, I would also recommend that future randomized controlled trials of substance use or mental health interventions include FI as a measured outcome variable. It would be particularly

beneficial if a researcher was able to corroborate my findings and demonstrate that methadone treatment, or another substance use intervention, does indeed have an impact on mitigating the risk of severe FI in a trial setting.

7.4 Conclusions

In Canada, 20% of individuals living with HIV are estimated to be co-infected with HCV.^{6,7} In addition to the high prevalence of IDU,¹³ the characteristics of individuals living with co-infection reflect socioeconomic and sociodemographic vulnerability.¹⁴⁻¹⁶ Central to the concept of FI, as measured and operationalized in this thesis, is the focus on uncertain or inadequate food access due to limited financial resources.¹⁹ In the HIV context, there are consistently high prevalences of FI, particularly severe FI, among individuals living with HIV. The consequences of FI, including poor clinical outcomes,^{32,34,35} motivated me to focus my thesis on the examination of a modifiable risk factor for FI with the goal of informing interventions to reduce FI. This thesis includes novel research that was needed to advance our understanding of the relationship between IDU, a prevalent behaviour in this vulnerable subset of the HIV-positive population,¹³ and FI.

In conclusion, the estimated associations between IDU and FI, particularly weekly IDU and severe FI, indicate that reductions in IDU may mitigate FI, especially severe FI, among individuals living with HIV-HCV co-infection. While further research is required to understand the mechanisms linking IDU and severe FI, the association between IDU and severe FI is primarily through pathways that are not mediated by unemployment. In addition, methadone treatment for opioid dependence may reduce the likelihood of severe FI. Therefore, the research undertaken in this thesis indicates that IDU is a risk factor for FI and that there is a substance use intervention which has the potential to decrease the risk of co-infected individuals experiencing

severe FI. Findings from this dissertation are relevant to researchers and clinical care providers involved with HIV-HCV co-infected individuals who are engaged in IDU.

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