Depressive symptoms in the HIV and Hepatitis C co-infected population in Canada - An investigation in the second-generation direct acting antiviral era (2013-2020)

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ABSTRACT

Depression is common in the human immunodeficiency virus (HIV)-Hepatitis C virus (HCV) co-infected population due to direct neurocognitive effects of HCV and HIV and/or associated stigma, discrimination, and socioeconomic burdens. HCV treatment has evolved from interferon (IFN)-based regimens to safer direct acting antivirals (DAA). Depression, a major IFN side effect, is therefore no longer a relative contraindication to HCV treatment thereby broadening access. However, it is not known if depressive symptoms will continue to have an effect on treatment initiation and if curing HCV could improve depressive symptoms.

The overall goal of this thesis was to investigate depressive symptoms in the Canadian HIV-HCV co-infected population in the second-generation DAA era (2013-2020). I used data from the Canadian HIV-HCV Co-Infection Cohort (CCC), an open multicentre prospective cohort with biannual follow-up visits. Demographic, behavioural, and clinical data were collected by standardized questionnaires and chart reviews. I also used data from the Food Security (FS) and HIV-HCV co-infection sub-study of the CCC. In the FS sub-study, depression screening was performed using the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10). The scale assesses presence and severity of depressive symptoms in the past one week; scores ≥10 are indicative of being at risk for major depression.

The first objective was to predict the presence of depressive symptoms using supervised machine learning in the CCC, as depression screening was performed only in the FS sub-

study. Candidate predictors (137) collected from the CCC and CES-D-10 data from the FS sub-study were used to develop a random forest algorithm to predict the CES-D-10 classes (≥10 vs <10) at each CCC visit. The algorithm had excellent classification performance with an area under the curve of 0.82. In the next objectives, I used these predicted depressive symptoms classes as a measure of depressive symptoms, correcting for misclassification using predictive value-based record-level correction.

In the second objective, I assessed the effect of depressive symptoms on time to HCV treatment initiation during the IFN (2003-2011) and DAA (2013-2020) eras using marginal structural Cox proportional hazards models with inverse weighting for death. The treatment initiation rate increased from 9 to 21 per 100 person-years from over the IFN to the DAA era. Treatment initiation was 19% lower among those with depressive symptoms than among those without in the IFN era, and 19% higher in DAA era.

In the third objective, I investigated the impact of sustained virologic response (SVR) or HCV cure on depressive symptoms using an interrupted time series analysis. The pre-SVR trend suggested depressive symptoms changed little over time, with no immediate level change. The post-SVR trend showed a reduction of 5% per year in depressive symptoms risk. This decline over time may reflect changes in biological pathways and/or better general health.

In the fourth objective, I examined the relationship between depressive symptoms, SVR and Health Services Utilization (HSU) using a zero-inflated negative binomial regression

model. SVR was associated with 24% fewer inpatient visits. Among those who achieved SVR, no association was observed between depressive symptoms and in- or outpatient visits. However, among those who did not achieve SVR, inpatient visits were 16% higher and outpatient visits were 5% higher among those with depressive symptoms than among those without. Thus, depressive symptoms were associated with a modest increase in HSU; SVR led to attenuation of this effect.

In conclusion, a high proportion of the co-infected population had baseline CES-D-10 scores ≥10, suggesting that depression management should be an integral part of HIV/HCV care. The doors to HCV elimination have opened in Canada in the DAA era. This body of work provides evidence that depressive symptoms are no longer a barrier to treatment initiation and that HCV cure leads to benefits beyond liver disease outcomes including reduction in depressive symptoms and HSU. This provides further rationale for treating HCV in all chronically infected persons.

RÉSUMÉ

La dépression est fréquente chez les personnes co-infectées au VIH et au virus de l'hépatite C (VHC), en raison d'effets neurocognitifs directs des deux virus et/ou de la stigmatisation, de la discrimination et du fardeau socio-économique associés à la co-infection VIH-VHC. Le traitement du VHC a évolué, passant de régimes à base d'interféron (IFN) à des antiviraux à action directe (AAD) plus sûrs. La dépression, un effet secondaire majeur de l'IFN, n'est donc plus une contre-indication relative au traitement du VHC, ce qui en élargit l'accès. Cependant, on ignore si les symptômes dépressifs continueront à avoir un effet sur l'initiation du traitement et si la guérison du VHC pourrait améliorer les symptômes dépressifs.

L'objectif général de cette thèse était d'étudier les symptômes dépressifs dans la population canadienne co-infectée aux VIH-VHC à l'ère des AAD de deuxième génération (2013-2020). J'ai utilisé les données de la cohorte canadienne de co-infection VIH-VHC (CCC), une étude prospective multicentrique ouverte avec des visites de suivi semestrielles. Les données démographiques, comportementales et cliniques ont été recueillies par questionnaires standardisés et examens de dossiers. J'ai également utilisé les données d'une sous-étude de la CCC portant sur la sécurité alimentaire (SA) . Dans cette sous-étude, le dépistage de la dépression a été effectué à l'aide de l'échelle de dépression 10 du *Center for Epidemiologic Studies* (CES-D-10). Cette échelle évalue la présence et la sévérité des symptômes dépressifs au cours de la dernière semaine. Des scores ≥10 indiquent un risque de dépression clinique.

Le premier objectif était de prédire la présence de symptômes dépressifs au sein de la CCC en utilisant l'apprentissage automatique supervisé, car le dépistage de la dépression n'a été effectué que dans la sous-étude SA. Les prédicteurs candidats (137) recueillis dans la CCC et les données CES-D-10 de la sous-étude SA ont été utilisés pour développer un algorithme de forêt aléatoire afin de prédire les classes CES-D-10 (≥10 vs <10) à chaque visite de la CCC. L'algorithme a montré une excellente performance de classification avec une aire sous la courbe de 0,82. Dans les objectifs suivants, j'ai utilisé les classes de symptômes dépressifs prédites, et corrigé les erreurs de classification au niveau de l'observation en fonction des valeurs prédictives.

Dans le deuxième objectif, j'ai évalué l'effet des symptômes dépressifs sur le délai d'initiation du traitement contre le VHC pendant les périodes IFN (2003-2011) et AAD (2013-2020) en utilisant des modèles de risques proportionnels de Cox structurels marginaux avec pondération inverse pour le décès. Le taux d'initiation du traitement est passé de 9 à 21 pour 100 années-personnes entre l'ère IFN et l'ère AAD. Le taux d'initiation était inférieur de 19% chez les personnes présentant des symptômes dépressifs par rapport à celles qui n'en présentaient pas à l'ère IFN, et supérieur de 19% à l'ère AAD.

Dans le troisième objectif, j'ai étudié l'impact d'une réponse virologique soutenue (RVS) -ou guérison du VHC– sur les symptômes dépressifs en utilisant une analyse de séries chronologiques interrompues. La tendance pré-RVS suggère que les symptômes dépressifs ont peu changé dans le temps, sans rupture immédiate. Les tendances post-

SVR ont montré une réduction de 5% par an du risque de symptômes dépressifs. Cette diminution dans le temps peut refléter des changements dans les processus biologiques et/ou une meilleure santé générale.

Dans le quatrième objectif, j'ai examiné la relation entre les symptômes dépressifs, la RVS et l'utilisation de services de santé (USS) à l'aide d'un modèle de régression binomial négatif à inflation de zéros. La RVS était associée à une diminution de 24 % des visites de patients hospitalisés. Parmi ceux ayant développé une RVS, aucune association n'a été observée entre les symptômes dépressifs et les visites en milieu hospitalier ou ambulatoire. Cependant, parmi ceux n'ayant pas développé de RVS, le nombre de visites en milieu hospitalier était supérieur de 16% et le nombre de visites en milieu ambulatoire supérieur de 5% chez les personnes présentant des symptômes dépressifs comparé à celles n'en présentant pas. Ainsi, les symptômes dépressifs étaient associés à une augmentation modeste de l'USS ; la RVS a permis d'atténuer cet effet.

En conclusion, une proportion élevée de la population co-infectée présentait des scores CES-D-10 de base ≥10. La prise en charge de la dépression devrait faire partie intégrante des soins VIH/VHC. L'élimination du VHC est devenue possible au Canada à l'ère des AAD. Ces travaux fournissent des preuves que les symptômes dépressifs ne sont plus un obstacle au traitement et que la guérison entraîne des bénéfices au-delà de l'amélioration des fonctions hépatiques, y compris la réduction des symptômes dépressifs et de l'USS. Ces résultats soutiennent l'importance du traitement du VHC chez toutes les personnes chroniquement infectées.

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CONTRIBUTION OF AUTHORS

Manuscript 1: Predicting the presence of depressive symptoms in the HIV-HCV co-infected population in Canada using supervised machine learning.

Authors: Gayatri Marathe, Erica EM Moodie, Marie-Josée Brouillette, Joseph Cox, Curtis Cooper, Charlotte Lanièce Delaunay, Brian Conway, Mark Hull, Valérie Martel-Laferrière, Marie-Louise Vachon, Sharon Walmsley, Alexander Wong, Marina B. Klein; Canadian Co-Infection Cohort.

Manuscript 2: Depressive symptoms are no longer a barrier to HCV treatment initiation in the HIV–HCV co-infected population in Canada.

Authors: Gayatri Marathe, Erica E. M. Moodie, Marie-Josée Brouillette, Joseph Cox, Charlotte Lanièce Delaunay, Curtis Cooper, Mark Hull, John Gill, Sharon Walmsley, Neora Pick, Marina B. Klein, Canadian Co-Infection Cohort.

Manuscript 3: Impact of HCV cure on depressive symptoms in the HIV-HCV co-infected population in Canada.

Authors: Gayatri Marathe, Erica EM Moodie, Marie-Josée Brouillette, Charlotte Lanièce Delaunay, Joseph Cox, Valérie Martel-Laferrière, John Gill, Curtis Cooper, Neora Pick, Marie-Louise Vachon, Sharon Walmsley, Marina B. Klein; Canadian Co-Infection Cohort.

Manuscript 4: Effect of depressive symptoms on health services utilization in the HIV and Hepatitis C co-infected population in Canada.

Authors: Gayatri Marathe, Erica E. M. Moodie, Marie-Josée Brouillette, Charlotte Lanièce Delaunay, Marina B. Klein; Canadian Co-Infection Cohort.

For all manuscripts, Gayatri Marathe, Erica E. M. Moodie, and Marina B. Klein conceived of and designed the study. Gayatri Marathe and Charlotte Lanièce Delaunay prepared the analytical dataset. Gayatri Marathe performed all statistical analyses, with input from Erica E.M. Moodie, Marina B. Klein, and Marie-Josée Brouillette. Gayatri Marathe drafted each manuscript. All authors revised manuscripts critically and gave final approval prior to submission.

Marina B. Klein is the principal investigator of the Canadian Co-infection Cohort (CCC). Erica E. M. Moodie, Joseph Cox, Curtis Cooper, Brian Conway, Mark Hull, John Gill, Neora Pick, Valérie Martel-Laferrière, Marie-Louise Vachon, Sharon Walmsley, and Alexander Wong are CCC co-investigators. The investigators provided substantive support, and/or recruited, and followed participants of the CCC. The data were extracted by Leo Wong and Shouao Wang from the CCC data management team, and Jessica Lumia (database coordinator) provided support in case of queries and assisted with data verification.

STATEMENT OF ORIGINALITY

The research presented in this thesis constitutes an original contribution in the study of depressive symptoms in the HIV and HCV co-infected population in Canada. All four manuscripts present novel findings related to depressive symptoms measurement and their association with patient outcomes. This research also provides new insights on long-term effects of HCV cure on depression in the DAA era, which will have implications on treatment strategies and mental health management in the Canadian co-infected population.

Specifically, Manuscript 1 generated the first supervised machine learning algorithms for depressive symptoms classification using available predictor data in the CCC, which were then used as a measure of depressive symptoms for the next thesis objectives. Additionally, when externally validated, these algorithms can have applications beyond the CCC. Manuscript 2 provided the first quantification of the effect of depressive symptoms on HCV treatment initiation and provided a comparison between the IFN and DAA eras. Manuscript 3 was the first longitudinal analysis describing the long-term trends of depressive symptoms post-SVR in the co-infected population. Finally, Manuscript 4 assessed the effect of depressive symptoms on health services utilization and first noted that SVR may have a modifying effect.

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

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LIST OF ABBREVIATIONS

AIDS: Acquired Immunodeficiency Syndrome

APRI: Aspartate Aminotransferase to Platelet Ratio Index

ART: Antiretroviral Therapy

AST: Aspartate Aminotransferase

AUC: Area under the curve

BDI: Beck Depression Inventory

BMI: Body Mass Index

CAD: Canadian dollar

cART: Combination Antiretroviral Therapy

CCC: Canadian Co-infection Cohort

CES-D: Center for Epidemiologic Studies Depression Scale

CI: Confidence interval

COVID-19: Coronavirus Disease 2019

PH: Proportional Hazards

DAA: Direct Acting Antivirals

DAG: Directed Acyclic Graph

DALY: Disability Adjusted Life Years

DNA: Deoxyribonucleic acid

EQ-5D: Euro-QoL 5-Dimension scale

FS: Food Security

GBD: Global Burden of Diseases, Injuries, and Risk Factors Study

gbMSM: Gay and Bisexual Men who have Sex with Men

GEE: Generalized Estimating Equations

HCV: Hepatitis C virus

HIV: Human Immunodeficiency Virus

HR: Hazard ratio

HSU: Health Services Utilization

IDU: Injection Drug use

IFN: Interferon

IL: Interleukin

IPCW: Inverse Probability Censoring Weights

IPTW: Inverse Probability Treatment Weights

IQR: Interquartile Range

IRR: Incidence rate ratios

ITS: Interrupted Time Series

LR-: Negative Likelihood Ratio

LR+: Positive Likelihood Ratio

LSD: Lysergic Acid Diethylamide

MDA: Methylenedioxyamphetamine

MSCM: Marginal Structural Cox Proportional Hazards Model

MSM: Marginal Structural Model

NPV: Negative Predictive Value

OOB: Out-of-Bag

PCP: Phenylcyclohexyl piperidine

PHQ: Patient Health Questionnaire

PLWH: People living with HIV

PPV: Positive Predictive Value

PWID: People Who Inject Drugs

QIC: Quasi-likelihood under the Independence model Criterion

RF: Random Forest

RMSE: Root Mean Squared Error

RNA: Ribonucleic acid

ROC: Receiver operating characteristic curve

SD: Standard Deviation

SES: Socio-economic Status

SVR: Sustained Virologic Response

TNF: Tumour Necrosis Factor

WHO: World Health Organization

ZINB: Zero-Inflated Negative Binomial Model

1. CHAPTER 1: GENERAL INTRODUCTION

1.1. Introduction

Globally, an estimated 37.7 million people live with Human Immunodeficiency Virus (HIV) and 71.1 million people live with a chronic Hepatitis C Virus (HCV) infection (1, 2). With the availability of antiretroviral therapy (ART) for HIV, people living with HIV (PLWH) can now live healthy, long, and productive lives, if they are adherent to treatment. However, PLWH still have to manage several co-morbid conditions including liver disease and mental illness. Due to the common modes of transmission, co-infection of HIV and HCV is common, with approximately 2.3 million people co-infected worldwide (2).

Depression is a major psychiatric co-morbidity related to both HIV and HCV and both biological and psychosocial mechanisms are at play. The reported prevalence of depression is as high as 20-30% among PLWH and almost 24% among those with chronic HCV infection (3, 4).. Depression prevalence is reported to be even higher in the co-infected population, due to the co-existence of risk factors and neuropsychiatric effects of both HIV and HCV (5).

Depression was a well described side effect of the earlier interferon (IFN)-ribavirin based HCV antiviral treatments, with studies showing more than 20% of those treated developed major depression (6). This often prevented IFN therapy from being prescribed to individuals with current or past psychiatric illness. However, after 2013, second-generation direct acting antiviral (DAA) regimens were introduced, which were safer and in real-world settings had >95% rates of cure (sustained virologic response (SVR)), even

in HIV-HCV co-infected persons (2). Importantly, there was no evidence of any significant psychiatric side effects, leading to HCV treatment guidelines being updated (7, 8). Thus, current, or past psychiatric illness is no longer a relative contraindication for HCV treatment.

The overall safety, simplicity, and high cure rates of the second generation DAA regimens have led to improved treatment access and development of elimination goals for HCV worldwide and within Canada. A study in the Canadian Co-infection cohort (CCC) suggested an almost threefold increase (from 8 to 28 per 100 person-years (PY)) in treatment initiation in the cohort after 2013; however in this study, it was also observed that treatment initiation rates were lower among people who actively inject drugs, women, and Indigenous populations compared with other co-infected people (9). Thus, despite the advantages of the new regimens, treatment access is still not uniform across sub-populations, posing a threat to HCV elimination goals. Patient- and system-level barriers to treatment and linkage to care still exist; the presence of depression could be one such barrier. In fact, the presence of significant depressive symptoms could have an impact on patient outcomes, even when not meeting diagnostic criteria for major depression. However, there is a lack of evidence on effect that depressive symptoms may still have on treatment initiation.

Furthermore, the changes in prescribing practices provide us with the opportunity to assess the potential impact of HCV treatment on depressive symptoms over time. We may expect lower depressive symptoms post-cure through biological pathways due to

HCV viral clearance. However, co-infected populations continue to face challenges including discrimination, socioeconomic burdens, and/or substance use. These could impact psychosocial and health outcomes such as overdoses and suicide, mitigating the benefits of HCV cure. It is therefore important to examine longitudinally whether HCV cure leads to a change in the level of depressive symptoms and moreover whether this change persists over time.

Finally, depression and both HIV and HCV infections are associated with increased health services utilization (HSU) (10, 11). There is evidence of high economic burden on health systems due to mental health disorders, HIV, HCV, and related risk factors including substance use (12, 13). Thus, HCV cure could impact this outcome due to possible overall improvements in mental as well as physical well-being. The effect of depressive symptoms on HSU and how it is affected by HCV cure requires investigation in the vulnerable HIV-HCV co-infected population.

1.2. Research objectives

The overall goal of my doctoral thesis was to investigate depressive symptoms in the HIV-HCV co-infected population in Canada.

The specific objectives were as follows:

1. To development an algorithm to predict the presence of depressive symptoms in participants of the CCC.

2. To examine the effect of depressive symptoms on HCV treatment initiation in the HIV-HCV co-infected population in Canada during the IFN (2003-2011) and second-generation DAA (2013-2020) eras.
3. To evaluate the impact of SVR after HCV treatment on the presence of depressive symptoms in the HIV-HCV co-infected population in Canada during the second-generation DAA era (2013-2020).
4. To examine the effect of depressive symptoms HSU in the HIV-HCV co-infected population in Canada during the second-generation DAA era (2013-2020).

1.3. Organization of Thesis

The format of the thesis is manuscript-based. It includes four original manuscripts, corresponding to the four thesis objectives. Chapter 2 provides the relevant thesis background and specific literature review to support the thesis objectives. Chapter 3 provides a detailed introduction to the data sources used in this thesis, including the CCC and its sub-study, the food security and HIV-HCV co-infection sub-study (FS sub-study). Chapter 4 comprises of Manuscript 1, which describes the development of supervised machine learning algorithms for predicting the presence of depressive symptoms in the HIV-HCV co-infected population in Canada. Chapter 5 contains Manuscript 2, which examines the effect of depressive symptoms on HCV treatment initiation in the IFN (2003-2011) and second-generation DAA (2013-2020) eras. Chapter 6 is Manuscript 3, which evaluates the impact of HCV cure on the presence of depressive symptoms in the HIV-HCV co-infected population in Canada. Chapter 7 comprises of Manuscript 4, which

examines the effect of depressive symptoms on HSU in the Canadian HIV-HCV co-infected population. Chapter 8 summarizes the key findings of the thesis, discusses the strengths and limitations, the implications of this work and future directions, and provides concluding remarks. The references for each manuscript are included in the corresponding chapters. The references for chapters 1, 2, 3, 8, and the manuscript prefaces are included at the end of this thesis.

2. CHAPTER 2: LITERATURE REVIEW

2.1. Epidemiology of HIV infection

The World Health Organization (WHO) estimated 37.7 million people were living with HIV worldwide in 2020, with Sub-Saharan Africa most severely affected and accounting for more than two-thirds of the PLWH (25.4 million) globally (1). In Canada, the number of PLWH was estimated to be around 62,000 (range 54,600-70,500) in 2018; an estimated 13% of these individuals were unaware of their infection (14). Globally, there has been a 29% decline in the number of new HIV infections from 2.1 million in 2010 to 1.5 million in 2020. That same year, there were 680,000 HIV-related deaths, representing a decrease of 47% from 2010 (1). Thus, although HIV continues to be a major global health concern, there have been major improvements over time.

The main reason for these improvements was the development of the ART regimens. The first medication for HIV, zidovudine, was available for use by 1987 and in 1995, the first protease inhibitor was approved for use (15). Treatment for HIV has since evolved over time and more than twenty-five drugs have been developed. Combination ART (cART) consists of a combination of drugs from different classes targeting the HIV life cycle with the aim of stopping HIV replication and preserving or restoring immune function (16). Although a cure for HIV is not yet available, this combination of drugs taken every day can maintain an undetectable viral load, which has been shown to prevent transmission (17). Guidelines recommend treating patients as soon as they are diagnosed and adherence to treatment leads to improved patient health outcomes and survival (18, 19). PLWH can thus live healthy, long, and productive lives if they are adherent to treatment.

In Canada, of those who were diagnosed, an estimated 45,000 people (85%) were on ART in 2018, 94% of whom had a suppressed viral load (14).

HIV is transmitted by body fluids via three main routes: sexual transmission through semen and vaginal secretions; mother-to-child transmission during pregnancy, delivery or through breastmilk; and parenteral transmission via contaminated blood and blood products, accidental needle sticks, and sharing contaminated needles (1, 15). The key populations who are disproportionately affected by HIV include gay and bisexual men who have sex with men (gbMSM), people who inject drugs (PWID), people in prisons and other closed settings, sex workers, and transgender people (1). In Canada, 50% of all new HIV infections were among gbMSM and 14% were in PWID; Indigenous communities showed an increase in HIV incidence from 2016 to 2018, making up 14% of all new infections in 2018 despite accounting for only 4.9% of the Canadian population (14, 20).

2.2. Natural history of HIV infection

HIV is a single-stranded positive-sense RNA virus that belongs to the family *Retroviridae* and genus *Lentivirus* (21). HIV infects the $CD4^+$ cells and macrophages, which are part of the human immune system. HIV causes depletion of the $CD4^+$ cells, which makes the host immunocompromised and thus vulnerable to opportunistic infections. Additionally, viral enzymes including reverse transcriptase and integrase help the HIV genome to integrate into the human DNA leading to the characteristic persistent infection (22). Figure 2.1 shows the natural history of HIV infection, as depicted by Melhuish et. al. (21). The

first stage of HIV infection is the primary infection, in which an acute illness occurs in 50% of those exposed to HIV within 2-5 weeks (15). The clinical symptoms are flu-like with fever, sore throat, malaise, nausea, diarrhoea, and rash. As seen in figure 2.1, during the primary infection the viral load increases and peaks and there is lowering of the $CD4^+$ cell count. In between 4-6 weeks after exposure, seroconversion occurs and antibodies against HIV are detectable (21). During the next asymptomatic stage of the disease after seroconversion, viral load declines and remains stable for as long as 6-8 years without treatment. During this time the $CD4^+$ cell count gradually declines. Without ART, the CD4+ cells continue to decline, which leads to opportunistic infections and other AIDS-defining conditions including tuberculosis, *pneumocystis jirovecii* pneumonia, cryptococcal meningitis, Kaposi's sarcoma, non-Hodgkin's lymphoma, and Burkitt's lymphoma, among others (21).

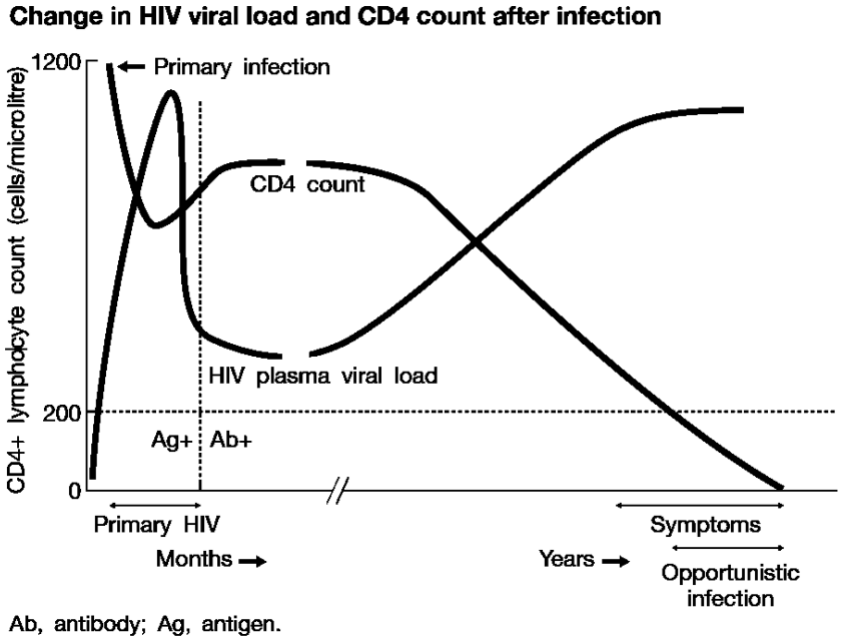

Figure 2.1: Natural history of HIV infection

Reproduced from Medicine, 46 (6), Melhuish A. and Lewthwaite P., Natural history of HIV and AIDS, 356-361., Copyright (2018), with permission from Elsevier

However, with the availability of ART, the natural history of HIV infection has changed dramatically. As the drugs act on inhibiting viral replication, the plasma viral load is reduced to undetectable levels, which helps in replenishing the host $CD4^+$ cells. A recent study suggested that ART initiation at high $CD4^+$ cell counts was associated with a longer life span and more comorbidity-free years for individuals with HIV infection (23). However, as PLWH on ART are aging, they now have to deal with several co-morbid conditions like cardiovascular disease, chronic kidney disease, liver disease, osteoporosis, cancer and neurocognitive disorders including depression and anxiety (24). Thus, study of these co-morbid conditions is necessary to further improve the quality of life of PLWH.

2.3. Epidemiology of HCV infection

Approximately 71.1 million people are living with HCV globally according to WHO estimates and there were 1.75 million new HCV infections in 2015, representing an incidence rate of 23.7 per 100,000 (2). The five countries, Pakistan, Nigeria, Egypt, India, and Russia, account for more than 50% of the infections worldwide (25). However, in 2015, HCV incidence was highest in the European and Eastern Mediterranean WHO regions (26). In Canada, approximately 250,000 people are estimated to be living with a chronic HCV infection, with the largest numbers in Ontario, British Columbia, and Quebec (27). HCV is known to have high genetic diversity and has eight known genotypes distributed globally; majority of infections in North America including Canada are of genotype 1 followed by 3 (26).

HCV is a bloodborne virus and is transmitted via small quantities of blood (2). The main modes of transmissions differ between low/middle and high income countries (28). Injection drug use is the major driver of HCV transmission in high-income countries (29). Transmission occurs via sharing of contaminated needles as well as other drug use paraphernalia and thus harm-reduction services like needle and syringe programmes and opioid substitution therapy are key for HCV prevention (30). In low- and middle-income countries, transmission occurs via unsafe medical practices and iatrogenic transmission through unscreened blood and blood products in addition to injection drug use (31). Other less common sources of infection include sexual and mother-to-child transmission (32).

The Canadian HCV epidemic is called the “twin epidemics” - one among young people, especially those who inject drugs, and the other among baby boomers (those born between 1945-75) (29). Studies have shown that baby boomers are five times more likely to be affected by detrimental effects of chronic HCV than the general population and many in this population were infected possibly via nosocomial or iatrogenic transmission by e.g., reuse of needles in health care settings and via donated blood and organs (33, 34). HCV affects certain key populations disproportionately and the “Canadian blueprint for HCV elimination (2019)” identified priority populations that need to be targeted for HCV elimination in Canada: PWID, Indigenous peoples, people with experience in prisons, immigrants and newcomers from countries with high rates of HCV, and gbMSM (29). Estimates suggest that up to 85% of new infections in Canada occur among PWID and prevalence of HCV is almost five times higher in Indigenous people compared to non-Indigenous people (29, 35, 36).

2.4. Natural history of HCV infection

HCV is a positive-sense RNA virus belonging to the family *Flaviviridae* and genus *Hepacivirus* (37). HCV causes both acute (short-term) and chronic (long-term) infection. Only about 25% of those infected spontaneously clear the virus after the acute phase (~6 months); the remaining 75% progress to chronic infection (38). In the natural history of this disease, approximately 10-15% of the people exposed to HCV have a symptomatic infection and 85-90% remain asymptomatic (39). Spontaneous clearance is higher among those with symptomatic infection compared those with asymptomatic infection (39). Other factors associated with spontaneous clearance include female sex, and younger age at infection among others. In terms of clinical manifestations, among those with acute HCV infections, the symptoms are non-descript and include malaise, right upper quadrant pain, and nausea (40). Among those with chronic HCV infection, data suggest that, over 20-30 years, approximately 10-20% develop advanced fibrosis, 10% develop cirrhosis, and 1-5% develop hepatocellular carcinoma (39, 41). HCV infection is also known to be associated with a number of extrahepatic manifestations, including type-2 diabetes, chronic kidney disease, B-cell lymphoma, and psychiatric manifestations like depression (42).

HCV RNA is detectable approximately 1 to 3 weeks after exposure to HCV. Anti-HCV antibodies are detectable from between 6-12 weeks from exposure and then they remain positive for life. The viral loads fluctuate initially during the first months, and, in the case

of spontaneous clearance, HCV RNA becomes undetectable approximately 6 months from infection. HCV virus clearance (either spontaneously or through treatment) does not provide immunity against future infection and no vaccine is currently available. Thus, the risk of re-infection remains. This genetic diversity of HCV has had an impact on both treatment and vaccine development (43).

2.5. HIV-HCV Co-infection - Epidemiology and impact on natural history

Due to the common modes of transmission, approximately 2.3 million people worldwide are co-infected with HCV and HIV (2). Of these, it is estimated that more than half (about 1.3 million) are PWID (44). Followed by PWID, the highest prevalence of HCV co-infection is among gbMSM. The odds of HCV infection was found to be six times higher in PLWH vs. those without HIV infection (44). In Canada, an estimated 15-25% of the 70,000 HIV-infected persons are co-infected with HCV (45). In addition to PWID, HIV-HCV co-infection is disproportionately seen in the Indigenous population and people incarcerated in the Canadian provincial and federal prison systems (46).

The natural history of both HIV and HCV are impacted due to co-infection. Given CD4+ T cells are key in raising the antiviral immune response against HCV, co-infection with HIV compromises these immune responses (47). There is evidence of impaired immune response among people who have cleared HCV previously, indicative of overall impaired immunity against HCV (48), even among people who have cleared an HCV infection. HIV infection can reduce the chance of spontaneous clearance of HCV as well (47, 49). In

general, chronic HCV infection with HIV leads to accelerated progression to serious hepatic conditions including liver cirrhosis and hepatocellular carcinoma (2).

Similarly, when co-infected with HCV, the natural history of HIV is affected. In the pre-ART era, HCV was shown to lead to increased immune activation which was associated with immune responses being impaired and also a rapid progression to AIDS (47). There is evidence of reduced CD4+ T cells restoration among PLWH on ART due to co-infection with HCV, as the liver is involved in T cell homeostasis (47).

2.6. HCV Treatment evolution

HCV treatment has evolved over time, from IFN-based regimens with or without ribavirin to IFN-free DAA regimens (50, 51). Treatment is deemed successful if a patient achieves SVR, that is, HCV viral load is undetectable 12 weeks after the end of treatment. SVR equates to a cure. SVR rates have improved over time, with each new treatment regimen, as seen in figure 2.2 by Webster et. al. 2015 (50, 51). In the early 1990s, the IFN-based

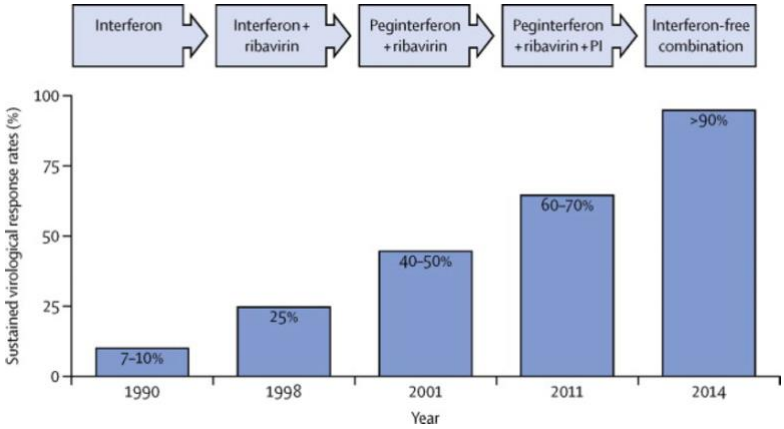

Figure 2.2: Evolution of HCV treatment and SVR rates

Reproduced from The Lancet, 385 (9973), Webster, D. P., Klenerman, P., Dusheiko, G. M., Hepatitis C, 1124-35, Copyright (2015), with permission from Elsevier.

treatment regimens became available for HCV. These regimens had many issues including longer regimens (24-48 week) with weekly injections and poor outcomes (<10% SVR rates) (50). The pegylated-IFN regimens with the addition of ribavirin available by the late 1990s improved the response rates (30-40%), however the regimens had many side effects including psychiatric illness.

By 2011, the first-generation DAAs were developed. These included boceprevir and telaprevir, which improved SVR rates to up to 75% with triple therapy (i.e., when combined with peg-IFN); however, these were limited to genotype 1 and still had many side effects (50). Thus, efforts to find better alternatives led to the development of the second-generation DAAs which include drugs from various classes including, NS3/4A protease inhibitors (e.g., Simeprevir), NS5A inhibitors (e.g., daclatasvir), non-nucleoside NS5B polymerase inhibitors (e.g., dasabuvir), and nucleotide/nucleoside NS5B polymerase inhibitors (e.g., sofosbuvir). These IFN-free DAA-based regimens, when used in combination, e.g., sofosbuvir/ledipasvir (8-12 weeks), sofosbuvir/velpatasvir (12 weeks) and glecaprevir/pibrentasvir (8 weeks), achieve SVR rates of >95% in real world settings (50). These regimens are shorter, between 8-12 weeks, have fewer side effects and the latter two are pan-genotypic, vastly simplifying HCV treatment (2).

Among PLWH, SVR rates were even lower when treated for HCV with IFN and ribavirin regimens (<30%); thus, the co-infected population was considered a special treatment group (52). However, with the advent of the IFN-free second-generation DAAs regimens, SVR rates among those co-infected with HIV-HCV improved to over 95%, as seen in the

HCV mono-infected population (53). Guidelines, therefore, now recommend all HIV co-infected patients be treated similarly to HCV mono-infected, with careful consideration of drug interactions with ART regimens (46).

These advances in treatment have consequently opened the doors to elimination of HCV. In 2016, the World Health Assembly, the decision-making body of WHO, adopted the global health sector strategy on viral hepatitis 2016-20, with a goal to eliminate HCV as a public health threat by 2030 (2).

2.7. Depression - Epidemiology, Screening, Diagnosis and Treatment

Major depressive disorder or depression is described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as presence of at least five of the nine listed symptoms, and at least one of these five has to be either a depressed mood or loss of all interest and pleasure for the same two-week period. The remaining symptoms are appetite or weight disturbance, sleep disturbance, psychomotor agitation or slowing, fatigue or loss of energy, abnormal inappropriate guilt, poor concentration, and thoughts of death or suicide (54, 55).

Under these DSM-5 criteria, a study suggested that approximately 227 combinations of symptoms could lead to a depression diagnosis (56). Due to these many possible symptom combinations, the clinical courses of depression are very varied, especially with symptoms with opposing behaviours for example, increased vs decreased appetite. Thus,

depression is described as a heterogeneous mental disorder (57, 58). Studies also show that the majority of people with depression have a chronic-recurrent course of illness; the lifetime prevalence estimates vary widely in literature across countries (59-61). The biological mechanism of depression includes several neurotransmitter systems and previous research has shown that the serotonergic (serotonin (5-HT)) and nor-epinephrine/noradrenergic systems are conclusively involved (57, 62, 63). The age of onset is typically in the early to mid 20s, however onset has a large age range (59). There are various other sociodemographic characteristics associated with occurrence of depression including sex, marital status, education, income, and employment (59, 60). Additional predictors include life events, social support, psychosocial impairment, and a number of clinical factors such as previous episodes, severity of episodes, and co-morbid conditions (60).

According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, depressive disorders were one of the leading causes of burden worldwide (ranked as the 13th leading cause of disability adjusted life years (DALY)), with prevalence estimates comparatively higher than many other diseases (64). A recent study estimated that the COVID-19 pandemic led to an additional 53 million cases of major depressive disorder globally (27·6% increase), increasing the total prevalence to 3,153 cases per 100,000 population (65). In Canada, a study in working age Canadian adults found the average annual prevalence of major depressive episodes to be 5.4% among those employed and as high as 11.7% among unemployed participants (66). The GBD 2019

estimates that there are approximately 804,700 prevalent cases of major depressive disorder in Canada (64).

Many tools have been developed to screen for and make a diagnosis of major depression. The diagnostic tools include structured or semi-structured psychiatric assessments and structured diagnostic interviews (54). The gold standard for diagnosis is generally considered to the structured clinical interview for DSM-5 (SCID-5), and different versions are available for clinical and research use.

In addition, a number of tools for identifying potential cases by assessing presence and severity of depressive symptoms are available. Some commonly used depression screening tools are self-rated, such as the 2-item and 9-item Patient Health Questionnaires (PHQs), the 20- or 10-item Center for Epidemiologic studies Depression scale (CES-D) and Beck Depression Inventory (BDI, while others are clinician-rated, such as the Hamilton Depression rating scale, among others (54). These tools, which are widely used in both clinical practice and research, were developed for a variety of purposes: for example, the CES-D-20 scale was developed to screen for depression in the general population, while the BDI was originally developed to assess severity of depressive symptoms in individuals with diagnosed depression (67).

A large number of studies in psychology literature have focused on understanding the constructs that screening tools measure. The Encyclopedia Britannica defines a psychological construct as a “label for a cluster or domain of covarying behaviours” (68).

The underlying constructs of depression cannot be measured directly and thus it is important to consider the validity, reliability, and other psychometric properties of the different tools. A study by Skorikov et al. in 2003 compared the factor structure for two scales, the CES-D-20 and BDI, in order to assess if they measure the same underlying latent construct; they concluded that "the BDI and CES-D represent related, but theoretically distinct and empirically different, aspects of the same higher order latent variable, corresponding to the general construct of depression", as represented in figure 2.3 (67). The figure shows the different components of depression measured by the CES-D versus the BDI scales.

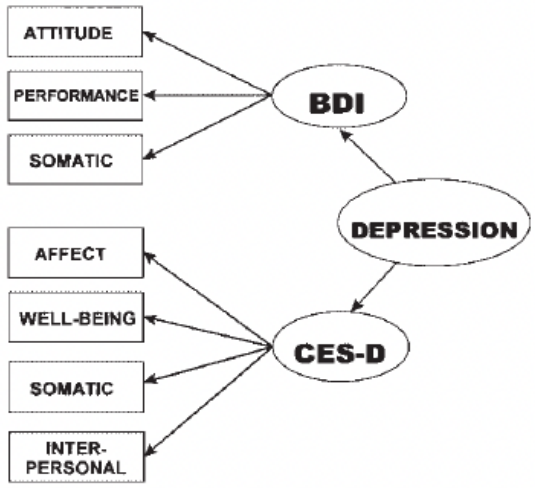

Figure 2.3: Model for BDI and CES-D factor structure

Reproduced from Educational and Psychological Measurement Skorka VB, VanderVoort DJ. Relationships Between The Underlying Constructs Of The Beck Depression Inventory And The Center For Epidemiological Studies Depression Scale.63(2):319-335 (2003)

It is very important to consider when using screening tools that one may not measure the same underlying construct as another tool developed to measure the severity of depressive symptoms in someone with a clinical diagnosis of depression, and their use in place of a formal diagnosis may lead to different estimates than the ones reached

following a diagnostic process. It is essential to recognize that screening tools are not used for clinical diagnosis of depression, and presence of depressive symptoms based on pre-established cut-offs on screening tools is not to equivalent to a clinical diagnosis of depression (69, 70). Additionally, these tools should not also be used as the basis for prescribing antidepressants, as this could lead to possible overtreatment (71).

The screening tools are, however, useful for case-finding, and can help guide detection and assessment of severity (54, 69). These tools are frequently used by clinicians and researchers to identify those at risk of depression, as these symptoms are along the spectrum for major depression. The presence of these symptoms will thus have an impact on different serious outcomes in patients, even before a diagnosis of depression is reached. This assessment can help clinicians recognise segments of the population at risk and intervene with tailored policies to improve outcomes. It is these symptoms that this thesis will focus on.

Both psychotherapy and medications are part of the available treatments for depression. Medications for depression belong to several classes which include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, and serotonin modulators. The older treatments include tricyclic antidepressants, and monoamine oxidase inhibitors (72). The use of a combination of medications would depend on patient tolerance due to several possible side effects; usually the use of both pharmacotherapy and psychotherapy is suggested (73).

2.8. Depression and HIV-HCV infection

There is evidence suggesting that HIV and HCV infections are associated with neuropsychiatric manifestations, mainly depression (3, 74). Studies have shown depression prevalence to be close to 20-30% among PLWH and up to 24% among those with chronic HCV (3, 4, 75). However, these estimates for prevalence vary widely, due to studies conducted in different sub-populations, with different diagnostic/screening methods, study sample sizes and clinical factors such as HIV stage (3, 4). Nevertheless, most studies have consistently shown higher occurrence (2-4-fold) of depression among PLWH compared to the general population. A meta-analysis suggests the prevalence of depression may be higher among HIV-HCV co-infected patients than both HIV and HCV mono-infected individuals respectively (5).

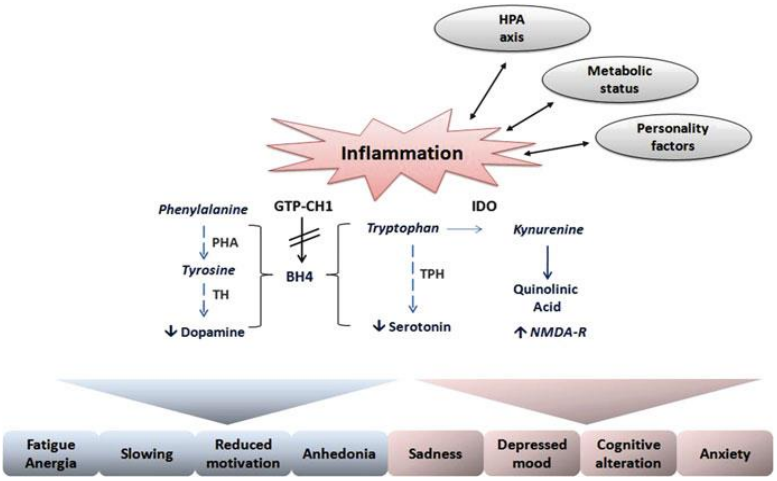

Figure 2.4: Pathways of inflammation-induced neuropsychiatric symptoms

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Depression mechanisms related to HIV and HCV are both biological and psychosocial. It is possible that co-existence of risk factors for depression related to these infections may

lead to this increased vulnerability of the co-infected population to depressive symptoms. Among co-infected persons, ongoing substance use is a common additional risk factor, and may also be affected by presence of depressive symptoms (76). HIV and HCV both affect the central nervous system directly, where they induce an activation of the immune system (3, 77); the release of pro-inflammatory cytokines such as tumour necrosis Factor (TNF)-α and interleukin (IL)-1 alter the levels of neurotransmitters involved in the maintenance of mood, such as serotonin and dopamine, resulting in the development of depression (3, 77, 78). Some of the pathways of depressive symptoms induction related to inflammation are shown in figure 2.3 illustrated by Capuron and Castanon (2017) (79). There are also many known psychosocial pathways to depression including social stresses caused by stigma, discrimination, and lack of social and financial support due to HIV and HCV infections (3, 74).

2.9. Depressive symptoms and HCV treatment

Depression is a well described major side effect of the earlier IFN-ribavirin based HCV antiviral treatments, with some studies showing that more than 20% of those treated developed depression (6). In terms of stages of depression symptoms after IFN treatment, studies have shown that the first set of symptoms that occur in the first week of treatment include fatigue, lack of energy (anergia), lassitude, decreased motivation, motor slowing, reduced appetite, and altered sleep. While these somatic symptoms are among the diagnostic criteria for depression, they are not specific to depression and when they develop in response to the initiation of IFN-α, they do not respond to antidepressant

treatment (79). The second set of symptoms include sadness, decreased mood, reduced ability to experience pleasure (anhedonia), and impaired cognitive function. These symptoms are more specific to a diagnosis of depression and are more responsive to treatment than the somatic symptoms (79). There was also evidence for an increased risk of suicidal ideation associated with IFN treatment among those infected with HIV (80). Due to this, people with current or a history of psychiatric illness often were not prescribed IFN therapy (81). However, with the second-generation IFN-free DAA regimens, there is no evidence of significant psychiatric side effects during and immediately after DAA treatment (7, 82, 83). HCV treatment guidelines have thus been updated and current or past psychiatric illness is no longer a contraindication for treatment (84).

There has been a marked increase in treatment initiation after the second-generation DAAs were licensed in Canada in 2013. Treatment initiation rates increased almost threefold from 8 to 28 per 100 person-years in the CCC (9). However, the study showed that there were major disparities in the initiation rates among people who actively inject drugs, women, and Indigenous populations, with rates as low as 5-12% (9). Thus, in spite of the advantages of DAAs, treatment initiation rates are still not optimal. Patient- and system-level barriers may explain incomplete treatment uptake in these vulnerable populations; depression could be one such barrier. Additionally, there are a few studies that have assessed depressive symptoms before treatment and at SVR ascertainment (83, 85-88). Assessments of long-term impacts of SVR on depression beyond SVR are also scarce in the literature. Thus, further studies are important to understand the possible trends of depression before and after HCV cure. There could be a possible decline over

time via the biological mechanism, or there may not be a change considering the remaining psychosocial risk factors of depression in the HIV and HCV co-infected populations.

3. CHAPTER 3: DATA SOURCES

3.1. Canadian Co-infection Cohort

3.1.1. Participant recruitment

Figure 3.1: Participants enrolled in the CCC from 2003 to 2022

I used data from the Canadian HIV-Hepatitis C Co-Infection Cohort (CCC), which is a publicly funded open multicentre prospective cohort study, ongoing since 2003. The cohort is described in detail elsewhere (89). Briefly, the initial objective of the cohort study was to determine the effect of ARTs for HIV and HCV therapies on liver disease progression in HIV-HCV co-infected populations and has since evolved to evaluate the impacts of DAA. The cohort serves as a significant resource for secondary analyses to better understand co-infection and related health outcomes. The participants are recruited from 18 urban and semi-urban HIV clinics from across six Canadian provinces, to reflect the Canadian epidemic. The cohort sites are the Montreal Chest Institute Immunodeficiency Clinic, Hôpital Notre-Dame, Montréal General Hôpital, and la clinique médical du Quartier Latin in Quebec; the British Columbia Centre for Excellence in HIV/AIDS, Oak Tree Clinic, Pender Community Health Centre, and Native Health Centre in British Columbia; the Southern Alberta HIV Clinic in Alberta; the Sunnybrook Hospital, Windsor Regional Hospital, McMaster University Medical Centre, Ottawa General Hospital, Sudbury Regional Hospital, and Toronto General Hospital in Ontario; the Queen Elizabeth Halifax Health Centre in Nova Scotia; the Regina General Hospital

and the University of Saskatchewan Hospital in Saskatchewan. The map in figure 3.1 shows distribution of participants enrolled across Canada from 2003 to 2022 (90).

The CCC inclusion criteria are: ≥16 years of age, documented HIV infection and evidence of HCV infection (HCV RNA positive and/or HCV seropositive) (89). The serologic evidence of HCV exposure is defined by a positive HCV antibody serology with or without detectable HCV viremia measured via molecular reverse transcription-polymerase chain reaction (RT-PCR) assay. As of February 2022, the CCC has enrolled 2057 participants. The participants are predominately white (70%), male (70%), single (68%), aged 41-50 (42%), with no post-secondary education (50%) and high levels of poverty (monthly income of $501-1000 (39%)). The cohort has a strong representation of Indigenous peoples (21%) (90). Of all recruited participants over time, 644 participants are currently active in the cohort and 437 participants have died. Very recently, overdose has surpassed end stage liver disease as a cause of death in the cohort, indicative of the scale and impact of the overdose epidemic in Canada (90, 91).

3.1.2. Data collection

After obtaining informed consent, sociodemographic and behavioural data are collected from participants by a standardized self-administered baseline questionnaire. Clinical data regarding HIV/HCV treatment histories and co-morbidities are collected during the baseline visit through medical chart reviews by the study coordinators. Blood samples are provided by participants for HIV/HCV testing - viral load, antibody and CD4 testing, and for basic laboratory tests including serum biochemistry, liver profiles, and blood counts.

The participants are then followed longitudinally, with visits every six months. The follow-up questionnaire collects updated demographic and behavioral information. Clinical data for the last six months are collected through medical chart review, including psychiatric diagnosis, medications and HCV treatment initiation and response data with exact start and stop dates for each regimen prescribed, and biological specimens are collected. Health Related-Quality of Life (HR-QoL) is a patient-reported measure collected at each visit using a standardized instrument, EQ-5D-3L (92, 93). It consists of a descriptive system (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a current health visual analog scale. HSU is determined in the cohort by the number of self-reported inpatient, outpatient, specialist, emergency, and walk-in visits in the past 6 months.

3.2. Food Security and HIV-HCV co-infection study

3.2.1. Participant recruitment

I used data from a mixed methods study conducted within the CCC, the Food Security and HIV-HCV co-infection study (FS sub-study), conducted between 2012-2015 (94). The primary objectives were to understand the relationship between food security and behavioural and clinical factors related to HIV-HCV co-infection, HR-QoL, health and treatment outcomes among co-infected patients participating in HIV care in Canada (95). All CCC participants were invited to participate, and the study visits were integrated into the biannual CCC study visits. The FS sub-study recruited 725 CCC participants who were followed for up to 5 visits. The participants had a baseline median age of 49 years, 73% were male, 75% white, and 57% experienced moderate or severe food insecurity at

baseline; the percentage of participants with food insecurity remained around 50% throughout follow-up (96).

3.2.2. Data collection

The FS sub-study used self-administered questionnaires, with an option of interviewer support for the participants. The questions were regarding food insecurity, general and mental health of the participants, ART adherence, health care and social service utilization, housing, and income (94). Food security in the past 6 months was measured using a 10-item adult scale of the Household Food Security Survey Module (HFSSM) (97). A categorical variable was created, with participants with 0-1, 2-5, or ≥6 affirmative responses classified respectively as being food secure, moderately food insecure, or severely food insecure, as per the health Canada criteria. Depression screening was performed in the sub-study using the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) (98), a 10-item Likert scale that assesses presence and severity of depressive symptoms in the past one week. Each item is measured on a 4-point scale, with reverse scoring for the 2 positive items and a total score range of 0-30. We dichotomized the score at 10 to create CES-D-10 classes (1/0), as a score ≥10 is considered depressive symptoms indicative of high risk for major depression (99).

3.3. Ethics approval

The CCC and the FS Sub-Study were approved by the Research Ethics Board of the McGill University Health Centre (2006-1875, BMB-06-006t, 2013-994) and the research

ethics boards of participating institutions. The studies were conducted according to the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the studies. The secondary analysis done for this thesis was approved by the Research Ethics Board of the McGill University Health Centre (2021-6985).

4. CHAPTER 4: PREDICTION OF DEPRESSIVE SYMPTOMS PRESENCE IN THE CANADIAN CO-INFECTION COHORT

4.1. Preface to Manuscript 1

4.1.1. Rationale

As described in the previous chapter, in the parent study, CCC, a major depression diagnosis was available for participants only if it was documented in medical charts reviewed at each visit every 6 months. Through the chart reviews, the CCC did have information about medications prescribed in every 6-month period, which included antidepressant medications. However, antidepressants are prescribed for a number of possible indications other than major depression and thus this alone could not be used as an indicator of major depression (100). Additionally, screening for depression was not part of the standardized CCC questionnaire. However, in the smaller sub-set of the participants (n=725) who were part of the FS sub-study that was carried out between 2012 and 2015, depression screening was performed using the CES-D-10 screening tool. Approximately 1200 participants were recruited into the CCC by end of 2012, and thus more than half of the participants were part of this sub-study. The population was found to be generalizable to the CCC, as shown in table 4.7 in the appendix for Manuscript 1.

There are multiple demographic, clinical, and behavioural characteristics that have been documented as risk factors for depression (101). The CCC collects extensive data regarding these characteristics in people co-infected with HIV and HCV at baseline as well as at follow-up visits. The study also collects participants' HR-QoL data and

medication history. These data can thus be used as predictors of presence of clinically relevant depressive symptoms.

There are several supervised and unsupervised machine learning techniques that enable accurate outcome predictions. These have been used to predict current or future onset, disease course, etc. for psychiatric disorders including depression, anxiety, and schizophrenia (102-104). Demographic and clinical data have been used to create depression prediction models in elderly and people with diabetes (105, 106). However, similar models have not been developed in people living with HIV-HCV co-infection.

In this manuscript, I developed Random Forest classification algorithms to predict presence of depressive symptoms using the depression screening data from the FS sub-study and predictive variables from the CCC.

This manuscript is submitted for publication and is under review at BMC Medical Research Methodology.

This analysis was presented as posters and oral talks at the following conferences/seminars:

1. Work in Progress seminar, Infectious Diseases, and Immunity in Global Health program, Research Institute of the McGill University Health Centre, Montreal, Canada - November 2019 - Oral presentation

2. International Workshop on HIV and Hepatitis Observational Databases (IWHOD) 2020, Sitges, Spain (Cancelled due to the COVID-19 pandemic) - March 2020 - Poster
3. 16th Annual EBOSS Research Day, McGill University, Montreal, Canada - March 2020 - Oral presentation
4. 29th Annual Canadian Conference on HIV/AIDS Research, Virtual - May 2020 – Poster

4.1.2. Application

The algorithms developed in this manuscript were used to predict the CES-D-10 class at each CCC visit to be then used in the next objectives.

In Manuscripts 2 and 3, I used the CES-D-10 classes predicted by the full algorithm, which used all 137 candidate predictors. These predicted classes were then used as exposure measure in Manuscript 2 and outcome measure in Manuscript 3. In Manuscript 4, I used the CES-D-10 classes predicted by the reduced algorithm, with 46 predictors, as exposure. I chose not to use the full algorithm for prediction of exposure in this analysis, as the full algorithm included HSU related predictors.

In all three objectives, I used record-level correction in order to correct for exposure/outcome misclassification. I decided to use the predictive value-based record-level correction, as positive and negative predictive values were estimated for both the full and reduced algorithm in Manuscript 1. This method includes simulation of corrected

exposure at each visit by repeated Bernoulli trials with probability equal to PPV for those classified as CES-D-10 class=1 and 1-NPV for those classified as CES-D-10 class=0 (107).

4.2. Manuscript 1: Predicting the presence of depressive symptoms in the HIV-HCV co-infected population in Canada using supervised machine learning

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Abstract

Background

Depression is common in the human immunodeficiency virus (HIV)-hepatitis C virus (HCV) co-infected population. Demographic, behavioural, and clinical data collected in research settings may be of help in identifying those at risk for major depression. We aimed to predict the presence of depressive symptoms indicative of a risk of depression and identify important classification predictors using supervised machine learning.

Methods

We used data from the Canadian Co-infection Cohort, a multicentre prospective cohort, and its associated sub-study on Food Security (FS). The Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) was administered in the FS sub-study; participants were classified as being at risk for major depression if scores ≥10. We developed two random forest algorithms using the training data (80%) and 10-fold cross validation to predict the CES-D-10 classes - 1. Full algorithm with all candidate predictors (137 predictors) and 2. Reduced algorithm using a subset of predictors based on expert opinion (46 predictors). We evaluated the algorithm performances in the testing data using area under the receiver operating characteristic curves (AUC) and generated predictor importance plots.

Results

We included 1,934 FS sub-study visits from 717 participants who were predominantly male (73%), white (76%), unemployed (73%), and high school educated (52%). At the

first visit, median age was 49 years (IQR:43-54) and 53% reported presence of depressive symptoms with CES-D-10 scores ≥10. The full algorithm had an AUC of 0.82 (95% CI:0.78-0.86) and the reduced algorithm of 0.76 (95% CI:0.71-0.81). Employment, HIV clinical stage, revenue source, body mass index, and education were the five most important predictors.

Conclusion

We developed a prediction algorithm that could be instrumental in identifying individuals at risk for depression in the HIV-HCV co-infected population in research settings. Development of such machine learning algorithms using research data with rich predictor information can be useful for retrospective analyses of unanswered questions regarding impact of depressive symptoms on clinical and patient-centred outcomes among vulnerable populations.

Keywords: HIV-HCV co-infection; Depressive symptoms; Supervised machine learning; Random forests

Background

With shared modes of transmission, co-infection of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is common, with approximately 2.3 million co-infected individuals worldwide [1] [2]. Depression is the most common neuropsychiatric manifestation among people living with HIV and those with chronic HCV. The prevalence of diagnosed major depression is 2-4-fold higher among people living with HIV than the general population and reported to be as high as 24% among those with chronic HCV infection [3, 4]. Potential biological mechanisms include direct infection of the central nervous system and peripheral immune responses which have been shown to induce depression [3, 5]. Psychosocial risk factors including stigma, discrimination, lack of support, and substance use have also been shown to be contributory [3, 5]. Studies report an even higher depression prevalence in the co-infected population, which may be due to the co-existence of risk factors [6].

The presence of significant depressive symptoms may have an impact on outcomes in patients, even in the absence of a major depression diagnosis; for example, the presence of depressive symptoms is associated with non-adherence to antiretroviral therapy among people living with HIV, which may lead to increased viral load and suppressed immune function [7, 8]. Screening tools can be used to assess presence and severity of depressive symptoms and identify those at risk for major depression [9, 10], permitting early intervention. Co-infected individuals often live with multiple co-morbid conditions and thus spend a considerable amount of time in healthcare settings [11]. Depression screening among HIV and HCV infected patients is seldom routinely performed during clinical assessments or in longitudinal cohort studies, despite the known high prevalence

of depression [12-14]. Multiple demographic, clinical and behavioural characteristics have been documented as risk factors for depression [15] and these data are generally collected in clinical and research cohorts. Thus, such data could be used retrospectively to predict the presence of depressive symptoms severe enough to be associated with negative health outcomes or an increased risk of being diagnosed with major depression and to follow this risk over time. Such measures will be useful for exploring important questions regarding depressive symptoms, their evolution and response to therapies in the co-infected population.

Machine learning includes robust techniques that enable accurate outcome predictions in medical research. In mental health research, machine learning has been used to predict current or future onset, disease course and treatment outcomes for psychiatric disorders including depression, anxiety, and schizophrenia [1, 16, 17]. A wide range of data sources have been used for developing these prediction algorithms including electronic medical records, neuroimaging, and social media. Demographic and clinical data have been used to create depression prediction models in the elderly and people with diabetes [18, 19]. However, similar models have not yet been developed in people living with HIV-HCV co-infection.

We leveraged a non-parametric supervised machine learning technique using cohort data to develop classification algorithms to predict the presence of depressive symptoms indicative of a risk for major depression and characteristics important for prediction of depressive symptoms in HIV-HCV co-infected individuals in Canada.

Methods

Data Sources and study sample

We used data from the Canadian HIV-HCV Co-Infection Cohort (CCC), an open multicenter prospective cohort study, ongoing since 2003 and an associated sub-study, the Food Security and HIV-HCV co-infection study (FS sub-study) [20, 21]. The CCC recruits from 18 HIV centers, both urban and semi-urban across six Canadian provinces (Quebec, British Columbia, Alberta, Ontario, Nova Scotia, and Saskatchewan). [20] Eligibility criteria include ≥16 years of age, documented HIV infection, and evidence of HCV infection (HCV RNA positive and/or HCV seropositive). The study had recruited 2018 participants as of July 2020. Participants are followed longitudinally, with follow-up visits every six months. Sociodemographic, behavioural, and health-related quality of life (HR-QoL) data are collected from participants by a standardized self-administered questionnaire at each visit. HR-QoL is measured using EuroQol-5 Dimension-3 Level (EQ-5D-3L) [22]. Clinical data including HIV/HCV treatment, co-morbidities, psychiatric diagnoses, and other medications are collected via medical chart reviews. Laboratory testing at each visit include HIV and HCV related tests, hematology, biochemistry, and liver profiles.

The FS sub-study is a mixed methods study conducted within the CCC between 2012 and 2015. All CCC participants were invited to participate and study visits were integrated into the biannual CCC visits. The FS sub-study recruited 725 participants and they were followed up for a maximum of 5 visits. The study collected data on food insecurity, general and mental health (including depression screening), treatment adherence and health care utilization using a self-administered questionnaire [21].

Depression screening was performed only in the FS sub-study; thus, the analytic sample in this study only included FS sub-study participant visits. The FS sub-study visits were merged with corresponding CCC visit data. As the two study visits for CCC and FS sub-study were, on occasion, not on the same day, information from visits within 3 months of each other were considered ‘concurrent’. We used three exclusion criteria to create the final study sample - 1) participant visits were excluded if no depression screening measure (see below) was available at that visit; 2) participant visits were excluded if there was no corresponding CCC visit (within the 3-month window), as the predictors used in this analysis were derived from the CCC; and 3) all visits for a participant were excluded if no data was available for a predictor in all of their study visits.

Outcome

Depression screening was conducted in the FS sub-study using the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10), which is a shortened version of the CES-D-20 scale [23]. The CES-D-10 is a 10-item Likert scale questionnaire that assesses presence and severity of depressive symptoms in the past one week. Each item is measured on a 4-point scale, with reverse scoring for the 2 positive items and a total score range of 0-30. We dichotomized the score at 10 to create the CES-D-10 classes (1/0), as a score ≥10 is widely considered for the presence of depressive symptoms indicative of high risk for major depression, hereafter referred to as depressive symptoms for brevity [23]. Both the scale and the dichotomization at 10 have been validated in HIV populations in Canada [24].

Predictors

We selected candidate predictors (x) from the CCC data based on the literature and subject matter expertise. We included predictors from five major categories: questions related to mental health, HR-QoL, sociodemographic, behavioural, and clinical characteristics; see Table 4.1. We selected a total of 137 candidate predictors, of which 136 were categorical and 1 was continuous (EQ-5D-3L - health state). From this list of candidate predictors, we selected a subset of predictors (x=46) that may be more regularly available in most research settings based on expert opinion. See Table 4.5 in Appendix A for an exhaustive list of candidate predictors (x=137) and their corresponding categories.

Statistical Analysis

Primary analysis

We assessed proportion of missing data for each predictor. For predictors with <5% missing data, we carried the value from the last visit forward. For predictors with ≥5% missing data and when data were missing for a predictor for all visits for a participant, we used an additional category of “no response” for categorical variables, which we hypothesized could be informative in the prediction algorithm (See Table 4.5 in appendix A) since the participant decision to respond (or not) is itself potentially clinically informative.

We used the supervised machine learning technique of Random Forests (RF), an ensemble learning approach which uses bootstrap aggregation of multiple decision trees, combining predictions from these many trees [25]; see more details about RF in Appendix

B. We used probability machines to estimate the CES-D-10 class probabilities at each visit and then determined CES-D-10 class at default probability threshold [26]. We developed two RF algorithms - 1. Full algorithm: Using all candidate predictors (x = 137) and 2. Reduced algorithm: Using a selected subset of more commonly available predictors (x=46) based on expert opinion, which could be more generalizable to research studies beyond the CCC; see appendix A. We split the analytical sample into training and testing data, using the recommended 80:20 split, such that we had data for performance evaluation (testing) that was completely independent of data used for model development (training) and thus ensure an unbiased evaluation [27]. We performed the 80/20 split using the "createdatapartition" function from the Caret package in R, such that both CES-D-10 classes were represented in each set [28]. The algorithm was then developed by 10-fold cross-validation using only the training data and RF hyperparameters (i.e., various RF settings like number of decision trees) were tuned to maximize accuracy [27]; see Appendix C for details.

Additional Analyses

We conducted several analyses to provide additional details about the classification characteristics from the main analysis and assess robustness of the results: A) Using one visit per individual (total 717 visits), to assess difference in performance compared to the use of multiple visits per individual; B) Algorithms using three different CES-D-10 thresholds - 8, 13, and 15 - based on suggested cut-offs in the literature [29, 30]; C) An algorithm that included food insecurity as a predictor, which was collected only in the FS sub-study. Food insecurity in the past 6 months was measured using a 10-item adult scale

of the Household Food Security Survey Module (HFSSM) [31]. A categorical variable was used, with participants with 0-1, 2-5, or ≥6 affirmative responses classified respectively as being food secure, moderately food insecure, or severely food insecure, as per the Health Canada criteria ; and D. RF regression algorithms to predict continuous CES-D-10 score, evaluated using R-squared and root mean squared error (RMSE), which provides information regarding differences between the predicted scores and the actual scores [32].

Performance evaluation

The final tuned algorithms were implemented in the testing data, which was not used in the development stage. The tuning parameters are shown in Table 4.6 in Appendix C. The overall performance and calibration measures are described in detail in Appendix C. To assess the ability to distinguish between classes (discrimination), we plotted receiver operating characteristic (ROC) and estimated the area under the ROC curve (AUC) [32, 33]. We used the default probability threshold of 0.50 for classification and at this threshold, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) measures were then estimated with the 95% confidence intervals (CI) [34]. Finally, the RF importance metrics were generated, and importance plots were generated to present the 25 most important predictors in classifying participants with depressive symptoms by the two algorithms. We used RStudio v.1.2 and Stata v.16.0 to develop and evaluate these algorithms [35, 36]. The development of the RF algorithms was done using R package

ranger and caret; for performance evaluation, we used the performance assessment function in R by Wong et. al. (2019) [28, 37-39].

Results

Study population

Of the 1973 FS sub-study visits in a total of 725 participants, 39 study visits were excluded based on the exclusion criteria described in the methods - 16 visits (2 participants) with no CES-D-10 score, 18 visits (5 participants) with no con-current CCC visit and all 5 visits from 1 participant with no predictor data (EQ-5D health state) in all visits. Thus, 717 participants with a total of 1934 visits contributed to the final study sample. The participant characteristics at the first visit included in the sample are described in Table 4.2. The median CES-D-10 score was 10 (IQR, 5, 15), with 53% of the participants reporting the presence of depressive symptoms with CES-D-10 scores ≥10; 45% were prescribed one or more psychotropic medications such as bupropion and citalopram at baseline, but only 10% had a diagnosis of depression documented in their medical chart. Participants were predominantly male (73%) and white (76%). The population was vulnerable in terms of socioeconomic status (SES) characteristics with 73% unemployed, 76% with monthly income <$1500, 52% with high school being the highest level of education and 46% receiving welfare at baseline. Approximately 34% were current injection drug users, 62% current alcohol drinkers and 75% were current tobacco smokers. Only a small proportion had advanced liver disease (4%) or a current AIDS related illness (4%) and 35% were asymptomatic with a current CD4 cell count >500 cells/μl (CDC clinical staging - A1).

Performance evaluation

The training data consisted of 1548 visits and testing data consisted of 386 visits. The algorithms in the primary analysis showed acceptable calibration, as seen in Figure 4.3 in appendix C. With regard to discrimination, the ROC curve for the primary analyses is shown in Figure 4.1, with the curve close to the upper left-hand corner. The estimated AUCs wert 0.82 (95% CI: 0.78-0.86) and 0.76 (95% CI: 0.71-0.81) for the full and reduced algorithms respectively. The estimated sensitivity, specificity, PPV, NPV, LR+ and LR- are presented in Table 4.3. The importance plots with 25 most important predictors for both algorithms are shown in Figure 4.2. Employment, HIV clinical stage, revenue source, body mass index (BMI), and education were the 5 most important predictors.

Additional analyses

The results for the additional analyses A-D are shown in Table 4.4 and summarized here. A) When using information from a single visit per individual, the overall performance was much lower, with AUC of 0.74 vs 0.82 for the full algorithm and 0.60 vs 0.76 for the reduced algorithm. B) For algorithms with the additional CES-D-10 thresholds, the AUC point estimate was higher for the full algorithm for cut-off 15 compared to 10 (0.87 vs 0.82). The other cut-off estimates were similar for to the corresponding algorithms for cut-off 10, with overlapping confidence intervals. C.) The algorithm including the additional predictor of food insecurity had a similar AUC estimate to the full algorithm, with overlapping confidence intervals. D.) The full algorithm predicting continuous CES-D-10 scores had a R-squared of 0.5 indicating that the algorithm explained only 50% of the variability in the CES-D-10 scores and had a high RMSE of 4.8, while for the reduced

algorithm with a r-squared of 0.3, the algorithm explained only 30% of the variability in the scores and also had a high RMSE of 5.5.

Discussion

We developed a random forest algorithms using patient data from a cohort study that reliably predicted the presence of depressive symptoms indicative of a risk of major depression in a vulnerable HIV-HCV co-infected population. The algorithms used a set of selected candidate predictors (x = 137) from the cohort. The full algorithm using all candidate predictors performed better, with an AUC of 0.82, which indicates a 82% chance of distinguishing between CES-D-10 classes compared 0.76 for the reduced algorithm which used a smaller subset (x = 46) [33]. The prevalence of depressive symptoms was very high in our study, with more than 50% individuals found to be at risk for depression by CES-D-10 at their first visit. Despite this, only 10% had a documented depression diagnosis in their medical record suggesting there could be a substantial underestimation of the burden of depressive illness in this population without screening.

We developed this tool to assess if patient data that is commonly collected in clinical charts and research studies could be useful in predicting presence of depressive symptoms, which is seldom directly measured routinely for all patients, nor measured repeatedly over time. This tool will be most useful for conducting longitudinal clinical and epidemiologic research rather than for clinical care. It may prove useful to help identify people at risk for depression, study how this risk changes over time and with various interventions.

Most studies using machine learning have predicted the future onset of depressive symptoms [19, 40, 41] while a few, like ours, have focused on current depression prediction [42, 43]. A variety of predictors including demographic and clinical data, past medical history and life events have been studied. A range of machine learning algorithms like artificial neural networks, support vector machines, naïve Bayes classifier, and random forest were used in the general population and for specific groups like geriatric population and people with diabetes. These algorithms yielded AUC measures similar to ours, ranging between 0.70-0.95.

CCC collects extensive demographic, behavioral and clinical data. Using the full range and diversity of available predictors did show excellent discrimination in the full algorithm. However, for greater applicability, we chose to use a subset of 46 predictors that may be more readily available in other research settings, and despite using one third the number of predictors and less granular data, the overall discrimination was still acceptable. The additional analysis using only one visit per participant had a comparatively lower AUC, which may have been due to the smaller sample size and thus lower variability in the available data.

The algorithm we developed was a purely prediction algorithm and hence estimation of the strength of the effect of individual predictors is not possible. Further analysis with different modeling strategies would be needed for this assessment. However, the algorithm does provide some insight into factors that may be important for classification. The five most important predictors are related two main themes - i. SES (education, revenue source and employment) and ii. overall health status (HIV clinical stage and BMI). SES is a known strong determinant of depression. Receiving welfare and being

from a low-income household has been associated with an elevated risk of food insecurity, and mental health issues [44, 45]. In Canada, almost 20% of people with major depression have been reported to be unemployed [46]. Another important health status related predictor was BMI. There have been studies with conflicting results regarding association between BMI and depression, and possible difference across race and gender [47, 48] and that BMI categories may not adequately capture people's health status and thus this predictor needs to be considered with caution [49]. Finally, in the full algorithm with all 137 predictors, the EQ-5D-3L anxiety/depression dimension was the most important predictor and all EQ-5D dimensions (mobility, self-care, usual activities, pain/discomfort, and health state) were among the 25 most important. This provides further evidence that participant's health status, and in the case of EQ-5D-3L, their perceived health status, are important in predicting depressive symptoms.

This study thus has many strengths. The CCC is generalizable to the HIV-HCV co-infected patients engaged in care in Canada, due to the recruitment from a variety of clinical settings (outreach, primary and tertiary care clinics in urban and semi-urban areas across the country). The sample used to develop these algorithms was generalizable to the parent CCC (see Appendix D; Table 4.7). The methodology used, RF, is non-parametric, highly accurate, and relatively robust to outliers, noise and does have safeguards from overfitting and thus improves chances of applicability beyond the data. Nevertheless, external validation is needed before application in other cohorts and research, to mitigate the risk of overfitting. In addition, the predictor importance plots provided some insight regarding predictors that play a major role in the accurate prediction of depressive symptoms.

The study however has limitations. The sample size is small as compared to big data applications of RF using electronic health records. Some predictors described in other studies such as childhood trauma, food insecurity among others, were not available for the full CCC. For example, in the additional analysis where we added the food security variable that was collected only in the food security sub-study was included, the AUC was slightly higher. Additionally, we categorized the CES-D-10 to create the binary classes, and thus may have lost some data by not predicting the individual CES-D-10 scores. We did develop a regression algorithm to predict the continuous CES-D-10 scores in additional analysis E, but it could only explain a small portion of the variability in the outcome. The gold standard depression diagnosis was not available in this study and thus the validity of the cut-off of 10 could not be assessed directly in this sample. In general, the overall AUCs were similar when using three other suggested CES-D- 10 cut-offs (8, 13, and 15) compared to a cut-off of 10. However, the full algorithm using a cut-off of 15 appears to have a higher AUC (0.87) than that of using a cut-off 10 (0.82). It will be important to assess in future studies whether this higher threshold may be more applicable to the co-infected population. However, since the CES-D-10 cut-off of 10 has been validated in HIV populations in Canada [24], we decided to use this threshold for comparability with available literature and future studies which may use this common threshold.

With a high proportion of participants with depressive symptoms in this population, it is important not to miss possible cases. Even if the algorithms we developed are considered to have acceptable discrimination (≥0.7) based on arbitrary thresholds, we would still

misclassify a fair proportion of cases and thus this possible misclassification needs to be considered. Finally, this algorithm is applicable when the majority of the predictors are collected. However, in settings where such data is not available, especially completely clinical non-research setting implementing routine screening tools like the CES-D-10 should be considered, especially given the high prevalence of depressive symptoms we observed in this co-infected population.

Conclusions

Depressive symptoms indicative of a risk for depression were common in our population of people living with HIV-HCV co-infection. The random forest algorithms we developed shows promise in accurately predicting an elevated risk of major depression using data on patient characteristics collected in research settings. The algorithms identified important characteristics for depressive symptoms classification including employment, HIV clinical stage, revenue source, BMI, and education. Such machine learning algorithms can be used in research settings especially cohort studies where such data may be available to predict presence of depressive symptoms and use this information to understand the impact of depressive symptoms on clinical, health service and patient-reported outcomes in vulnerable populations.

Table 4.1: Candidate predictors used in the random forest algorithms

Category	All Candidate Predictors
Questions related to mental health	Psychiatric institution or psychiatric hospital stay; Psychiatric diagnoses in chart reviews; Use of psychotropic medications (e.g., antidepressants, sedative hypnotics, atypical and typical anti-psychotics)
HR-QoL	EQ-5D-3L - standardized instrument - Descriptive system (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) - Current health state with a visual analog scale – scores range between 0-100
Sociodemographic characteristics	Age; Gender; Race/ethnicity; Immigration status; Living situation; Shared accommodation details; Education; Employment; Monthly income; Source of income
Behavioral characteristics	Injection drug use (ever/P6M); Non-injection drug use (ever/P6M); Needle/equipment sharing behaviors (ever/P6M); Snort (ever/P6M); Sharing behaviors for snorting apparatus (ever/P6M); Marijuana use; Therapy for drug addiction; Alcohol use (ever/P6M); Alcohol abuse; Smoking (ever/P6M); Sexual orientation; number of sexual partners; Sex work; Incarceration (ever/P6M); Tattoos; Body piercing
Clinical characteristics	BMI category; HIV viral load; CD4 count; HCV RNA; HIV disease stage; AIDS defining illness; health services used in the past 6 months (walk-in clinic, emergency room, inpatient, general practitioner, HIV clinic and specialist); Previous interferon-based HCV treatment; current antiretroviral therapy; Hepatitis B diagnosis; sexually transmitted disease diagnosis; end-stage liver disease (cirrhosis, ascites, varices, portal hypertension, encephalopathy, hepatocellular carcinoma); APRI, a measure of liver fibrosis; cardiovascular disease; autoimmune disease; hypertension; thyroid disease; psoriasis; lipodystrophy; hypercholesterolemia

Abbreviations: HR-QoL: Health related quality of life; EQ-5D-3L: EuroQoL-5Dimension-3Level; P6M: in the past 6 months; BMI: Body Mass Index; HIV: Human Immunodeficiency Virus; CD4: Cluster of differentiation 4 receptor; HCV: Hepatitis C virus; RNA: Ribonucleic acid; AIDS: Acquired Immunodeficiency Syndrome; APRI: Aspartate Aminotransferase (AST) to platelet ratio

Table 4.2: Baseline characteristics of participants in the study sample (n=717)

Characteristics	**Participants (n = 717) n (%) or median (IQR)**
Age	49 (43, 54)
Gender – Male	522 (73)
Race/Ethnicity	
Asian	11 (2)
Black	28 (4)
White	541 (76)
Metis	32 (5)
First nation	102 (14)
Hispanic/Latino	7 (1)
Born outside Canada	64 (9)
Education - High school educated	376 (52)
Employment - Unemployed	525 (73)
Monthly income - < $1500	543 (76)
Revenue Source - Welfare	332 (46)
Current injection drug use	244 (34)
Current alcohol use	444 (62)
Current smoking	534 (75)
BMI category	
Underweight (< 18.5 kg/m^2)	40 (6)
Normal weight (18.5-25 kg/m^2)	312 (44)
Overweight (25-29.9 kg/m^2)	189 (26)
Obese (30.0 kg/m^2)	87 (12)
End-stage Liver disease	27 (4)
HIV clinical stage - A1 (Asymptomatic and CD4 >500 cells/μl)	248 (35)
Past AIDS related illness	28 (4)
CES-D-10 score	10 (5, 15)
CES-D-10 category - ≥10	382 (53)
Depression diagnosis	68 (10)
Prescribed antidepressant medications	320 (45)
HR-QoL using EQ-5D-3L instrument Anxiety/depression Not anxious or depressed Moderately anxious or depressed Extremely anxious or depressed Current health state (visual analog scale)	 352 (49) 302 (42) 60 (8) 70 (56, 80)

Abbreviations: IQR: Interquartile range; CES-D-10: Center for Epidemiologic Studies Depression Scale-10; AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus; BMI: Body Mass Index; HR-QoL: Health related quality of life; EQ-5D-3L: EuroQoL-5Dimension-3Level

Table 4.3: Performance evaluation in the primary analysis

Evaluation measure (95% CI)	Full algorithm (x = 137)	Reduced algorithm (x=46)
AUC	0.82 (0.78-0.86)	0.76 (0.71-0.81)
Sensitivity	0.77 (0.70-83)	0.70 (0.63-0.76)
Specificity	0.73 (0.66-0.79)	0.70 (0.63-0.76)
PPV	0.74 (0.68-0.80)	0.70 (0.63-0.76)
NPV	0.76 (0.69-0.82)	0.69 (0.62-0.76)
LR +	2.8 (2.2-3.6)	2.3 (1.8-2.9)
LR -	0.3 (0.2 – 0.4)	0.4 (0.3-0.6)

Abbreviations: CI: Confidence interval; AUC: Area under the Receiver Operating Characteristic curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR +: Positive likelihood ratio; LR -: Negative likelihood ratio

Table 4.4: Comparison of performance evaluation measures for primary and additional analyses

Sr. No.	Analysis	OOB error	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Primary Analyses					
1	Full algorithm (x = 137)	0.16	0.82 (0.78-0.86)	0.77 (0.70-0.83)	0.73 (0.66-0.79)
2	Reduced algorithm (x = 46)	0.20	0.76 (0.71-0.81)	0.70 (0.63-0.76)	0.70 (0.63-0.76)
Additional Analyses					
A	**One visit per individual**				
1	Full algorithm (x = 137)	0.17	0.74 (0.66-0.82)	0.70 (0.58-0.80)	0.64 (0.52-0.76)
2	Reduced algorithm (x = 46)	0.23	0.60 (0.50-0.69)	0.73 (0.61-0.82)	0.37 (0.26-0.50)
B	**Different CES-D-10 cut-offs**				
I	**Cut-off – 8**				
1	Full algorithm (x = 137)	0.17	0.85 (0.81-0.89)	0.91 (0.87-0.95)	0.67 (0.59-0.74)
2	Reduced algorithm (x = 46)	0.19	0.79 (0.74-0.83)	0.83 (0.77-0.87)	0.60 (0.52-0.67)
II	**Cut-off – 13**				
1	Full algorithm (x = 137)	0.15	0.80 (0.76-0.85)	0.62 (0.54-0.70)	0.81 (0.76-0.86)
2	Reduced algorithm (x = 46)	0.20	0.79 (0.74-0.83)	0.45 (0.37-054)	0.87 (0.82-0.91)
III	**Cut-off - 15**				
1	Full algorithm (x = 137)	0.14	0.87 (0.83-0.91)	0.55 (0.45-0.65)	0.95 (0.91-0.97)
2	Reduced algorithm (x = 46)	0.17	0.73 (0.67-0.79)	0.27 (0.19-0.36)	0.94 (0.91-0.97)
C	**With food insecurity variable (x = 138)**	0.16	0.84 (0.80-0.87)	0.77 (0.70-0.83)	0.73 (0.67-80)

Abbreviations: OOB: Out-of-Bag Samples; AUC: Area under the Receiver Operating Characteristic curve; CI: Confidence interval; CES-D-10: Center for Epidemiologic Studies Depression Scale-10

Figure 4.1: Receiver Operating Characteristic (ROC) curve for the A. Full algorithm (x = 137) and B. Reduced algorithm (x=46)

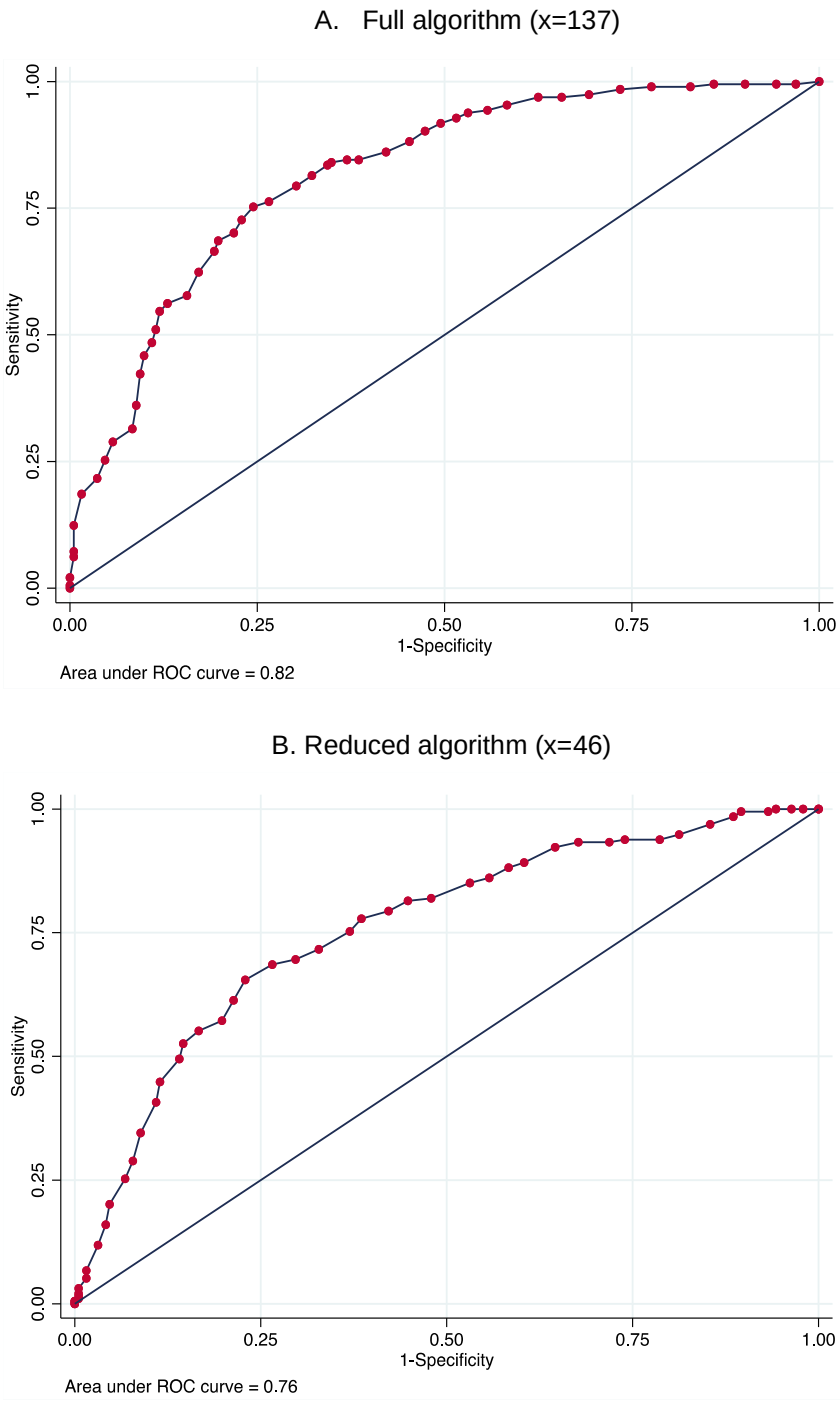
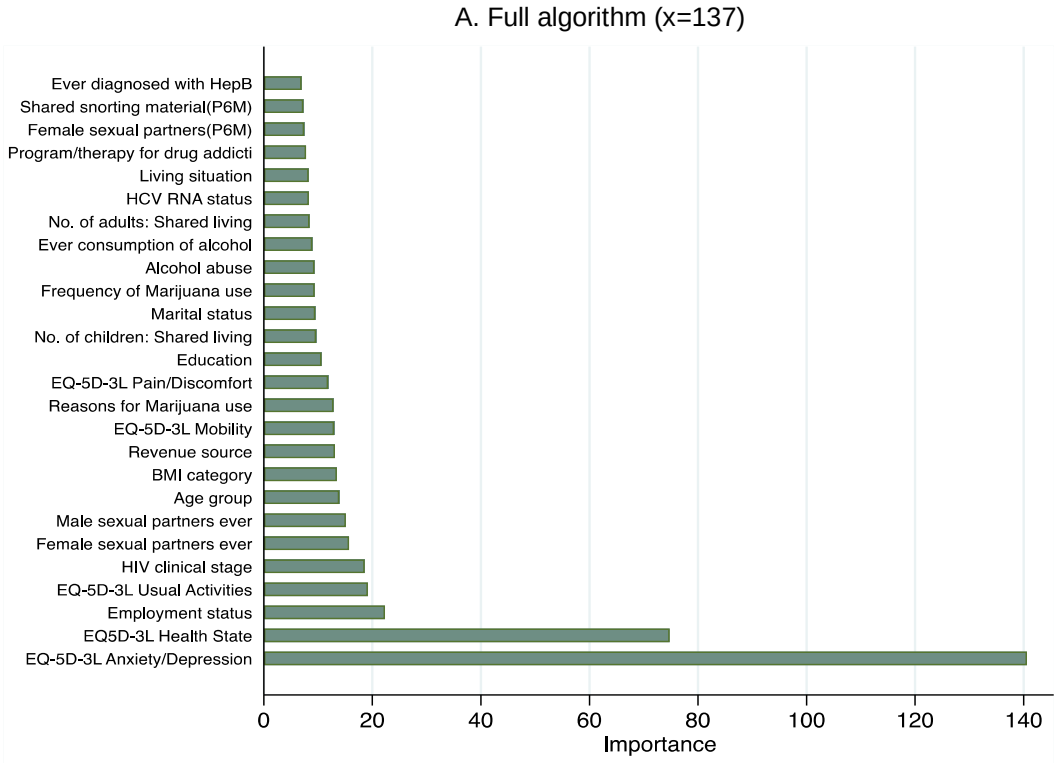
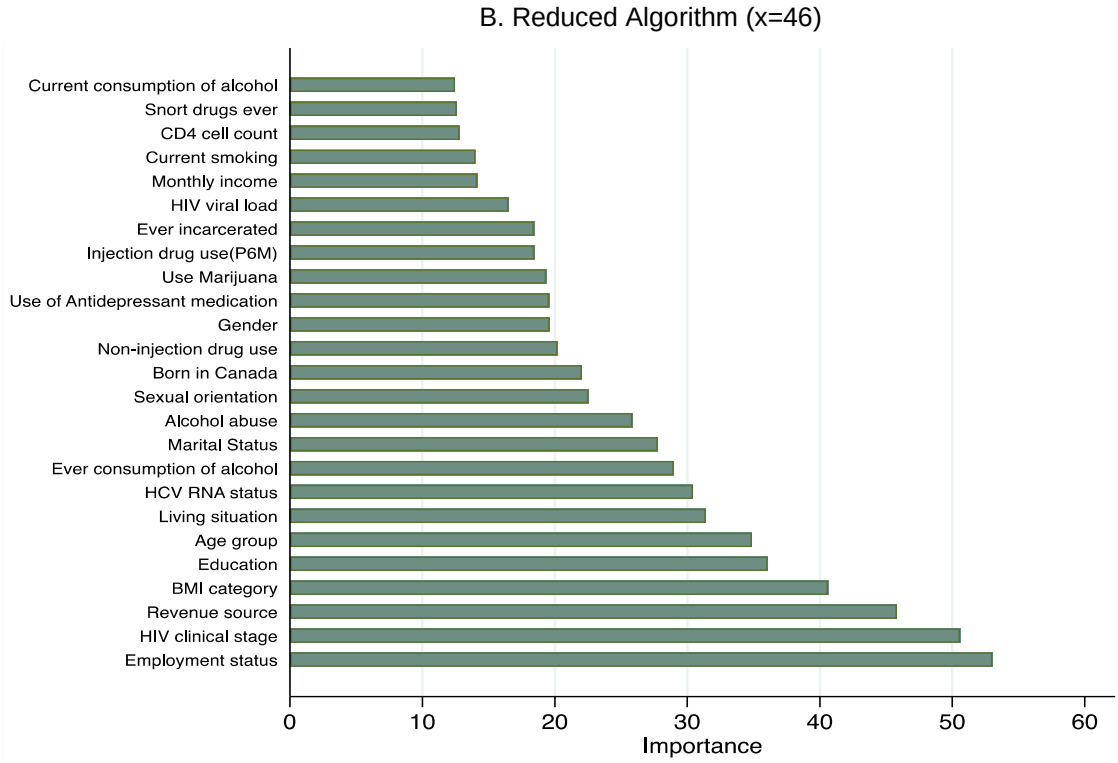


Figure 4.2: Predictor importance plots: A. Full algorithm and B. Reduced algorithm





Abbreviations: BMI: Body Mass Index; P6M: In the past 6 months; CD4: Cluster of differentiation 4 receptor; EQ-5D-3L: EuroQoL-5Dimension-3Level; RNA: Ribonucleic acid; Hep B: Hepatitis B virus

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Board of the McGill University Health Centre (2021-6985). The CCC and the FS Sub-Study were approved by the Research Ethics Board of the McGill University Health Centre (2006-1875, BMB-06-006t, 2013-994) and the research ethics boards of participating institutions. The study was conducted according to the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available. According to the stipulations of patient consent provided and our Institutional Ethics review boards, study records including confidential information collected during the study must be stored securely for 25 years after study completion, as required by Canadian clinical trial regulations. However, data stripped of personal identifiers, may be shared upon request to the corresponding author, or to: Mr. Sheldon Levy, Clinical Trials 2 Research Ethics Board (REB) Coordinator, MUHC Centre for Applied Ethics (sheldon.levy@muhc.mcgill.ca).

Competing interests

JC received grants and consulting fees from ViiV Healthcare, Merck, and Gilead and personal fees from Bristol-Myers Squibb. CC has received personal fees for being a member of the national advisory boards of Gilead, Merck, Janssen, and Bristol-Myers Squibb. BC is a board member, consultant, and has received grants and payment for lectures from AbbVie, Gilead, and Merck, and payment for educational presentations from AbbVie. MH has served as a consultant for Merck, Vertex Pharmaceuticals, Pfizer, Viiv Healthcare, and Ortho-Jansen. MH has also received grants from the National Institute on Drug Abuse, as well as payment for lectures from Merck and Ortho-Janssen. MLV reports personal fees from Abbvie, personal fees from Merck, personal fees from Gilead, outside the submitted work. SW received grants, consulting fees, lecture fees, nonfinancial support, and fees for the development of educational presentations from Merck, ViiV Healthcare, GlaxoSmithKline, Pfizer, Gilead, AbbVie, Bristol-Myers Squibb, and Janssen. MBK reports grants for investigator-initiated studies from ViiV Healthcare, AbbVie, Merck, and Gilead; and consulting fees from ViiV Healthcare, Merck, AbbVie, and Gilead. GM, EEMM, MJB, CLD, VML, and AW have no conflicts of interest to disclose.

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Author contributions

All authors contributed to this study, as required by the International Committee of Medical Journal Editors. MBK, EEMM and GM conceived of and designed the study. GM and CLD prepared the analytical dataset. GM performed all statistical analyses. GM, EEMM and MBK drafted the initial manuscript. All co-authors MJB, JC, CC, BC, MH, VML, MLV, SW, and AW revised the document critically and gave final approval prior to completion. All authors take responsibility for the accuracy and integrity of this work.

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Authors' information

Not applicable.

List of Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

APRI: Aspartate Aminotransferase (AST) to platelet ratio

AUC: Area under the Receiver Operating Characteristic Curve

BMI: Body Mass Index

CCC: Canadian Co-infection Cohort

CD4: Cluster of differentiation 4 receptor

CDC: Centre for Disease Control

CES-D-10: Center for Epidemiologic Studies Depression Scale-10

CI: Confidence Interval

EQ-5D-3L: EuroQol-5 Dimension-3 Level

FS: Food Security

HCV: Hepatitis C virus

Hep B: Hepatitis B virus

HFSSM: Household Food Security Survey Module

HIV: Human Immunodeficiency Virus

HR-QoL: Health-related Quality of Life

IQR: Interquartile Range

LR-: Negative likelihood ratio

LR+: Positive likelihood ratio

NPV: Negative Predictive Value (NPV),

OOB: Out-of-Bag Samples

P6M: in the past 6 months

PPV: Positive Predictive Value

RF: Random Forests

RMSE: Root Mean Squared Error

RNA: Ribonucleic acid

ROC: Receiver Operating Characteristic

SES: Socioeconomic Status

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4.3. Manuscript 1: Appendix

Appendix A: Candidate predictors

Appendix B: Introduction to Random Forests

Appendix C: Supplementary methods and results

Appendix D: Sample generalizability

Appendix A: Candidate Predictors

Table 4.5 below provides an exhaustive list of predictors and their corresponding categories used in this analysis.

Table 4.5: Supplementary table - List of candidate predictors

Sr. no.	Predictors	Categories	Participant visits (n=1934) n (%) or Median (IQR)	Included in	
				Reduced Algorithm (x = 46)	Full Algorithm (x = 137)
1	Have you ever been in a psychiatric institution or psychiatric hospital? (Ever or since the last interview)	Yes No No response	106 (5.5) 1825 (94.4) 3 (0.2)	Yes	Yes
2	Use of psychotropic medications	Yes No	884 (45.7) 1050 (54.3)	Yes	Yes
	Has the patient ever had any of the following psychiatric diagnoses? (Ever at baseline)				
3	Depression	Yes No No response	102 (5.3) 1829 (94.6) 3 (0.2)	Yes	Yes
4	Bipolar disorder	Yes No No response	12 (0.6) 1918 (99.2) 4 (0.2)	No	Yes
5	Schizophrenia	Yes No No response	15 (0.8) 1915 (99.0) 4 (0.2)	No	Yes
6	Personality disorder	Yes No No response	18 (0.9) 1912 (98.9) 4 (0.2)	No	Yes
7	Other psychiatric disorder	Yes No	40 (2.1) 1894 (97.9)	No	Yes
8	Any psychiatric diagnoses (other than depression)	Yes No No response	69 (3.6) 1862 (96.3) 3 (0.2)	Yes	No
	Use of specific substances				
9	Cocaine	Yes No	553 (28.6) 1381 (71.4)	No	Yes
10	Crack	Yes No	373 (19.3) 1561 (80.7)	No	Yes
11	Heroin	Yes No No response	216 (11.2) 1717 (88.8) 1 (0.1)	No	Yes

12	Speedball (Cocaine + Heroine)	Yes No No response	34 (1.2) 1899 (98.2) 1 (0.1)	No	Yes
13	PCP/Mescaline	Yes No No response	6 (0.3) 1927 (99.6) 1 (0.1)	No	Yes
14	Methadone	Yes No	125 (6.5) 1809 (93.5)	No	Yes
15	Morphine	Yes No No response	125 (6.5) 1808 (93.4) 1 (0.1)	No	Yes
16	LSD	Yes No No response	9 (0.5) 1924 (99.4) 1 (0.1)	No	Yes
17	Amphetamines	Yes No No response	91 (4.7) 1842 (95.2) 1 (0.1)	No	Yes
18	Methamphetamine	Yes No No response	152 (7.8) 1781 (92.1) 1 (0.1)	No	Yes
19	Talwin/Ritalin	Yes No No response	8 (0.4) 1925 (99.5) 1 (0.1)	No	Yes
20	Ritalin alone	Yes No No response	43 (2.2) 1890 (97.7) 1 (0.1)	No	Yes
21	Benzodiazepines	Yes No	86 (4.5) 1848 (95.5)	No	Yes
22	Barbiturates	Yes No No response	16 (0.8) 1917 (99.1) 1 (0.1)	No	Yes
23	Dilaudid	Yes No	130 (6.7) 1804 (92.3)	No	Yes
24	Percocet	Yes No No response	39 (2.0) 1894 (97.9) 1 (0.1)	No	Yes
25	Oxycodone	Yes No No response	61 (3.2) 1872 (96.7) 1 (0.1)	No	Yes
26	Alcohol	Yes No No response	13 (0.7) 1920 (99.2) 1 (0.1)	No	Yes

27	Freebase	Yes No	71 (3.7) 1863 (96.3)	No	Yes
28	Demerol	Yes No	3 (0.2) 1931 (99.8)	No	Yes
29	MDA	Yes No	17 (0.9) 1917 (99.1)	No	Yes
30	Mushrooms	Yes No	15 (0.8) 1919 (99.2)	No	Yes
31	Solvent - drink (Aqua Velva)	Yes No	4 (0.2) 1930 (99.8)	No	Yes
32	Solvent - sniff (gas, glue, Lysol, Pam)	Yes No	3 (0.2) 1931 (99.8)	No	Yes
33	Tylenol with codeine	Yes No	69 (3.6) 1865 (96.4)	No	Yes
	EQ-5D- 3L instrument				
34	Mobility	No problem in walking Some problem in walking Confined to bed No response	1319 (68.2) 605 (31.3) 8 (0.4) 2 (0.1)	No	Yes
35	Self-care	No problem with self-care Some problem with self-care Unable to wash or dress myself No response	1760 (91.0) 158 (8.2) 15 (0.8) 1 (0.1)	No	Yes
36	Usual activities	No problem in performing my usual activities	1328 (68.7) 575 (29.8)	No	Yes

		Some problem in performing my usual activities Unable to perform my usual activities No response	 28 (1.5) 3 (0.2)		
37	Pain and discomfort	No pain or discomfort Moderate pain or discomfort Extreme pain or discomfort No response	759 (39.3) 929 (48.0) 245 (12.7) 1 (0.1)	No	Yes
38	Anxiety and Depression	Not anxious or depressed Moderately anxious or depressed Extremely anxious or depressed No response	1002 (51.8) 772 (39.9) 157 (8.1) 3 (0.2)	No	Yes
39	Health State	Continuous; Range: 0 – 100; 0 = worst, 100 = best	70 (60, 80)	No	Yes
40	Age	15-25 26-35 36-45 46-55 56-65 66-75 >=75	3 (0.12) 147 (7.6) 387 (20.0) 944 (48.8) 414 (21.4) 36 (1.9) 3 (0.20	Yes	Yes
41	Gender	Male Female Transgender No response	1421 (73.5) 489 (25.3) 21 (1.1) 3 (0.2)	Yes	Yes
42	Marital status	Single Married or common-law Widow(er) Divorced	1359 (70.3) 324 (16.8) 50 (2.6) 163 (8.4)	Yes	Yes

		No response	38 (1.9)		
	Race/ethnicity				
43	Asian	Yes No No response	26 (1.3) 1899 (98.2) 9 (0.5)	Yes	Yes
44	Black	Yes No No response	75 (3.9) 1843 (95.3) 16 (0.8)	Yes	Yes
45	White	Yes No No response	1483 (76.7) 437 (22.6) 14 (0.7)	Yes	Yes
46	Metis	Yes No No response	80 (4.1) 1841 (95.2) 13 (0.7)	Yes	Yes
47	First Nation	Yes No No response	260 (13.4) 1663 (86.0) 11 (0.6)	Yes	Yes
48	Hispanic/Latino	Yes No No response	18 (0.9) 1907 (98.6) 9 (0.5)	Yes	Yes
49	Country of origin – Born in Canada	Yes No No response	1470 (76.0) 175 (9.1) 289 (14.9)	Yes	Yes
50	Living situation	Fixed address Share accommodations Live in shelter or residence Homeless No response	971 (50.2) 786 (40.6) 127 (6.6) 48 (2.5) 2 (0.1)	Yes	Yes
51	Education	Less than elementary Elementary school High school College University No response	16 (0.8) 348 (18.0) 1046 (54.1) 303 (15.7) 190 (9.8) 31 (1.6)	Yes	Yes
52	Employment	Not working for health reasons	1234 (63.8) 95 (4.9)	Yes	Yes

		Not working for lifestyle reasons Not working but able to work Studying Part-time work Full-time work Homeworker Retired Other No response	84 (4.3) 25 (1.3) 187 (9.7) 181 (9.4) 10 (0.5) 66 (3.4) 46 (2.4) 6 (0.3)		
53	Monthly income	<= $1500 > $1500 No response	1504 (77.8) 422 (21.9) 8 (0.4)	Yes	Yes
54	Revenue source	None Welfare Employment insurance Disability insurance Pension Self-employment Employment Other No response	25 (1.3) 915 (47.3) 22 (1.1) 574 (29.7) 92 (4.8) 39 (2.0) 190 (9.8) 73 (3.8) 4 (0.2)	Yes	Yes
55	Shared accommodation – number of adults	0 1-5 6-10 >10 No response	362 (18.7) 751 (38.8) 29 (1.5) 23 (1.2) 769 (39.8)	No	Yes
56	Shared accommodation – number of children	0 1-5 6-10 No response	865 (44.7) 174 (9.0) 1 (0.1) 894 (46.2)	No	Yes
57	Sexual orientation	Heterosexual	1316 (68.1)	Yes	Yes

		Homosexual Bisexual No response	396 (20.5) 198 (10.2) 24 (1.2)		
58	Current injection drug use	Yes No	627 (32.4) 1307 (67.6)	Yes	Yes
59	Current non-injection drug use	Yes No	633 (32.7) 1301 (67.3)	Yes	Yes
60	Current alcohol use	Yes No	1163 (60.1) 771 (39.9)	Yes	Yes
61	Alcohol abuse	Yes No Not applicable No response	313 (16.2) 874 (45.2) 739 (38.2) 8 (0.4)	Yes	Yes
62	Current smoking	Yes No No response	1443 (74.6) 488 (25.2) 3 (0.2)	Yes	Yes
63	Been in jail	Yes No No response	1203 (62.2) 726 (37.5) 5 (0.3)	Yes	Yes
64	Therapy or in a program for drug addiction	Yes No No response	1233 (63.8) 649 (33.6) 52 (2.6)	No	Yes
65	Therapy or in a program for drug addiction (last 6 months)	Yes No No response	385 (19.9) 1497 (77.4) 52 (2.7)	No	Yes
66	Therapy or in a program for alcohol addiction	Yes No Not applicable No response	544 (28.1) 1220 (63.1) 2 (0.1) 168 (8.7)	No	Yes
67	Marijuana	Yes No No response	1039 (53.7) 892 (46.1) 3 (0.2)	Yes	Yes
68	Frequency of Marijuana use	Not applicable (if don't use pot) Occasionally - not every week Regularly - 1-2 days per week Regularly - 3-6 days per week Everyday No response	892 (46.1) 296 (15.3) 142 (7.3) 149 (7.7) 452 (23.4) 3 (0.2)	No	Yes

69	Why do you use Marijuana?	Not applicable Relieve symptoms Increase appetite Fun Symptoms and appetite Symptoms and fun Appetite and fun All three No response	893 (46.2) 270 (14.0) 229 (11.8) 333 (17.2) 90 (4.7) 26 (1.3) 17 (0.9) 37 (1.9) 39 (2.0)	No	Yes
70	Engaged in sex work in the past 6 months	Yes No No response	88 (4.6) 1832 (94.7) 14 (0.7)	No	Yes
71	Used services of sex workers in the past 6 months	Yes No No response	61 (3.2) 1860 (96.2) 13 (0.7)	No	Yes
72	Body piercing	Yes No No response	122 (6.3) 1808 (93.5) 4 (0.2)	No	Yes
73	Tattoo	Yes No No response	189 (9.8) 1735 (89.7) 10 (0.5)	No	Yes
74	IDU ever	Yes No No response	1616 (83.6) 308 (15.9) 10 (0.5)	Yes	Yes
75	Shared needles ever if IDU=1	Yes No Not applicable No response	1191 (61.6) 421 (21.8) 280 (14.5) 42 (2.2)	No	Yes
76	Equipment share ever if IDU=1	Yes No Not applicable No response	1151 (59.5) 470 (24.3) 282 (14.6) 31 (1.6)	No	Yes
77	Injected Drugs in jail ever if IDU=1	Yes No Never been in jail Not applicable No response	269 (13.9) 1023 (52.9) 317 (16.4) 289 (14.9) 36 (1.9)	No	Yes

78	Snort ever	Yes No No response	1609 (83.2) 282 (14.6) 43 (2.2)	Yes	Yes
79	Snort share ever	Yes No Not applicable No response	1177 (60.9) 552 (28.5) 144 (7.5) 61 (3.2)	No	Yes
80	Shared needles in the past 6 months if IDU_6m=1	Yes No Not applicable No response	38 (2.0) 602 (31.3) 1145 (59.2) 149 (7.7)	No	Yes
81	Equipment share in the past 6 months if IDU_6m=1	Yes No Not applicable No response	62 (3.2) 705 (36.5) 1119 (57.9) 48 (2.5)	No	Yes
82	Injected Drugs in jail in the past 6 months if IDU_6m=1	Yes No Not been in jail in the past 6 months Not applicable No response	9 (0.5) 225 (11.6) 921 (47.6) 773 (39.9) 6 (0.3)	No	Yes
83	Snort in the past 6 months	Yes No No response	425 (21.9) 1502 (77.7) 7 (0.4)	No	Yes
84	Snort share in the past 6 months	Yes No Not applicable No response	103 (5.3) 1224 (63.3) 560 (28.9) 47 (2.4)	No	Yes
85	Did you get used equipment in the past 6 months?	Yes No Not applicable No response	79 (4.1) 668 (34.5) 1139 (58.9) 48 (2.5)	No	Yes
86	Did you give used equipment in the past 6 months?	Yes No Not applicable No response	55 (2.8) 831 (42.9) 989 (51.1) 59 (3.1)	No	Yes
87	Ever smoked	Yes No No response	1738 (89.9) 175 (9.1) 21 (1.1)	Yes	Yes
88	Previously consumed alcohol	Yes No Not applicable No response	767 (39.7) 166 (8.6) 992 (51.3) 9 (0.5)	Yes	Yes
89	No. of male sexual partners ever had in life	0 1	769 (39.8) 41 (2.1)	No	Yes

		2-5 6-10 11-50 51-100 >100 No response	162 (8.4) 164 (8.5) 219 (11.3) 140 (7.2) 401 (20.7) 38 (2.0)		
90	No. of female sexual partners ever had in life	0 1 2-5 6-10 11-50 51-100 >100 No response	507 (26.2) 115 (6.0) 359 (18.6) 255 (13.2) 409 (21.2) 138 (7.1) 116 (6.0) 35 (1.8)	No	Yes
91	No. of male sexual partners in the past 6 months	0 1 2-5 6-10 11-50 51-100 >100 No response	1332 (68.9) 332 (17.2) 169 (8.7) 47 (2.4) 23 (1.2) 6 (0.3) 12 (0.6) 13 (0.7)	No	Yes
92	No. of female sexual partners in the past 6 months	0 1 2-5 6-10 11-50 51-100 >100 No response	1457 (75.3) 338 (17.5) 83 (4.3) 15 (0.8) 16 (0.8) 7 (0.4) 5 (0.3) 13 (0.7)	No	Yes
93	Shot up with steady sex partner in the past 6 months	Yes No Not applicable No response	113 (5.8) 370 (19.1) 1294 (66.9) 157 (8.1)	No	Yes
94	Shot up with close friend or family member in the past 6 months	Yes No Not applicable No response	135 (6.9) 351 (18.2) 1296 (67.0) 152 (7.9)	No	Yes
95	Shot up with people the patient doesn't know very well in the past 6 months	Yes No Not applicable No response	63 (3.3) 407 (21.0) 1296 (67.0) 168 (8.7)	No	Yes
96	Shot up with people the patient doesn't know at all in the past 6 months	Yes No Not applicable No response	26 (1.3) 434 (22.4) 1296 (67.0) 178 (9.2)	No	Yes
97	Shot up with nobody (alone) in the past 6 months	Yes No Not applicable No response	353 (18.3) 262 (13.6) 1311 (67.8) 8 (0.4)	No	Yes

98	Got needles or injecting equipment from steady sex partner in the past 6 months	Yes No Not applicable No response	24 (1.2) 9 (0.5) 1799 (93.0) 102 (5.3)	No	Yes
99	Got needles or injecting equipment from close friend or family member in the past 6 months	Yes No Not applicable No response	24 (1.2) 11 (0.6) 1799 (93.0) 100 (5.2)	No	Yes
100	Got needles or injecting equipment from people the patient doesn't know very well in the past 6 months	Yes No Not applicable No response	22 (1.1) 10 (0.5) 1800 (93.1) 102 (5.3)	No	Yes
101	Got needles or injecting equipment from people the patient doesn't know at all in the past 6 months	Yes No Not applicable No response	6 (0.3) 15 (0.80) 1800 (93.1) 113 (5.8)	No	Yes
102	Got needles or injecting equipment from nobody in the past 6 months	No Not applicable No response	15 (0.8) 1800 (93.1) 99 (6.2)	No	Yes
103	Give needles or injecting equipment to steady sex partner in the past 6 months	Yes No Not applicable No response	23 (1.2) 3 (0.2) 1833 (94.8) 75 (3.9)	No	Yes
104	Give needles or injecting equipment to close friend or family member in the past 6 months	Yes No Not applicable No response	16 (0.8) 14 (0.7) 1829 (94.6) 75 (3.9)	No	Yes
105	Give needles or injecting equipment to people the patient doesn't know very well in the past 6 months	Yes No Not applicable No response	9 (0.5) 7 (0.4) 1815 (93.9) 103 (5.3)	No	Yes
106	Give needles or injecting equipment to people the patient doesn't know at all in the past 6 months	Yes No Not applicable No response	8 (0.4) 8 (0.4) 1815 (93.9) 103 (5.3)	No	Yes
107	Give needles or injecting equipment to nobody (alone) in the past 6 months	No Not applicable No response	8 (0.4) 1816 (93.9) 110 (5.7)	No	Yes
108	BMI	Underweight Normal weight Overweight Obese No response	117 (6.1) 860 (44.5) 479 (24.8) 238 (12.3) 240 (12.4)	Yes	Yes

109	HIV Viral load	<= 50 (undetectable) > 50 No response	1591 (82.3) 316 (16.3) 27 (1.4)	Yes	Yes
110	CD4 count	<= 250 (low) > 250 No response	323 (16.7) 1599 (82.7) 12 (0.6)	Yes	Yes
111	HCV RNA status	Detectable Not detectable Not done	815 (42.1) 383 (19.8) 736 (38.1)	Yes	Yes
112	HIV disease stage	A1 A2 A3 B1 B2 B3 C1 C2 C3 No response	719 (37.2) 566 (29.3) 168 (8.7) 63 (3.3) 45 (2.3) 11 (0.6) 28 (1.5) 35 (1.8) 38 (2.0) 261 (13.5)	Yes	Yes
113	Sexually transmitted disease (STD) in the past 6 months	Yes No No response	73 (3.8) 1843 (95.3) 18 (0.9)	Yes	Yes
114	Ever diagnosed with hepatitis B	Yes No Unknown No response	364 (18.8) 1184 (61.2) 336 (17.4) 50 (2.6)	No	Yes
115	Cirrhosis	Yes No	46 (2.4) 1888 (97.6)	Yes	Yes
116	Ascites	Yes No	5 (0.3) 1929 (99.7)	Yes	Yes
117	Varices	Yes No	7 (0.4) 1927 (99.6)	Yes	Yes
118	Portal hypertension	Yes No	6 (0.3) 1928 (99.7)	Yes	Yes
119	Encephalopathy	Yes No	1 (0.1) 1933 (99.9)	Yes	Yes
120	Hepatocellular carcinoma	Yes No	2 (0.1) 1932 (99.9)	Yes	Yes
121	AIDS defining illness	Yes No No response	38 (2.0) 1885 (97.5) 11 (0.6)	Yes	Yes
122	Cardiovascular disease	Yes No No response	27 (1.4) 1906 (98.5) 1 (0.1)	No	Yes
123	Hypercholesterolemia	Yes No No response	22 (1.1) 1911 (98.8) 1 (0.1)	No	Yes
124	Autoimmune disease	Yes No No response	4 (0.2) 1928 (99.7) 2 (0.1)	No	Yes
125	Hypertension	Yes No	47 (2.4) 1885 (97.5)	No	Yes

		No response	2 (0.10		
126	Thyroid disease	Yes No No response	9 (0.5) 1922 (99.4) 3 (0.2)	No	Yes
127	Lipodystrophy	Yes No No response	12 (0.6) 1916 (99.1) 6 (0.3)	No	Yes
128	Psoriasis	Yes No No response	15 (0.8) 1913 (98.9) 6 (0.3)	No	Yes
129	Diabetes	Yes No No response	15 (0.8) 1914 (98.9) 5 (0.3)	No	Yes
130	Previous Interferon-based HCV treatment	Yes No No response	249 (12.9) 1671 (86.4) 14 (0.7)	Yes	Yes
	In the past 6 months, how many times did you visit the following health services?				
131	Walk-in clinic	0 1-10 11-20 21-30 >30 No response	1588 (82.1) 325 (16.8) 11 (0.6) 2 (0.1) 2 (0.1) 6 (0.3)	No	Yes
132	Emergency room	0 1-10 11-20 21-30 No response	1377 (71.2) 537 (27.8) 9 (0.5) 1 (0.1) 10 (0.5)	No	Yes
133	Hospital inpatient – overnight	0 1-10 11-20 21-30 >30 No response	1616 (83.6) 260 (13.44) 23 (1.2) 14 (0.7) 11 (0.6) 10 (0.5)	No	Yes
134	General practitioner	0 1-10 11-20 21-30 >30 No response	1176 (60.8) 666 (34.4) 70 (3.6) 9 (0.5) 5 (0.3) 8 (0.4)	No	Yes
135	HIV clinic	0 1-10 11-20 21-30 >30 No response	508 (26.3) 1328 (68.7) 78 (4.0) 12 (0.6) 3 (0.2) 5 (0.3)	No	Yes
136	A specialist	0 1-10 11-20 21-30 >30 No response	1231 (63.7) 666 (34.4) 14 (0.70 7 (0.4) 2 (0.1) 14 (0.7)	No	Yes
137	APRI for significant liver fibrosis	APRI <1.5	304 (15.7)	No	Yes

		APRI > 1.5 No response	1509 (78.0) 121 (6.3)		
138	Currently on ARV	Yes No	1809 (93.5) 125 (6.5)	Yes	Yes
139	Food insecurity using the Household Food Security Survey Module (HFSSM)*	Food secure Moderately food insecure Severely food insecure	906 (46.9) 424 (21.9) 604 (31.2)	No	No
		Total number of predictors		**46**	**137**

* Used only in the additional analysis.

Abbreviations: IQR: Interquartile range; PCP: Phenylcyclohexyl piperidine; LSD: Lysergic acid diethylamide; MDA: Methylenedioxyamphetamine; EQ-5D-3L: EuroQoL-5Dimension-3Level; IDU: Injection drug use; BMI: Body Mass Index; HIV: Human Immunodeficiency Virus; CD4: Cluster of differentiation 4 receptor; HCV: Hepatitis C virus; RNA: Ribonucleic acid; AIDS: Acquired Immunodeficiency Syndrome; APRI: Aspartate Aminotransferase (AST) to platelet ratio

Appendix B: Introduction to Random Forests

We used the supervised machine learning technique of random forests (RF), an ensemble learning technique developed by Leo Breiman (1, 2). Ensemble learning is based on the idea of combining the strengths of many simpler “base” models. The base models in the case of RF are decision trees, specifically classification and regression trees (CART) for binary and continuous outcomes, respectively (3). RF classification uses bootstrap aggregation of multiple decision trees, combining the predictions from these many trees. A decision tree is made up of nodes (root node, decision node and terminal nodes) and branches. Each node represents a predictor variable, which is chosen from a random subset of all predictor variables, which is a characteristic of the RF algorithm (3). Multiple decision trees are generated from bootstrapped samples of the training data, which is usually about a 2/3 subset of the data. The test set, which is the remaining data, is then run through these trees and the response estimate is the average over all the individual predictions in the forest (1-5).

The main characteristics of RF are:

1) Ensemble technique with multiple decision trees help reduce overfitting (3).

2) Selection of a random subset of predictors from all candidates at each node of which one predictor that most improves accuracy is then selected; the random selection makes each tree more independent of the other and reducing correlation (3, 4)

3) Out-of-Bag (OOB) samples are the observations that are not selected in a given bootstrap resample and using these samples, OOB error is calculated as the average

discrepancy between actual outcome and the outcome predicted by the RF, which provides an additional internal validation (3, 4).

When developing the RF, the parameters of the algorithm are tuned, i.e., a set of parameters are selected which minimize the OOB error and thus maximizing accuracy. These tuning parameters include the number of trees (B), the number of predictors chosen from all candidate predictors at each node (m), and three characteristics of tree depth: node size (s), which is maximum number of observations at each node, maximum terminal nodes (u), and tree level (k), which is maximum number of splits (6).

The algorithm also provides importance metrics to provide an idea which variables were the most influential in the classification algorithm. Overall, RFs are non-parametric, accurate, and relatively robust to outliers and noise. RF variable importance graphs provide insights regarding which variables play a major role in the accurate prediction. Regression RF algorithms can be used to predict for continuous outcomes and classification algorithms can be used to classify into binary or categorical outcomes. Additionally, probability machines for the classification can be used to estimate the probabilities for class membership, which can then be used to determine the class at the optimal probability thresholds (7).

Appendix C: Supplementary methods and results

RF tuning

The RF hyperparameters used to tune the RF algorithms to maximize accuracy were as follows:

- Number of trees (B): Range used: 50-1500
- Number of predictors, randomly chosen from all predictors in the algorithm at each node (mtry): Range used: sqrt(x) to x/2), where x= total number of candidate predictors
- Tree depth, which is maximum number of splits (D): Range used: 1-30 and 0 = no limit
- Node size, which is minimum number of observations at each node (S): Range used: 1-21

The ranges for the hyperparameters were selected based on recommendations in literature (6, 8).

Using the training data, we conducted 10-fold cross validation using grids of the above hyperparameter ranges, the final parameters which maximized accuracy were chosen and these are given in Table 4.6 for all algorithms.

Overall performance

The overall performance was evaluated using a scaled Brier score (BS_{scaled}), which is the Brier score (BS) or mean squared error scaled with the maximum mean squared error in a model that randomly classifies into either CES-D-10 class (BS_{max}): BS_{scaled}=1-

(BS/BS_{max}) (9). Relative efficiency was calculated by comparing the BS_{scaled} for the two algorithms (10, 11).

In the testing data, the full algorithm had a BS_{scaled} of 0.31 (95% CI: 0.22-0.39), that is a 31% reduction in mean squared error as compared to random classification and the reduced algorithm had a BS_{scaled} of 0.20 (95% CI: 0.12-0.27), which means a 20% reduction (10). The relative efficiency comparing the reduced to the full algorithm was 0.65 (95% CI: 0.38-1.01), i.e., a 65% loss in efficiency, indicating better performance of the full algorithm compared to reduced algorithm.

Calibration

Calibration is assessment of the agreement between observed and predicted outcomes. We generated calibration graphs by plotting the predicted probabilities for being in CES-D-10 class=1 (CES-D-10 score >=10) against the observed frequency of CES-D-10 class=1 (11). The Stata package pmcalplot was used to create the calibration graph (12). The calibration graphs are shown in Figure 4.3.

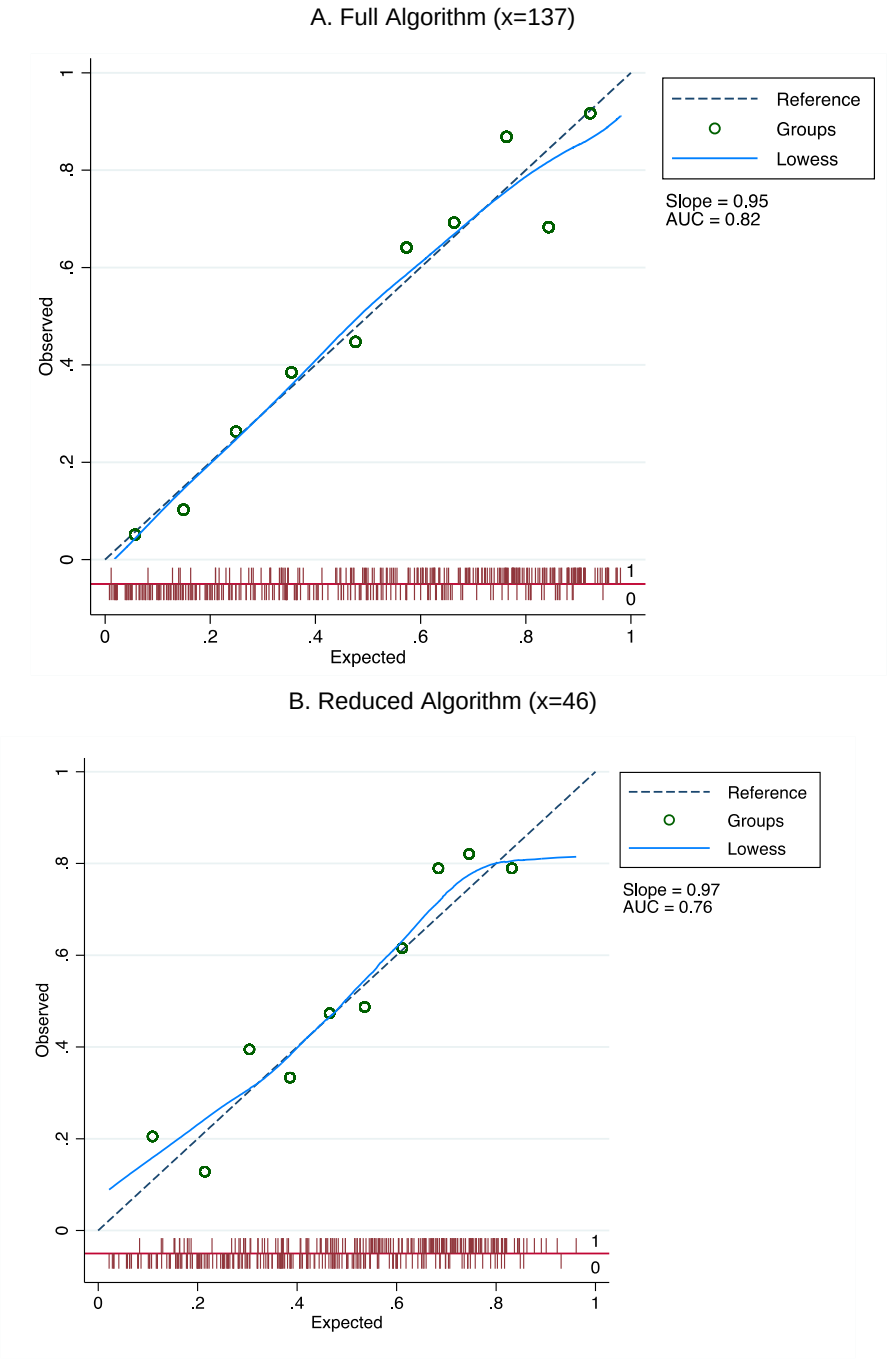
The calibration measure, calibration slope was estimated, with bootstrapped 95% confidence intervals (CI). For the full algorithm, the calibration slope measure was 0.95 (95% CI: 0.72-1.21) for the reduced algorithm and this estimate was close to the ideal calibration slope of 1 for a well-calibrated algorithm (11). Similarly, For the reduced algorithm, the calibration slope measure was 0.97 (95% CI: 0.72-1.21) and this estimate was close to the ideal calibration slope.

Table 4.6: Supplementary table - Final RF hyperparameters for the algorithms

Sr. No.	Algorithms	OOB error	B	mtry	D	S
Primary analysis						
1	Full algorithm (x = 137)	0.16	600	70	0 (no limit)	1
2	Reduced algorithm (x=46)	0.20	800	20	0 (no limit)	1
Additional analyses						
A	**One visit per individual (x=46)**					
1	Full algorithm (x = 137)	0.17	1000	80	10	1
2	Reduced algorithm (x=46)	0.23	100	15	10	5
B	**Different CES-D-10 cut-offs**					
I	**Cut-off - 8**					
1	Full algorithm (x = 137)	0.17	100	70	0 (no limit)	5
2	Reduced algorithm (x=46)	0.19	400	10	0 (no limit)	1
II	**Cut-off - 13**					
1	Full algorithm (x = 137)	0.15	1400	50	0 (no limit)	1
2	Reduced algorithm (x=46)	0.20	1200	20	0 (no limit)	1
III	**Cut-off - 15**					
1	Full algorithm (x = 137)	0.14	200	30	0 (no limit)	1
2	Reduced algorithm (x=46)	0.17	100	10	20	1
C	**With food insecurity variable (x=138)**	0.16	100	80	10	1
D	**Regression algorithm**					
1	Full algorithm (x = 137)	0.24	1400	80	0 (no limit)	1
2	Reduced algorithm (x=46)	0.35	200	15	0 (no limit)	1

Abbreviations: OOB: Out-Of-Bag sample; B: Number of trees; mtry: Number of predictors chosen randomly at each node; D: tree depth; S: minimum node size; CES-D-10: Center for Epidemiologic Studies Depression Scale-10; EQ-5D-3L: EuroQoL-5Dimension-3Level

Figure 4.3: Supplementary figure - Calibration graphs - A. Full algorithm (x = 137) and B. Reduced algorithm (x = 46)



Abbreviations: AUC: Area under the Receiver Operating Characteristic curve

Appendix D: Sample generalizability

Table 4.7: Supplementary table - Participant characteristics in visit 1 in the study sample (n=717) as compared to baseline visit for all CCC participants (n=2008)

Characteristics	**Participants (n = 717) n (%) or median (IQR)**	**Participants (n=2008) n (%) or median (IQR)**
Age	49 (43, 54)	45 (39, 52)
Gender - Male	522 (73)	1412 (70)
Race/Ethnicity		
Asian	11 (2)	36 (2)
Black	28 (4)	70 (4)
White	541 (76)	1401 (70)
Metis	32 (5)	102 (5)
First nation	102 (14)	412 (21)
Hispanic/Latino	7 (1)	29 (1)
Born outside Canada	64 (9)	181 (9)
Education - High school and higher	565 (79)	1532 (76)
Employment - Not employed	525 (73)	1334 (66)
Monthly income □ $1500	543 (76)	1526 (76)
Revenue Source - Welfare	332 (46)	954 (48)
Current injection drug use	244 (34)	819 (41)
Current alcohol use	444 (62)	950 (47)
Current smoking	534 (75)	1505 (75)
BMI category - Normal weight (18.5-25 kg/m^2)	312 (44)	798 (40)
End-stage Liver disease	27 (4)	57 (3)
HIV clinical stage - A1 (asymptomatic)	248 (35)	438 (22)
Past AIDS related illness	28 (4)	458 (23)
Depression diagnosis	68 (10)	742 (37)
Prescribed antidepressant medications	320 (45)	607 (30)
HR-QoL using EQ-5D-3L instrument Anxiety/depression Not anxious or depressed Moderately anxious or depressed Extremely anxious or depressed Current health state (visual analog scale)	 352 (49) 302 (42) 60 (8) 70 (56, 80)	 747 (37) 818 (41) 183 (9) 70 (50, 80)

Abbreviations: IQR: Interquartile range; AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus; BMI: Body Mass Index; HR-QoL: Health related quality of life; EQ-5D-3L: EuroQoL-5Dimension-3Level

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5. CHAPTER 5: EFFECT OF DEPRESSIVE SYMPTOMS ON HCV TREATMENT INITIATION

5.1. Preface to Manuscript 2

In this chapter, I aimed to assess the effect of depressive symptoms on HCV treatment initiation. A few studies have addressed depression and other psychiatric illnesses as possible risk factors for reduced linkage to care and treatment in the HCV mono-infection cascade of care (108-110). In a retrospective study of barriers to HCV linkage to care and treatment initiation in Florida, uncontrolled psychiatric illness was found to be a smaller barrier to treatment initiation in the DAA era compared to the IFN era (110). Although these studies assessed depression as a possible barrier for treatment initiation, they did not quantify this effect. Thus, there is limited research regarding the impact that the presence of depressive symptoms may have on initiation of these DAA regimens since their approval in Canada in 2013.

Therefore, in this manuscript, I quantified this effect of depressive symptoms on HCV treatment initiation. I conducted this analysis in both the IFN era (2003-2011) and second generation DAA era (2013-2020) in order to observe possible differences.

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This analysis was presented as posters at the following conferences/seminars:

1. 17th Annual EBOSS Research Day, McGill University, Virtual - March 2021
2. 30th Annual Canadian Conference on HIV/AIDS Research, Virtual - May 2021
3. Canadian Liver Meeting (CLM) 2021, Virtual - May 2021
4. 5th IDIGH Student Research Day, McGill University, Virtual - May 2021
5. 11th IAS conference on HIV Science (IAS 2021), Virtual - July 2021

5.2. Manuscript 2: Depressive symptoms are no longer a barrier to HCV treatment initiation in the HIV-HCV co-infected population in Canada

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Running head: Depressive symptoms - a HCV treatment barrier?

Abstract

Background

Psychiatric illness was a major barrier for HCV treatment during the Interferon (IFN) treatment era due to neuropsychiatric side effects. While direct acting antivirals (DAA) are better tolerated, patient-level barriers persist. We aimed to assess the effect of depressive symptoms on time to HCV treatment initiation among HIV-HCV co-infected persons during the IFN (2003-2011) and second-generation DAA (2013-2020) eras.

Methods

We used data from the Canadian Co-infection Cohort, a multicentre prospective cohort, and its associated sub-study on Food Security (FS). We predicted Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) classes for depressive symptoms indicative of a depression risk using a random forest classifier and corrected for misclassification using predictive value-based record-level correction. We used marginal structural Cox proportional hazards models with inverse weighting for competing risks (death) to assess the effect of depressive symptoms on treatment initiation among HCV RNA-positive participants.

Results

We included 590 and 1,127 participants in the IFN and DAA eras. The treatment initiation rate increased from 9 (95% confidence interval (CI):7-10) to 21 (95%CI:19-22) per 100 person-years from the IFN to DAA era. Treatment initiation was lower among those with depressive symptoms compared to those without in the IFN era

(hazard ratio: 0.81 (95% CI:0.69-0.95)) and was higher in the DAA era (1.19 (95% CI:1.10-1.27)).

Conclusion

Depressive symptoms no longer appear to be a barrier to HCV treatment initiation in the co-infected population in the DAA era. The higher rate of treatment initiation in individuals with depressive symptoms suggests those previously unable to tolerate IFN are now accessing treatment.

Background

Treatment for Hepatitis C Virus (HCV) has evolved over time, from less effective interferon (IFN)-based regimens to direct acting antiviral (DAA) regimens with cure rates of >95% in real world settings, including among HIV-HCV coinfected patients [1-4]. IFN-based treatment regimens were long (lasting one year) with weekly injections and had low response rates (on average 30%) and many unpleasant side effects including serious neuropsychiatric outcomes such as mild to severe depression [5, 6]. Up to 35% of patients treated with IFN-ribavirin based regimens developed depression [7, 8]. Due to these side effects, interferon treatment was relatively contraindicated for patients with current or past major psychiatric illness. Consequently, interferon-based regimens were often not prescribed to those with depression, leading to low treatment rates in this population [9]. Treatment emergent depression was of particular concerns among people living with HIV as depressive symptoms are associated with decreased adherence to HIV medication, thus modifying the risk-benefit analysis of HCV treatment towards a more conservative approach[10-13]. The second-generation DAA regimens are shorter (8-12 weeks) and have very few adverse effects [14]. Importantly, DAAs have shown few if any psychiatric side effects thus far. Thus, treatment guidelines for HCV have been updated and the presence of current or past psychiatric illness is no longer considered a relative contraindication for treatment [15, 16].

A study in the Canadian Co-infection cohort suggested an almost threefold increase (8 to 28 per 100 person years) in treatment initiation in the HIV-HCV co-infected population after the second-generation DAAs were licensed in Canada in 2013 [17]. However,

treatment initiation rates were lower among people who actively inject drugs, women, and Indigenous populations (5-12 per 100 person-years) compared with other co-infected people [17]. Thus, despite the advantages of the new regimens, treatment initiation is still not the same across subgroups posing a threat to HCV elimination goals[14]. Patient- and system-level barriers exist; psychiatric illness, including depression, could be one such barrier.

There is a high prevalence of depression (20-30%) among people living with HIV. Similarly, 24% of those with chronic HCV infection experience depression [18-21]. Both biological and psychosocial mechanisms are at play [18, 22]. Prevalence of depression is reported to be even higher in the co-infected population, which may be due to the co-existence of risk factors and neuropsychiatric effects of both HIV and HCV [23]. The presence of significant depressive symptoms could have an impact on clinical outcomes in patients, even when not meeting diagnostic criteria for major depression.

Studies in both the IFN and DAA eras conducted in people with chronic HCV infection have found psychiatric illness among the barriers to linkage to care, treatment initiation, and adherence [9, 24-27]. Whether depressive symptoms continue to prevent treatment initiation in the second generation DAA era is unknown, especially in the co-infected population, which has higher prevalence of depression. The major improvements in HCV treatment safety increases the opportunity to treat people with psychiatric illness and hence we hypothesized improved tolerability would lead to an increase in treatment initiation in this group. Thus, in this study, we evaluated the effect of depressive symptoms

on time to HCV treatment initiation comparing the IFN (2003-2011) and second generation DAA eras (2013-2020) in the HIV-HCV co-infected population in Canada.

Methods

Study population

We used data from the Canadian Co-Infection Cohort (CCC), an open multicentre prospective cohort study, ongoing since 2003. The study has been described in detail elsewhere [28]. Briefly, the CCC recruits from 18 HIV urban and semi-urban centres across six Canadian provinces (Quebec, British Columbia, Alberta, Ontario, Nova Scotia, and Saskatchewan). Eligibility criteria include ≥16 years of age, documented HIV infection, and evidence of HCV infection (HCV RNA positive and/or HCV seropositive). The study had recruited 2018 participants as of July 2020. Participants are followed longitudinally, with follow-up visits every six months. Sociodemographic and behavioural data are collected from participants by a standardized self-administered questionnaire at each visit. Clinical data including HIV and HCV treatment dates, medications, co-morbidities, and psychiatric diagnoses are collected via medical chart reviews and HIV and HCV related blood tests performed.

In addition, we used data from an associated sub-study within the CCC, the Food Security and HIV-HCV co-infection study (FS sub-study), to predict the presence of depressive symptoms in the CCC as a whole. Participants for the FS sub-study were recruited from the CCC (n=725) with a maximum of 5 visits integrated into the CCC visits. In the sub-study, fully described in detail elsewhere [29], depression screening was performed using

the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) that assesses presence and severity of depressive symptoms in the past week. [30]. The scale has 8 items focusing on negative symptoms like feeling restless, fearful, and lonely, feeling bothered by things that usually would not bother you and not being able to concentrate. The remaining 2 items focus on positive symptoms like feeling hopeful about the future and being happy. Each item is measured on a 4-point scale, with reverse scoring for the positive items; score ≥10 is widely considered to represent the presence of depressive symptoms indicative of being at risk for depression; this cut-off of 10 has been validated in HIV populations in Canada [30-32].

Definition of treatment eras and follow-up

The IFN era was defined as the beginning of the CCC on April 28, 2003, until August 1, 2011, when the 1st generation DAA, boceprevir was approved for use by Health Canada. The IFN-free DAA era began at the time that the first 2nd generation DAA, simeprevir, was approved for use by Health Canada November 25, 2013, and continued until end of study period, July 15, 2020. We excluded the period between 2011-2013 in this analysis, because IFN regimens were used widely in combination with the first generation DAA regimens.

Participants were included in the analysis for the IFN era if eligible for treatment i.e., if they tested HCV RNA positive on or after April 28, 2003. Participants were then followed from their first documented positive HCV RNA test in this period (time zero) until treatment initiation or until censoring due to loss to follow-up (no visit for 18 months since last visit),

withdrawal, death, or end of the study period (August 1, 2011). Participants were included in the analysis for the DAA era if eligible for second generation DAA treatment initiation i.e., if they tested HCV RNA positive on or after November 25, 2013. Participants were excluded if they were accessing DAAs through a clinical trial or were treated with IFN. Participants were then followed from their HCV RNA positive test date in this period until second generation DAA treatment initiation or until censoring due to loss to follow-up, withdrawal, death, or end of the study period (July 15, 2020). Participants from the IFN era who remained HCV RNA positive by August 1, 2011, were included in the DAA era analysis if they were still being followed in the CCC and were HCV RNA positive on November 25, 2013.

Measurement

Exposure

The exposure of interest was presence of depressive symptoms indicative of being at risk for major depression, hereafter called depressive symptoms for brevity. CCC participants are not screened for depression during baseline or follow-up. As described earlier, depression screening was however performed in the FS sub-study. Thus, to obtain a measure of depressive symptoms in the full CCC, we developed a random forest (RF) classifier using the CES-D-10 to classify presence/absence of depressive symptoms derived from the FS sub-study as the outcome (target of prediction), and sociodemographic, behavioural, and clinical characteristics from the parent CCC as predictors [33]. The details of the RF classifier development are in Appendix A. Using this RF classifier, the CES-D-10 score ≥10 (presence of depressive symptoms) was predicted

for each CCC visit included in this analysis. We addressed exposure misclassification for the predicted depressive symptoms using the predictive value-based record-level correction method [34]. In this method, we applied the positive predictive value (PPV) and negative predictive value (NPV) estimated for the RF algorithm; PPV: 0.74 (95% CI: 0.68-0.80) and NPV: 0.76 (95% CI: 0.69-0.82). The procedure included simulation of corrected exposure at each visit by repeated Bernoulli trials with probability equal to PPV for those classified as CES-D-10 class=1 and 1-NPV for those classified as CES-D-10 class=0 [34].

Outcome

The outcome of interest was time to HCV treatment initiation in each era. The date of treatment initiation in both eras was measured at each visit using exact treatment start and stop dates obtained via medical chart reviews.

Confounders

We considered both baseline and time-varying confounders in this analysis, which were selected a priori based on prior literature, as illustrated in the Directed Acyclic Graph (DAG) shown in figure 1. The baseline confounders included age, gender, race/ethnicity, education level, sexual orientation, previous HCV treatment, immigration status (as a proxy for possible system related factors like medical insurance), marital status, and province (as a proxy for sociodemographic characteristics and changes in treatment policies over time). The time varying confounders measured at each biannual visit included living situation, employment status, monthly income, revenue source, current injection drug use, current alcohol use, current smoking status, incarceration in the past

6 months, advanced fibrosis/cirrhosis (measured by the AST to Platelet Ratio Index (APRI) >= 1.5), detectable HIV viral load (> 50 copies/ml), low CD4 cell count (≤ 250 cells/μl) and antidepressant use. We conducted multiple imputation by chained equations (MICE) to address the missing data in the baseline and time varying confounders [35, 36], as at least one confounder value was missing in > 20% of the included visits in both eras. We created five imputed datasets using linear regression to impute continuous variables, logistic regression for binary variables and multinomial logistic regression for nominal categorical variables.

Statistical analysis

Primary analysis

We estimated the overall treatment initiation rates per 100 person-years in both the IFN and DAA eras. To determine the effect of predicted depressive symptoms on time to treatment initiation, we developed models separately for each era. We fit all models with and without exposure misclassification correction.

First, we developed conventional Cox proportional hazards (Cox PH) model and obtained hazard ratios with 95% confidence intervals (CI), adjusting for baseline and time-varying confounders. The proportionality assumption was assessed by scaled Schoenfeld residuals using a test for zero slope [37, 38]. Conventional Cox PH models can yield biased estimators if time-varying covariates act as confounders and mediators simultaneously; that is, if the covariate predicts HCV treatment initiation (outcome) and subsequent presence of depressive symptoms (exposure), but past presence of depressive

symptoms predicts subsequent level of the covariate; DAG in figure 5.1 [39]. Thus, we developed marginal structural Cox PH models (MSCM) to address this issue of time-varying confounding [39, 40]. In this method, stabilized inverse probability treatment weights (IPTW) were constructed (details in appendix B) [41]. The IPTWs were incorporated in the Cox PH model to obtain the hazard ratio estimates with 95% CIs.

Finally, we needed to consider possible competing risks, specifically deaths due to liver disease, drug overdose or other reasons. In a CCC analysis for the time-period 2013-2017, overall death rates were found to be high, with rates of 23.8 per 1000 person-years (PY) for those aged 20-49 years and 38.3 per 1000 PY among those 50-80 years of age [42]. A naïve survival analysis would censor individuals at death and assume independence of censoring and event times. This assumption is unlikely to be met in this population [43, 44]. To account for death as a competing risk, we calculated inverse probability censoring weights (IPCW) (details in appendix B). We calculated the final weights as the product of IPTW and IPCW and incorporated them in the MSCM model to obtain hazard ratio estimates with 95% CIs.

Secondary analyses

We conducted two planned secondary analyses to assess the robustness of the results. First, we used a restricted subset of participants from the FS sub-study from 2012-2015, majority of which was in the second-generation DAA era, in which measured CES-D-10 scores were available, to measure the effect of exposure misclassification due to the use of predicted depressive symptoms in models. The model development was as in the

primary analysis. Second, we a used a time-fixed exposure at each visit, i.e., baseline predicted CES-D-10 class and developed the conventional Cox models for the IFN and DAA eras separately.

Results

Participant characteristics

The flowcharts for participants included in the final analytical samples are shown in figure 5.2.: 2A - IFN era, and 2B - DAA era. We included 590 and 1,127 of HCV RNA-positive participants in the IFN and DAA eras, respectively. The baseline characteristics of the participants are shown in table 5.1. The proportion of individuals with predicted depressive symptoms, i.e., CES-D-10 scores ≥10, was high in both the IFN (55%) and DAA (60%) eras at baseline. Participants in both IFN and DAA eras were both predominantly male (77%; 70%) and not employed (70%; 68%). In the DAA era, there were comparatively higher proportions of Indigenous participants (29% vs. 10%), current injection drug users (44% vs. 31%), those recently incarcerated (16% vs 8%) and those with lower levels of education (73% vs. 68% with no post-secondary education) compared with the IFN era, hence more potential barriers to HCV care. A small proportion of the participants in the IFN era (14%) and DAA era (11%) were receiving antidepressants, however whether they were prescribed for depression or for other disorders was not known.

Primary analyses

There were 126 and 566 treatment initiations with median follow-up times of 2.3 years (range: 0.02-8.3 years) and 2.0 years (range: 0.01-6.6 years) in the IFN and DAA eras, respectively. The overall treatment initiation rate increased from 9 (95%CI: 7-10) per 100 person-years (PY) in the IFN era to 21 (95%CI: 19-22) per 100 PY in the DAA era. The primary analyses results are shown in table 5.2. There was no evidence to suggest the proportionality assumption was violated. The hazard ratios were similar across the three primary models in each era. In the IFN era, the MSCM model accounting for competing risks showed lower treatment initiation among those with depressive symptoms compared to those without (hazard ratio (HR): 0.63 (95% CI: 0.43-0.93)). Exposure misclassification correction moved the HR towards the null (0.81 (95% CI: 0.69-0.95)), but still indicated a 19% lower risk of initiation among those with depressive symptoms. In the DAA era, in the MSCM model accounting for competing risks, we observed higher treatment initiation among those with depressive symptoms compared to those without (HR: 1.42 (95% CI: 1.17-1.71)). Again, exposure misclassification correction moved the HR towards the null (1.19 (95% CI: 1.10-1.27)), still indicating a 19% higher risk of initiation among those with depressive symptoms.

Secondary analyses

The secondary analyses results are shown in table 5.3. In the first analysis, in the restricted subset with measured CES-D-10 classes available from the FS sub-study, 485 participants were included with 102 treatment initiations, all in the DAA era. Taking into consideration time-varying confounders and competing risks, the HR for treatment

initiation was 0.82 (95% CI: 0.52-1.29). While this point estimate was comparable to the IFN era estimates, the precision was low. In the second analysis, using time-fixed exposure (baseline depressive symptoms), the results were comparable to the primary analyses, with lower treatment initiation among those with depressive symptoms than those without in the IFN era and higher in the DAA era.

Discussion

In this multicentre prospective cohort study, we observed lower HCV treatment initiation among those with depressive symptoms compared to those without in the IFN era whereas higher initiation among those with depressive symptoms in the DAA era. There was a high prevalence of depressive symptoms (over 50% in both eras); thus, the ability of DAAs to overcome a significant barrier to HCV treatment historically faced by this substantial population should help the goal of eliminating HCV.

Our results are in line with expectations that, during the IFN era, providers would be less likely to prescribe IFN-based regimens to those with depressive symptoms and that neuropsychiatric side-effects of IFN would deter such patients from initiating therapy. A multicentre cohort study of veterans in the US similarly found that those with pre-existing psychiatric conditions (18%) had a much higher odds of not being treated (OR: 9.62; 95% CI: 6.85-13.50) [45]. In the DAA era, there have been studies examining depression prevalence before and after DAA treatment [15, 46-49]. A few studies have addressed depression and other psychiatric illness as

possible risk factors for reduced linkage to care and treatment in the HCV mono-infection cascade of care [24-26]. Higher Patient Health questionnaire-8 (PHQ-8) scores indicating more severe depression have been found among those not treated for HCV [24]. In a retrospective study of barriers to HCV linkage to care and treatment initiation in Florida, uncontrolled psychiatric illness was found to be a smaller barrier to treatment initiation in the DAA era compared to the IFN era [26]. Though these studies assessed depression as a possible barrier for treatment initiation, they did not explore the effect of depressive symptoms independently. In our study, we present the first quantitative estimates of the effect of depressive symptoms on time to HCV treatment initiation, contrasting uptake in the IFN and second-generation DAA eras among HIV-HCV co-infected people, who may differ from those with HCV mono-infection due to distinct patient- and system-level barriers to care. Unlike other studies, we accounted for potential time-dependent confounding and competing risk of death which could bias estimates of treatment uptake.

An overall increase in HCV treatment initiation rates was observed from the IFN to the DAA era. The percentage of eligible participants that initiated treatment increased from 21% to 50% in this analysis; this is important progress towards reaching the HCV elimination goals in Canada [50]. Additionally, it was encouraging that this increase occurred in the DAA era in spite of higher prevalence of many possible barriers to treatment such as lower education, higher rates of injection drug use and incarceration and being Indigenous – barriers that may themselves be linked with depression.

Interestingly, we not only observed that treatment initiation increased among those with depressive symptoms, which was anticipated, but also that in the DAA era, initiation was found to be higher among those with depressive symptoms compared those without, which was surprising. One of the possible explanations for this could be that a backlog of patients for whom IFN-based treatments were contraindicated, or were not tolerated, are now accessing treatment, i.e., a warehousing effect. This effect could either persist or plateau over time, which would be expected with a warehousing effect. In our study, we observed that almost 65% of the people with baseline depressive symptoms initiated DAAs between 2015-2017 and comparatively lower number of people (31%) initiated between 2018-2020, which provides some evidence for possible plateauing, however additional data would be needed to confirm this change over time. With the percentage of the eligible participants initiating HCV treatment still being much lower than the WHO elimination goal of 80% and possible plateauing, it is possible that depressive symptoms may have additional impacts on the care cascade beyond medication safety that need to be addressed to further enhance treatment uptake. This might be achieved, for example, by integration of mental health education, screening, and treatment as a part of routine care for HIV-HCV co-infected people.

This study has several strengths. The CCC recruits participants from primary and tertiary care clinics in urban and semi-urban areas across Canada. Thus, our estimates are generalizable to HIV-HCV co-infected patients engaged in care in Canada. We leveraged longitudinally collected data over 15 years, applied robust methods to account for time-dependent confounding, competing risk and conducted multiple

secondary analyses. However, the study does have limitations. The clinically relevant depressive symptoms were predicted via a random forest algorithm, and not measured directly in the cohort. Thus, misclassification was expected and therefore we corrected for potential misclassification in our analysis, resulting in attenuation of our estimates. We predicted the depressive symptoms based on a screening questionnaire, CES-D-10, and not a major depression diagnosis. Thus, this study does not provide an effect estimate for depression but rather for presence of these clinically relevant depressive symptoms.

We demonstrated a high baseline prevalence of depressive symptoms in the HIV-HCV co-infected people and showed a substantial increase in treatment initiation rates with the availability of DAAs. Our study suggests that depressive symptoms are no longer a barrier to HCV treatment initiation in the second-generation DAA era in the HIV-HCV co-infected population in Canada.

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Ethics approval and consent to participate

This study was approved by the Research Ethics Board of the McGill University Health Centre (2021-6985). The CCC and the FS Sub-Study were approved by the Research Ethics Board of the McGill University Health Centre (2006-1875, BMB-06-006t, 2013-994) and the research ethics boards of participating institutions. The study was conducted according to the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available. According to stipulations of the patient consent form signed by all study participants, ethical restrictions imposed by our Institutional Ethics review boards, and

legal restrictions imposed by Canadian law, anonymized data are available upon request by contacting Dr. Marina B. Klein.

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Declaration of Conflicting Interests

MBK reports grants for investigator-initiated studies from ViiV Healthcare, AbbVie, Merck, and Gilead; and consulting fees from ViiV Healthcare, Merck, AbbVie, and Gilead. JC received grants and consulting fees from ViiV Healthcare, Merck, and Gilead and personal fees from Bristol-Myers Squibb. CC has received personal fees for being a member of the national advisory boards of Gilead, Merck, Janssen, and Bristol-Myers Squibb. MH has served as a consultant for Merck, Vertex Pharmaceuticals, Pfizer, Viiv Healthcare, and Ortho-Jansen. MH has also received grants from the National Institute on Drug Abuse, as well as payment for lectures from Merck and Ortho-Janssen. JG has served as ad hoc member on National HIV advisory boards to ViiV healthcare, Gilead, and Merck. SW received grants, consulting fees, lecture fees, nonfinancial support, and

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Table 5.1: Baseline characteristics for participants included from IFN and DAA eras

Baseline characteristics	IFN era (2003-2011) Participants (n = 590) n (%) or median (IQR)	DAA era (2013-2020) Participants (n = 1127) n (%) or median (IQR)
Predicted CES-D-10 class - 1: score >=10	325 (55)	678 (60)
Age (years)	45 (40-50)	45 (38 -51)
Gender - Male	456 (77)	786 (70)
Race/ethnicity		
White	472 (80)	722 (64)
Indigenous (First Nations, Inuit, and Metis)	59 (10)	324 (29)
Asian	13 (2)	18 (2)
Black	27 (5)	36 (3)
Hispanic/Latino	9 (2)	20 (2)
Living situation - Homeless	60 (10)	122 (11)
Education - High school educated and less	401 (68)	827 (73)
Employment - Not employed	413 (70)	769 (68)
Monthly income - <= $1500 CAD	430 (73)	876 (78)
Revenue source - Welfare	265 (45)	561 (50)
Sexual orientation - Heterosexual	418 (71)	792 (70)
Immigrant to Canada	65 (11)	92 (8)
Marital status - Single	376 (64)	787 (70)
Previous IFN-based HCV treatment	96 (16)	154 (14)
Injection drug use in the past 6 months	184 (31)	490 (44)
Alcohol use in the past 6 months	313 (53)	543 (48)
Smoking in the past 6 months	430 (73)	847 (75)
Incarceration in the past 6 months	49 (8)	176 (16)
Fibrosis stage (e.g., APRI) >= 1.5	143 (24)	192 (17)
HIV viral load > 50 copies/ml	209 (35)	358 (32)
CD4 count - <= 250 cells/uL	153 (26)	266 (24)
Antidepressant prescribed	81 (14)	120 (11)

Abbreviations: IFN: Interferon; DAA: Direct acting antivirals; IQR: Interquartile range; CES-D-10: Center for Epidemiologic Studies Depression Scale-10; CAD: Canadian dollar; HCV: Hepatitis C virus; APRI: AST to Platelet Ratio Index; HIV: Human Immunodeficiency Virus; CD4: Cluster of differentiation 4 receptor

Table 5.2: Effect of depressive symptoms on time to HCV treatment initiation in IFN and DAA eras

Models	No misclassification correction		Misclassification correction	
	HR	**95% CI**	**HR**	**95% CI**
IFN era (2003-2011)				
Cox proportional hazards model *	0.66	0.43-0.99	0.84	0.72-0.99
MSCM not accounting for competing risks **	0.64	0.43-0.94	0.82	0.70-0.96
MSCM accounting for competing risks ***	0.63	0.43-0.93	0.81	0.69-0.95
DAA era (2013-2020)				
Cox proportional hazards model *	1.53	1.27-1.84	1.20	1.12-1.29
MSCM not accounting for competing risks **	1.37	1.14 -1.66	1.17	1.09-1.25
MSCM accounting for competing risks ***	1.42	1.17-1.71	1.19	1.10-1.27

* Conventional Cox proportional hazards model - Biased estimate due to time varying confounders acting as mediators

** Marginal structural Cox proportional hazards model adjusting for confounding bias due to time-varying confounders acting as mediators

*** Marginal structural Cox proportional hazards model with inverse probability censoring weights to adjust for death as a competing risk

All models were adjusted for following Baseline confounders: age, gender, race/ethnicity, education level, sexual orientation, previous IFN-based HCV treatment, immigration, marital status, and province; Time varying confounders: living situation, employment, income, revenue source, injection drug use, alcohol use, smoking, incarceration, fibrosis stage (e.g., AST to Platelet Ratio Index (APRI) ≥1.5), HIV viral load, CD4 count and antidepressant use.

Abbreviations: IFN: Interferon; DAA: Direct acting antivirals; HR: Hazard ratio; CI: Confidence interval; MSCM; Marginal structural Cox proportional hazards model

Table 5.3: Secondary analyses using measured CES-D-10 classes in a restricted subset and baseline predicted depressive symptoms

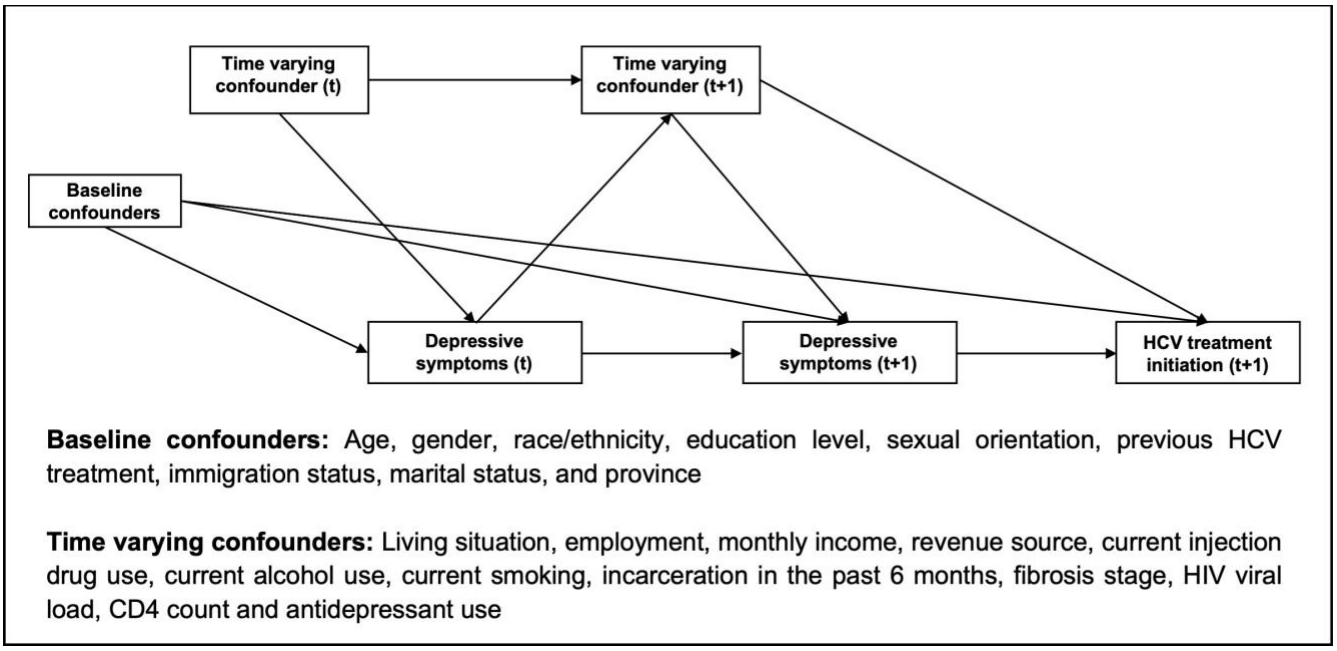
Models	No misclassification correction		Misclassification correction	
	HR	**95% CI**	**HR**	**95% CI**
Restricted subset with measured CES-D-10 classes (2012-2015) *				
Cox proportional hazards model	0.88	0.57-1.35	-	-
MSCM not accounting for competing risks	0.90	0.57-1.40	-	-
MSCM accounting for competing risks	0.82	0.52-1.29	-	-
Exposure: Baseline predicted depressive symptoms **				
IFN era (2003-2011)	0.78	0.50-1.23	0.92	0.77-1.08
DAA era (2013-2020)	1.17	0.97-1.42	1.12	1.05-1.20

* The subset was from the FS sub-study in which data was collected from 2012-2015 during the DAA era. Models were adjusted for - Baseline confounders: age, gender, race/ethnicity, education level, sexual orientation, previous IFN-based HCV treatment, immigration, marital status, and province; Time varying confounders: living situation, employment, income, revenue source, injection drug use, alcohol use, smoking, incarceration, fibrosis stage (e.g., AST to Platelet Ratio Index (APRI) ≥1.5), HIV viral load, CD4 count and antidepressant use.

** Models were adjusted for baseline confounders: age, gender, race/ethnicity, education level, sexual orientation, previous IFN-based HCV treatment, immigration, marital status, and province

Abbreviations: IFN: Interferon; DAA: Direct acting antivirals; HR: Hazard ratio; CI: Confidence interval; CES-D-10: Center for Epidemiologic Studies Depression Scale-10; MSCM; Marginal structural Cox proportional hazards model

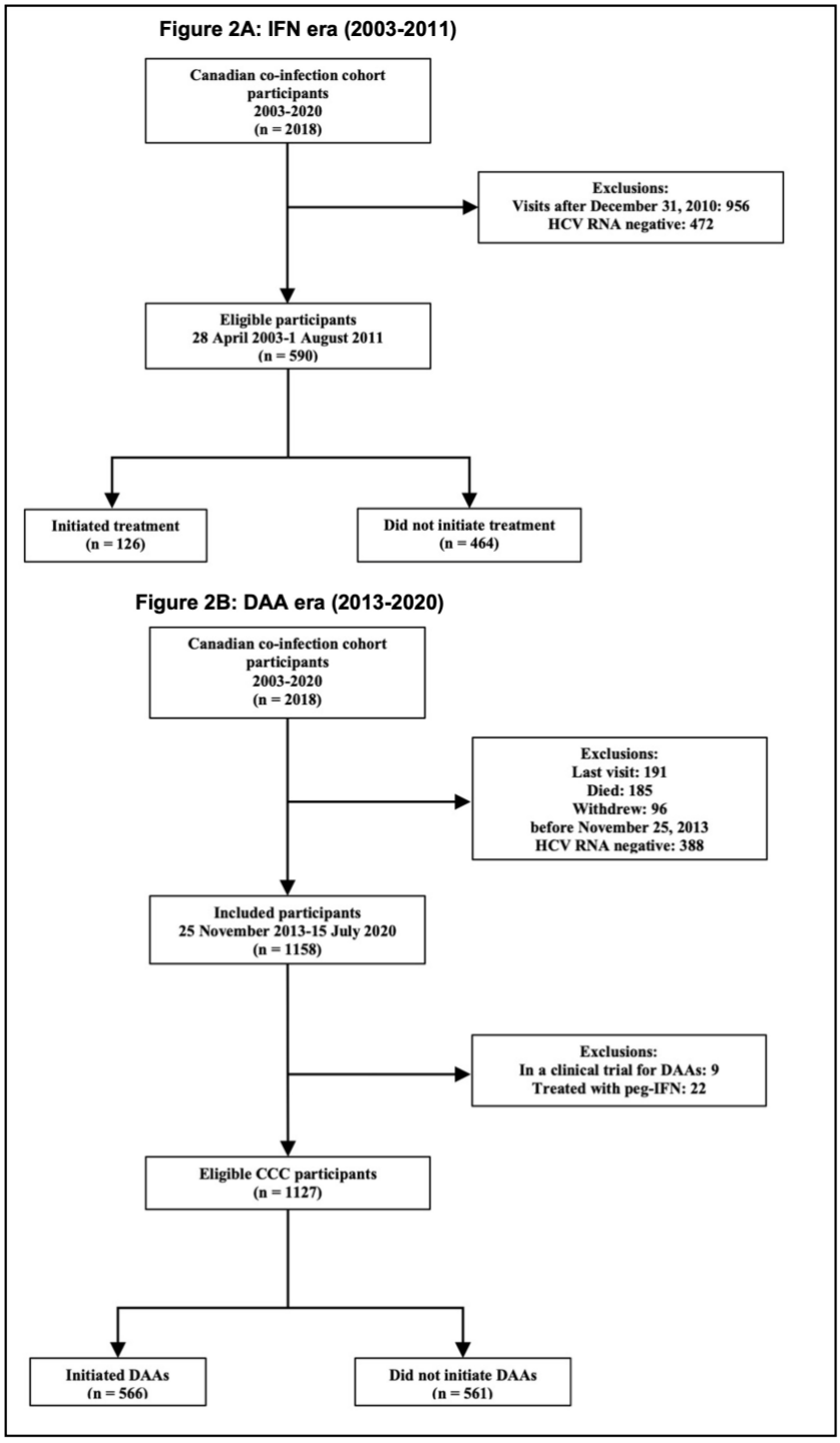
Figure 5.1: Directed Acyclic Graph for effect of depressive symptoms on HCV treatment initiation



Baseline confounders: Age, gender, race/ethnicity, education level, sexual orientation, previous HCV treatment, immigration status, marital status, and province

Time varying confounders: Living situation, employment, monthly income, revenue source, current injection drug use, current alcohol use, current smoking, incarceration in the past 6 months, fibrosis stage, HIV viral load, CD4 count and antidepressant use

Figure 5.2: Flowcharts of participants included in the analytical samples - A. IFN era (2003-2011) and B. DAA era (2013-2020)



Abbreviations: IFN: Interferon; HCV: Hepatitis C virus; DAA: Direct acting antivirals; peg-IFN: Pegylated interferon; CCC: Canadian Co-infection Cohort

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5.3. Manuscript 2: Appendix

Appendix A: Random Forest algorithm for depressive symptoms prediction

Appendix B: Construction of stabilized inverse probability treatment weights and stabilized inverse probability censoring weights

Appendix A: Random Forest algorithm for depressive symptoms prediction

Depression screening was not performed in the Canadian Co-infection Cohort (CCC) and hence a measure of depressive symptoms was not available. Thus, in our previous work (submitted to the Journal of Psychosomatic Research), we developed an algorithm to predict the presence of depressive symptoms indicative of risk of major depression using data from a sub-study within the CCC, the Food Security and HIV-HCV co-infection study (FS sub-study) [1, 2]. In the FS sub-study, depression screening was conducted using the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) [3, 4]. The CES-D-10 is a 10-item Likert scale questionnaire that assesses presence and severity of depressive symptoms in the past week, with a total score range of 0-30. We dichotomized the score at 10 to create the CES-D-10 classes (0/1), as a score ≥10 is widely considered to be indicative of being at risk for major depression with clinically relevant depressive symptoms.[4] Both the scale and the dichotomization at 10 have been validated in HIV populations in Canada [5].

We used the supervised machine learning technique of Random Forests (RF), an ensemble learning approach which uses bootstrap aggregation of multiple decision trees, combining predictions from these many trees [6-10]. We developed probability machines to estimate the CES-D-10 class probabilities at each visit and then determined the CES-D-10 class at the 0.5 probability threshold [11]. The algorithm used 137 candidate predictors available in the CCC, selected based on the literature and subject matter expertise. Predictors fell into one of five major categories: questions related to mental health, health related quality of life, sociodemographic, behavioral, and clinical characteristics. The

performance evaluation characteristics of the algorithm are shown in table 5.4. The algorithm performed well, with an 82% (95% CI: 78-86) chance of distinguishing between the two CES-D-10 classes.

Table 5.4: Supplementary table - Performance evaluation measures for the RF algorithm

Evaluation measures (95% CI)	**RF Algorithm (x=137)**
AUC	0.82 (0.78-0.86)
Sensitivity	0.77 (0.70-0.83)
Specificity	0.73 (0.66-0.79)
PPV	0.74 (0.68-0.80)
NPV	0.76 (0.69-0.82)
LR **+**	2.8 (2.2-3.6)
LR -	0.3 (0.2-0.4)

Abbreviations: CI: Confidence interval; AUC: Area under the Receiver Operating Characteristic curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR +: Positive likelihood ratio; LR -: Negative likelihood ratio

Appendix B: Construction of stabilized inverse probability treatment weights and stabilized inverse probability censoring weights

Stabilized inverse probability treatment weights

We aimed to assess the effect of the predicted depressive symptoms on time to HCV treatment initiation. We thus developed Cox proportional hazards models to obtain this estimate since exact date of treatment initiation was available. However, due to the presence of time-varying covariates, there is a possibility of some of the covariates to be confounders and mediators simultaneously. In this case, adjustment in a conventional Cox PH model can lead to biased estimates. Thus, in addition to the conventional model, we developed marginal structural Cox PH models (MSCM) to address time-varying confounding [12, 13]. The weighting in marginal structural models (MSMs) creates a pseudo-population, where the exposure is independent of the measured baseline and time varying confounders, permitting unbiased estimation of the joint effects of time-dependent exposures under the causal assumptions. Stabilized inverse probability treatment weights (IPTW) were constructed. The stabilized IPTW for patient *i* at visit *t* is shown in equation (1) below.

$$w^s = \frac{\Pi_{t=0}^{T}\ P(E_{it} = e_{it} | E_{i(t-1)} = e_{i(t-1)}, X_{i0} = x_{i0})}{\Pi_{t=0}^{T} P(E_{it} = e_{it} | E_{i(t-1)} = e_{i(t-1)}, X_{i0} = x_{i0}, V_{i(t-1)} = v_{i(t-1)})} \quad \ldots\ldots (1)$$

The numerator was the estimated probability of observed exposure (E_t) for each time interval given baseline covariates (X_0) and past exposure (E_{t-1}), and the denominator was the estimated probability of observed exposure for the time interval given baseline covariates (X_0), past exposure (E_{t-1}), and time-varying covariates (V_t). These weights were obtained by fitting a logistic regression model to obtain the probability of CES-D-10

class=1 (significant depressive symptoms presence) at each visit. The weights were then truncated at the 99th percentile. Summary statistics for the stabilized IPTWs are given in table 5.5.

Stabilized inverse probability censoring weights

A naïve survival analysis would censor individuals at death and assumes independence of censoring and event times. This assumption would be unlikely to be met in this population. Thus, stabilized inverse probability censoring weights (IPCW) were calculated. The stabilized IPCW for death for patient *i* at visit *t* is shown in equation (2) below.

$$w^s = \frac{\Pi_{t=0}^{T}\ P(C_{it}=0|C_{i(t-1)}=0,\ E_{i(t-1)}=e_{i(t-1)}, X_{i0}=x_{i0})}{\Pi_{t=0}^{T} P(C_{it}=0|C_{i(t-1)}=0,\ E_{i(t-1)}=e_{i(t-1)}, X_{i0}=x_{i0}, V_{i(t-1)}=v_{i(t-1)})} \quad \text{..... (2)}$$

where, C=1 if censored, and other variable definitions are same as IPTW above. The numerator was the estimated probability of being uncensored (C_t = 0) for each time interval given baseline covariates (X_0), past exposure (E_{t-1}) and past being uncensored (C_{t-1} = 0) and the denominator was the estimated probability of being uncensored (C_t = 0) given baseline covariates (X_0), past exposure (E_{t-1}), past being uncensored (C_{t-1} = 0) and time-varying covariates (V_t). These weights were obtained by fitting a logistic regression model to obtain the probability of past being uncensored (C_{t-1} = 0) at each visit. The stabilized IPTW and IPCWs will be multiplied to obtain the final weight. The final weight was truncated at the 99th percentile. Summary statistics for the stabilized final weights are provided in table 5.5.

Table 5.5: Supplementary table - Summary of the inverse probability weights

Weights	No Misclassification correction			Misclassification correction		
	Mean (SD)	**Median (IQR)**	**Range**	**Mean (SD)**	**Median (IQR)**	**Range**
Primary Analyses						
IFN era (2003-2011)						
Stabilized IPTW	01.01 (0.48)	0.89 (0.75-1.18)	0.12-3.43	1.00 (0.30)	0.98 (0.86-1.10)	0.12-5.63
Final weight (Stabilized IPTW * Stabilized IPCW)	1.00 (0.49)	0.89 (0.74-1.19)	0.11-3.39	1.00 (0.34)	0.98 (0.83-1.11)	0.11-6.46
DAA era (2013-2020)						
Stabilized IPTW	1.00 (0.31)	0.95 (0.82-1.14)	0.03-2.23	1.00 (0.21)	0.99 (0.90-1.08)	0.10-4.01
Final weight (Stabilized IPTW * Stabilized IPCW)	0.99 (0.33)	0.94 (0.82-1.15)	0.03-2.34	0.99 (0.25)	0.98 (0.88-1.08)	0.08-6.75
Secondary analysis - Restricted subset with CES-D-10 scores available (2012-2015)						
Stabilized IPTW	1.01 (0.35)	0.95 (0.81-1.12)	0.29-2.65	-	-	-
Final weight (Stabilized IPTW * Stabilized IPCW)	1.01 (0.36)	0.95 (0.79-1.14)	0.11-2.70	-	-	-

Abbreviations: SD: Standard deviation; IQR: Interquartile range; IFN: Interferon; DAA: Direct acting antivirals; IPTW: Inverse probability treatment weight; IPCW: Inverse probability censoring weight; CES-D-10: Center for Epidemiologic Studies Depression Scale-10

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6. CHAPTER 6: IMPACT OF HCV CURE ON THE PRESENCE OF DEPRESSIVE SYMPTOMS

6.1. Preface to Manuscript 3

In this analysis, I aimed to assess the impact that SVR may have on depressive symptoms over time in people co-infected with HIV-HCV. To assess these long-term impacts of HCV cure, we need to consider both the biological and psychosocial underlying mechanisms of depression in the co-infected population. Since the DAA regimens lead to HCV clearance, we can hypothesize that induction of depression by the biological pathway via immune activation may be alleviated. However, the co-infected population may continue to face challenges including discrimination, socioeconomic burdens, and/or substance use even after HCV cure. This could potentially have an impact on psychosocial and health outcomes like overdoses reducing the benefits of HCV cure. Thus, the broadening of HCV treatment to all people, irrespective of mental health, now provides us with the opportunity to assess the potential impact of HCV treatment on depressive symptoms over time.

A few studies have assessed depressive symptoms before treatment and at SVR ascertainment (83, 85-88). For example, in a study by Moez et. al., the BDI scores were found to be lower (reduced depression severity) at SVR-12 compared to baseline (111). In contrast, in a prospective follow-up study conducted by Khalil et. al., psychiatric assessment using three scales, BDI, symptom checklist 90-R and Structured Clinical Interview for DSM-IV (SCID-IV) was done at baseline and at SVR, and the all scores were shown to have increased post-treatment, with 32% developing moderate to severe

depression (112). All the above studies, however, were conducted in the HCV mono-infected population. Only one study to my knowledge was conducted among HIV-HCV co-infected people; it showed a decline in BDI scores from baseline to 1-8 weeks after end of DAA treatment (113). Additionally, none of the studies examined depression beyond SVR, and it could be possible that depressive symptoms may decrease transiently at the time of cure, but very little is known about post-SVR depressive symptoms trends and persistence in both HCV mono-infected and HIV-HCV co-infected populations.

To address this gap in knowledge, in this manuscript, I assessed the impact of SVR on depressive symptoms in the HIV-HCV co-infected population in the second-generation DAA era (2013-2020).

This manuscript is submitted for publication and is under review at Clinical Infectious Diseases (CID).

This analysis was presented as posters at the following conferences:

1. 29th Conference on Retroviruses and Opportunistic Infections (CROI 2022), virtual - February 2022
2. Canadian Liver Meeting (CLM) 2022, Hybrid, Ottawa, Canada - May 2022

6.2. Manuscript 3: Impact of HCV cure on depressive symptoms in the HIV-HCV co-infected population in Canada

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Key points (Word limit: 40 words)

Depressive symptoms are common among HIV-HCV co-infected people. This study suggests that, in the direct acting antivirals era, depressive symptoms declined over time

following HCV cure. Thus, HCV cure leads to benefits beyond reduced risk of liver disease.

Abstract

Background

Depression is common in people living with HIV-HCV, with biological and psychosocial mechanisms at play. Direct acting antivirals (DAA) result in high rates of sustained virologic response (SVR), with minimal side-effects. We assessed the impact of SVR on presence of depressive symptoms in the HIV-HCV co-infected population in Canada during the second-generation DAA era (2013-2020).

Methods

We used data from the Canadian Co-infection Cohort (CCC), a multicentre prospective cohort of people with a HIV and HCV co-infection, and its associated sub-study on food security. Since depression screening was performed only in the sub-study, we predicted Center for Epidemiologic Studies Depression Scale-10 classes in the CCC using a random forest classifier and corrected for misclassification. We included participants who achieved SVR and fit a segmented modified Poisson model using an interrupted time series design, adjusting for time-varying confounders.

Results

We included 470 participants; 58% had predicted depressive symptoms at baseline. The median follow-up was 2.4 years (IQR: 1.0-4.5.) pre-SVR and 1.4 years (IQR: 0.6-2.5) post-SVR. The pre-SVR trend suggested depressive symptoms changed little over time, with no immediate level change at SVR. However, post-SVR trends showed a reduction

of 5% per year (risk ratio: 0.95 (95%CI: 0.94-0.96)) in the prevalence of depressive symptoms.

Conclusions

In the DAA era, predicted depressive symptoms declined over time following SVR. These improvements reflect possible changes in biological pathways and/or better general health. If such improvements in depression symptoms are durable, this provides an additional reason for treatment and early cure of HCV.

Background

Both Hepatitis C virus (HCV) and HIV infections are associated with neuropsychiatric manifestations, mainly depression [1, 2]. Among people living with either HIV or chronic HCV, prevalence of depression ranges from 20-30% [1, 3, 4]. Depression is reported to be even higher in the HIV-HCV co-infected population [5]. Depression mechanisms related to HIV and HCV are both biological and psychosocial. HIV and HCV affect the central nervous system directly, which causes immune activation leading to depression [1, 6]. In addition, pro-inflammatory cytokines like TNF-α and IL-1 and altered neurotransmitter action like dopamine and serotonin play roles in inducing depression [1, 6, 7]. There are also many known psychosocial pathways to depression including social stresses caused by stigma, discrimination, and lack of social and financial support [1, 2]. Among HCV-HIV co-infected persons, ongoing substance use is a common additional risk factor, and may also be affected by presence of depressive symptoms [8].

Depression was a well described major side effects of earlier interferon (IFN)-ribavirin based HCV antiviral treatments, with some studies showing more than 20% of those treated developed depression [9]. This led to those with current or past psychiatric illness often not being prescribed IFN therapy [10]. However, after 2013, second-generation IFN-free direct acting antiviral (DAA) regimens now result in >95% rates of sustained virologic response (SVR), even among HIV-HCV coinfected persons [11, 12]. Importantly, there is no evidence of any significant psychiatric side effects associated with DAA treatment [13-15]. HCV treatment guidelines have thus been updated and depression is no longer a contraindication for treatment [16].

These changes in prescribing practices provide us with the opportunity to assess the potential impact of HCV treatment on depressive symptoms over time. We may expect lower depressive symptoms post-cure via biological pathways due to HCV viral clearance. However, co-infected populations continue to face challenges including discrimination, socioeconomic burden, and/or substance use, increasing risk of overdoses and poor mental health, mitigating the benefits of HCV cure. Thus, it is important to examine longitudinally whether HCV cure leads to change in the level of depressive symptoms and moreover whether such a change persists over time. This will provide evidence for healthcare providers to appropriately monitor and manage depression. Evidence of possible improvement in mental health after cure could encourage individuals hesitant to start treatment to do so. Thus, in this study we evaluated the impact of SVR on presence of depressive symptoms in the HIV-HCV co-infected population in Canada during the second-generation DAA era (2013-2020).

Methods

Study population

We used data from the Canadian Co-Infection Cohort (CCC), an open multicentre prospective cohort study, established in 2003 and described in detail elsewhere [17]. Briefly, the CCC recruits from 18 urban and semi-urban HIV centres across 6 Canadian provinces (Quebec, British Columbia, Alberta, Ontario, Nova Scotia, and Saskatchewan). Eligibility criteria include ≥16 years of age, documented HIV infection, and evidence of HCV infection (HCV RNA positivity and/or HCV seropositivity). As of July 2020, the study had recruited 2018 participants. Participants are followed longitudinally, with visits every

six months. Sociodemographic and behavioural data are collected by a standardized self-administered questionnaire at each visit. Clinical data including HIV and HCV treatment dates, medications, co-morbidities, and psychiatric diagnoses are collected via medical chart reviews and HIV and HCV related blood tests performed.

We also used data from a sub-study conducted within the CCC, the Food Security and HIV-HCV co-infection study (FS sub-study), to predict the presence of depressive symptoms in the parent CCC. Participants for the FS sub-study were recruited from the CCC (n=725) with a maximum of 5 visits integrated into CCC visits from 2012-2015. In the sub-study, described elsewhere [18], depression screening was performed using the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) that assesses presence and severity of depressive symptoms in the past week [19]. A score ≥10 is widely considered to represent the presence of depressive symptoms indicative of being at risk for depression; this cut-off has been validated in HIV populations in Canada [20].

Measurement

Exposure

The exposure of interest was successful HCV treatment or cure in individuals treated with DAA regimens. Successful treatment or sustained virological response (SVR) was defined as an undetectable viral load (HCV RNA) 12 weeks after the end of treatment. We included participants who were HCV RNA positive, were treated and then achieved SVR during the second-generation (IFN free) DAA era. The second-generation DAA era was defined from when the first second-generation DAA, Simeprevir, was approved for

use by Health Canada November 25, 2013, and continued until end of study period, July 15, 2020.

Outcome

The outcome of interest was presence of depressive symptoms indicative of being at risk for major depression, hereafter referred to as depressive symptoms. CCC participants are not screened for depression as part of usual study procedures (baseline or follow-up), however depression screening was performed in the FS sub-study. Since the FS sub-study was conducted between 2012 and 2015, we only had such measurements for about 1.5 years in the second-generation DAA era, thus, insufficient data with which to conduct an analysis using measured depressive symptoms. Thus, to obtain a measure of depressive symptoms in the full CCC, we developed a random forest (RF) classifier using the CES-D-10 to classify presence/absence of depressive symptoms derived from the FS sub-study as the outcome (target of prediction), and sociodemographic, behavioural, and clinical characteristics from the parent CCC as predictors [21]. We used the CES-D-10 score cut-off of 10, such that “CES-D-10 class=1” corresponds to a score ≥10 for presence and “CES-D-10 class=0” corresponds to a score < 10 for absence of depressive symptoms indicative of being at risk for depression. The details of the RF classifier development are in appendix A and table 6.4. Using this RF classifier, the CES-D-10 classes were predicted for each CCC visit included in this analysis. We addressed outcome misclassification for the predicted depressive symptoms using the predictive value-based record-level correction method [22]. In this method, we applied the positive predictive value (PPV) and negative predictive value (NPV) estimated for the RF

algorithm; PPV: 0.74 (95% CI: 0.68-0.80) and NPV: 0.76 (95% CI: 0.69-0.82). The procedure included simulation of corrected outcome at each visit by repeated Bernoulli trials with probability equal to PPV for those classified as CES-D-10 class=1 and 1-NPV for those classified as CES-D-10 class=0 [22].

Confounders

We considered time-varying confounders, which were selected a priori [23-25]. These confounders were measured at each biannual visit and included advanced fibrosis/cirrhosis, HIV viral load, CD4 cell count, current injection drug use, current alcohol use, recent incarceration, and antidepressant use. We dichotomized three confounders: advanced fibrosis/cirrhosis (AST to Platelet Ratio Index (APRI) >=1.5 and/or end stage liver disease diagnosis), HIV viral load (at 50 copies/ml), CD4 cell count (at 250 cells/μl). Though using continuous measures may have improved precision, these dichotomizations were chosen to reflect clinical cut-offs for assessment of fibrosis stage and HIV control. In addition, we opted to adjust for HIV viral load directly, rather than antiretroviral therapy status as these two factors are correlated and viral load would be more relevant regarding biological mechanisms underlying HIV and depression [1]. At least one confounder value was missing in 38% of the included visits. We assessed if this missingness was informed by other covariates by using logistic regressions with the missing data indicator as the outcome for each confounder and found missingness to be informed by other covariates in two confounders, recent incarceration, and alcohol use. We used multiple imputation by chained equations (MICE) to address this missing

data in the confounders [26]. We created five imputed datasets using logistic regression for these binary confounder variables.

Statistical analysis

Primary analysis

We used a segmented regression model with interrupted time series (ITS) design to evaluate the impact of SVR on depressive symptoms. In an ITS, a time series of a particular outcome of interest is used to establish an underlying trend, which is 'interrupted' by an exposure at a known point in time, with a clear differentiation between the pre-exposure and post-exposure periods [27]. In this analysis, the extrapolation of the pre-exposure outcome trend acts as a counterfactual for the post-exposure trend for each individual. It is assumed that, since the same individual is observed before and after the exposure, this design accounts for known and unknown confounders that do not vary with time [27, 28]. The pre-exposure period included time from cohort entry when participants were HCV RNA positive to treatment initiation in the second-generation DAA era. The post-exposure period included time after the ascertainment of SVR for each individual. We did not include the time between DAA initiation and SVR ascertainment in the analysis. Based on subject matter knowledge, we hypothesized that depressive symptoms may have an immediate decrease at SVR as well as a decrease over time. The causal diagram can be seen in appendix B-figure 6.3. Subgroup analyses were performed to explore possible difference by sex (male, female), race (white, Indigenous), employment status (employed, not employed), and baseline liver disease (no liver disease, with liver disease).

We used Generalized Estimating Equations (GEEs) with robust standard errors, which account for correlation between repeated measurements on the same participant over time. GEEs are a population-level approach and provides population-averaged estimates of the parameters (as opposed to the individual-level analysis provided by mixed effect models) [29]. We used an exchangeable working correlation structure in these models, which assumes positive correlation between repeated measurements over time for an individual. The segmented modified Poisson model, which involves using a robust variance estimation, was defined as below [27]. We developed these models with and without outcome misclassification correction. The model can be seen in appendix C.

Sensitivity analyses

We conducted planned sensitivity analyses to assess robustness of the results, specifically due to two possible methodological challenges for ITS - lead time bias and non-linear effect. Lead time bias is possible in this analysis as depressive symptoms may change in anticipation of the exposure, SVR [28]. To check for lead time bias, we moved the time axis to set the exposure one year before SVR ascertainment. To address the possibility that the effect may not be linear on the log scale, we developed adjusted models with polynomials (squared and cubic transformations of time) and also with restricted cubic spline with 5 knots - see further details in appendix D [30]. We then used the quasi-likelihood under the independence model criterion (QIC) for model selection among the linear and the non-linear models [31]. Additionally, we conducted a sensitivity analysis exploring depressive symptom trends for those who did not respond to DAAs, by

comparing the trends before and after the date of no-response ascertainment. All primary and sensitivity analyses were performed using Stata v.17 [32].

Results

Participant characteristics

The flowchart for participants in the final analytical sample is shown (figure 6.1). We included 470 participants who achieved SVR in the DAA era. Baseline characteristics are shown in table 6.1. Participants were vulnerable and could face potential barriers to HCV and mental health care. They were predominantly male (68%) and unemployed (68%); 23% were Indigenous, 50% were on welfare as their primary revenue source, 73% had no post-secondary education, and 34% were current injection drug users. At baseline, 58% of the cohort had predicted depressive symptoms indicative of a risk of depression.

Primary analyses

The results of the primary analyses are shown in table 6.2 and illustrated in figure 6.2 A. The median follow-up was 2.4 years (Interquartile range (IQR): 1.0-4.5) pre-SVR and 1.4 years (IQR: 0.6-2.5) post-SVR. After correcting for outcome misclassification, the pre-treatment trends show an adjusted risk ratio (aRR) of 1.01 (95% CI: 1.01-1.02), which indicates little change in the annual rate of predicted depressive symptoms over time prior to treatment. The model does not show any immediate level change at SVR (aRR) of 1.01 (95% CI: 0.97-1.04). However, the post-SVR trends shows a decrease in depressive symptoms over time, of 5% per year (aRR of 0.95 (95% CI: 0.94-0.96)). There were no major differences noted between the various subgroups (sex, race, employment status,

and liver disease) in the pre-treatment initiation and changes at SVR. There was some difference noted in the post-SVR downward trend by sex and race, however sample sizes were limited, precluding definitive conclusions (see appendix E-table 6.6).

Sensitivity analyses

The results of the sensitivity analysis used to assess possible lead time bias are shown in table 6.3 and illustrated in figure 6.2 B. The trends are similar for pre-treatment period as the primary analysis. There is an increase in the immediate level of depressive symptoms prevalence one-year pre-SVR (aRR: 1.06 (1.02-1.10)), showing no evidence of lead time bias. The second sensitivity analysis did not support non-linearity of the effect on the log scale: the linear model was selected based on the lowest values of the QIC statistic. These results of the non-linearity sensitivity analysis are shown in table 6.5 in appendix D. The results for the sensitivity analysis with DAA non-responders are shown in table 6.7 and figure 6.4 in appendix F. In DAA non-responders, the pre-treatment probability trend was stable over time, with no evidence of immediate change at date of no-response ascertainment. However, the probability trend post-no-response indicates a gradual increase in depressive symptoms over time.

Discussion

We measured using segmented regression models the impact of HCV cure on predicted depressive symptoms. While depressive symptoms changed little over time in the lead up to DAA treatment, we observed a gradual decline in prevalence of depressive symptoms over time post-SVR among patients co-infected with HIV. There was no

evidence of immediate change at SVR. The improvement after cure may reflect changes in biological pathways leading to HCV-related depression due to viral clearance and/or improved general physical health.

The use of DAAs has increased and improved HCV treatment among people with a history of depression or with current depressive symptoms. Several studies have assessed health-related quality of life post-SVR with DAAs and have shown a modest improvement after HCV cure [33, 34]. This is in line with our observation of decline of depressive symptoms over time, which are strongly correlated with health-related quality of life [35].

Several studies have compared depressive symptoms at baseline and at SVR-12. In a study by Moez et. al., Beck depression inventory (BDI) scores were found to be lower (reduced depression severity) at SVR-12 compared to baseline [36]. Similar results were observed in a few other studies [14, 15, 37]. In contrast, in a prospective study with psychiatric assessments at baseline and at SVR-12, scores were shown to have increased post-treatment, with 32% developing moderate to severe depression [38]. The authors suggested an explanation for this increase might include biological mechanisms related to increased levels of IFN, the higher percentage of women in the cohort, continued stigma, other co-morbid conditions, and persisting unemployment [38, 39]. Similar results were seen in other studies [40, 41]. All the above studies, however, were conducted in HCV mono-infected populations. Only one study to our knowledge was among HIV-HCV co-infected people which showed a decline in BDI scores from baseline to 1-8 weeks after end of DAA treatment [42]. There are several possible methodological reasons for these conflicting results, like different sample sizes (e.g., n=150 (Moez. et.

al.) vs. n=47 (Khalil et. al.), different depression scales, and varying measurement time points (between 4 and 12 weeks of treatment; not all at SVR, e.g., Egmond et. al.) [36, 38, 41]. Additionally, none of the studies examined depression in the time frame beyond SVR and thus very little is known about post-SVR depressive symptoms trends and persistence in both HCV mono-infected and HIV-HCV co-infected populations.

One major strength of our study is we used longitudinal data collected in numerous, diverse patients. Using a quasi-experimental design, ITS, we were able to obtain robust marginal effect estimates of the impact of SVR on depressive symptoms in the co-infected population. We believe our estimates are generalizable to HIV-HCV co-infected patients engaged in care in Canada, as CCC participants are recruited from primary and tertiary care clinics in urban and semi-urban areas across six provinces in Canada. We also conducted multiple sensitivity analyses and adjusted for time-varying confounders.

Our study, however, does have some limitations. The depressive symptoms were predicted via a RF algorithm, and not measured directly in the cohort. Misclassification was therefore expected, and we corrected for it. We predicted the depressive symptoms based on a screening questionnaire, CES-D-10, and not a major depression diagnosis. Thus, this study does not provide an effect estimate for depression but rather for depressive symptoms that are indicative of a depression risk. Further, we predicted the CES-D-10 classes based on the validated cut-off of 10 and not a CES-D-10 continuous score. The continuous score prediction algorithm could only explain a small portion of the outcome variability. This could have been because the FS sub-study sample was relatively small and did not capture the full range of the continuous scale. We used an

ITS because an appropriate control group was difficult to find. Those not treated may be inherently different from those treated, and in the DAA era, very few of those treated fail to achieve SVR. Finally, the crucial assumption of the ITS design that the extrapolated pre-exposure trend is considered the counterfactual trend, makes it vulnerable to unmeasured time-varying confounding, which we tackled by adding known time-varying confounders; however, some residual confounding could still be possible. Finally, the median post-SVR follow-up was 1.4 years, so the durability of the observed effect is yet to be explored. Persisting psychosocial and economic burdens post-cure such as stigma and discrimination in social, professional as well as healthcare settings could still lead to shame, suffering and lack of disease-related education and recurrence of depressive symptoms over the long-term [43].

In conclusion, following SVR, there appears to be a continuous decline in the presence of depressive symptoms in highly vulnerable patients co-infected with HCV and HIV. This finding suggests that the health benefits of curing HCV extend beyond improving liver disease and provides additional rationale for treating HCV in all chronically infected persons.

Table 6.1: Baseline characteristics of the included participants (n = 470)

Baseline characteristics	**Participants (n = 470) n (%) or median (IQR)**
Predicted presence of depressive symptoms (CES-D-10 score ≥ 10)	272 (58%)
Age (years)	47 (41-52)
Gender - Male	321 (68%)
Self-reported race/ethnicity	
White	323 (69%)
Indigenous (First Nations, Inuit, and Metis)	107 (23%)
Asian	14 (3%)
Black	17 (4%)
Hispanic/Latinx	7 (2%)
Living situation - Homeless	48 (10%)
Education - High school educated and less	344 (73%)
Employment - Not employed	317 (68%)
Monthly income - <= $1500 CAD	356 (76%)
Revenue source - Welfare	233 (50%)
Sexual orientation - Heterosexual	319 (68%)
Immigrant to Canada	42 (9%)
Marital status - Single	329 (70%)
Previous IFN-based HCV treatment	69 (15%)
Injection drug use in the past 6 months	159 (34%)
Alcohol use in the past 6 months	243 (52%)
Incarceration in the past 6 months	31 (7%)
Liver disease - APRI score >= 1.5 and/or liver disease diagnosis	90 (19%)
Hepatitis B infection	17 (4%)
HIV viral load - > 50 copies/ml	121 (26%)
CD4 count - <= 250 cells/uL	107 (23%)
Antidepressant prescribed in the past 6 months	40 (9%)

Abbreviations: IQR: Interquartile range; CES-D-10: Center for Epidemiologic Studies Depression Scale-10; CAD: Canadian dollars; IFN: Interferon; HCV: Hepatitis C virus; APRI: AST to Platelet Ratio Index; HIV: Human Immunodeficiency Virus; CD4: Cluster of differentiation 4 receptor

Table 6.2: Impact of SVR on depressive symptoms in the HIV-HCV co-infected population - primary analysis models with and without outcome misclassification correction (n=470)

Sr. No.	Models	Risk ratios (95% CI)		
		Pre-treatment trends per year	Level change at SVR	Post-SVR trends per year
I	**Unadjusted models**			
A	No misclassification correction	1.01 (0.99-1.04)	1.01 (0.93-1.09)	0.92 (0.88-0.96)
B	Misclassification correction	1.01 (1.00-1.01)	1.01 (0.97-1.04)	0.95 (0.94-0.96)
II	**Adjusted models ***			
A	No misclassification correction	1.02 (0.99-1.04)	1.01 (0.94-1.10)	0.92 (0.88-0.96)
B	Misclassification correction	1.01 (1.01-1.02)	1.01 (0.97-1.04)	0.95 (0.94-0.96)

* Adjusted for time-varying confounders: Advanced fibrosis/cirrhosis (AST to Platelet Ratio Index (APRI) >=1.5 and/or end stage liver disease diagnosis), detectable HIV viral load (>50 copies/ml), low CD4 cell count (≤250 cells/μl), current injection drug use, current alcohol use, incarceration in the past 6 months and antidepressant use
Abbreviations: SVR: Sustained virologic response; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; CI: Confidence interval

Table 6.3: Sensitivity analysis to assess possible lead time bias - models with and without outcome misclassification correction (n=332)

Sr. No.	Models	Risk ratios (95% CI)		
		Pre-treatment trends per year	Level change at SVR	Post-SVR trends per year
I	**Unadjusted models**			
A	No misclassification correction	1.01 (0.98-1.03)	1.10 (0.99-1.22)	0.93 (0.89-0.98)
B	Misclassification correction	1.00 (0.99-1.01)	1.10 (1.01-1.10)	0.96 (0.95-0.98)
II	**Adjusted models ***			
A	No misclassification correction	1.01 (0.98-1.04)	1.10 (0.99-1.23)	0.93 (0.90-0.97)
B	Misclassification correction	1.01 (0.99-1.01)	1.06 (1.02-1.10)	0.96 (0.95-0.98)

* Adjusted for time-varying confounders: Advanced fibrosis/cirrhosis (AST to Platelet Ratio Index (APRI) >=1.5 and/or end stage liver disease diagnosis), detectable HIV viral load (>50 copies/ml), low CD4 cell count (≤250 cells/μl), current injection drug use, current alcohol use, incarceration in the past 6 months and antidepressant use
Abbreviations: CI: Confidence interval; SVR: Sustained virologic response

Figure 6.1: Flowchart of participants included in the analytical sample

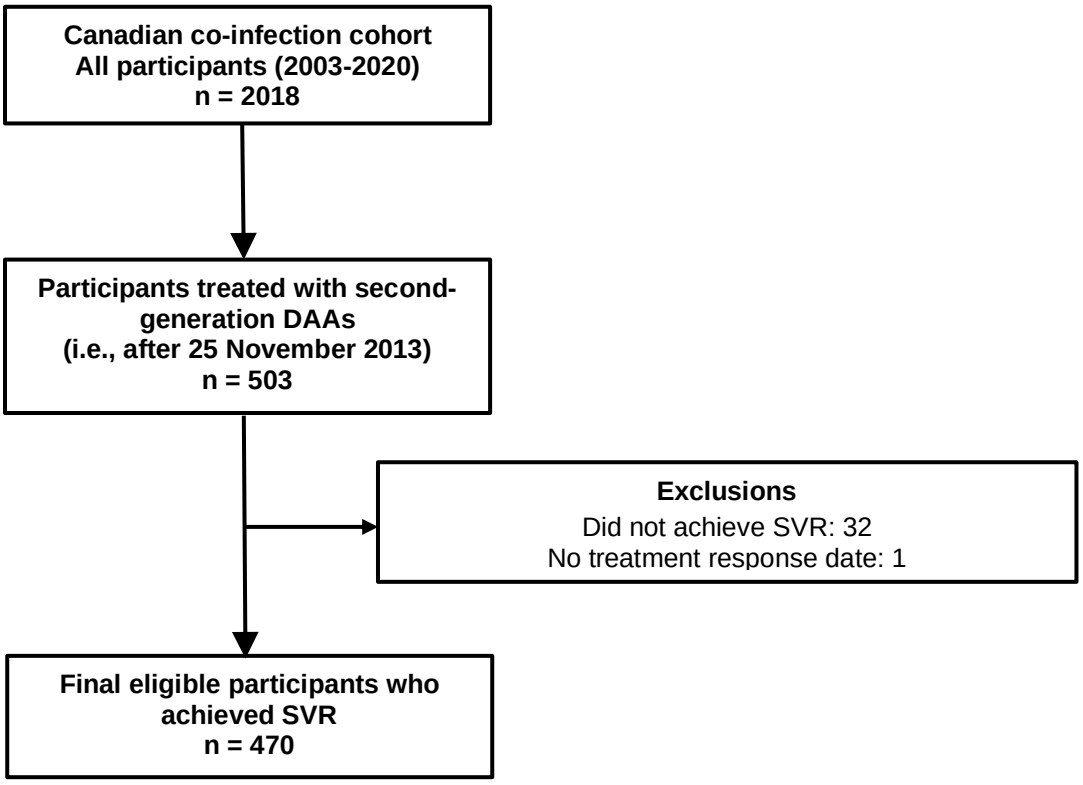

Figure description: The Canadian Co-infection Cohort (CCC) had recruited 2018 HIV-HCV co-infected participants (HCV RNA positive/HCV seropositive) until July 2020. In our analysis, we included 503 participants who were treated with IFN-free second-generation Direct Acting Antivirals (DAA) regimens after November 25, 2013, when the first second-generation DAA, Simeprevir, was approved for use by Health Canada. Of the participants who were treated, we excluded those who did not achieve sustained virologic response (SVR) (n = 32) and did not have a treatment response date (n = 1). Thus, in the final analytical sample we included a total of 470 participants who had achieved SVR.

Figure 6.2: Impact of sustained virologic response (SVR) on depressive symptoms in the HIV-HCV co-infected population

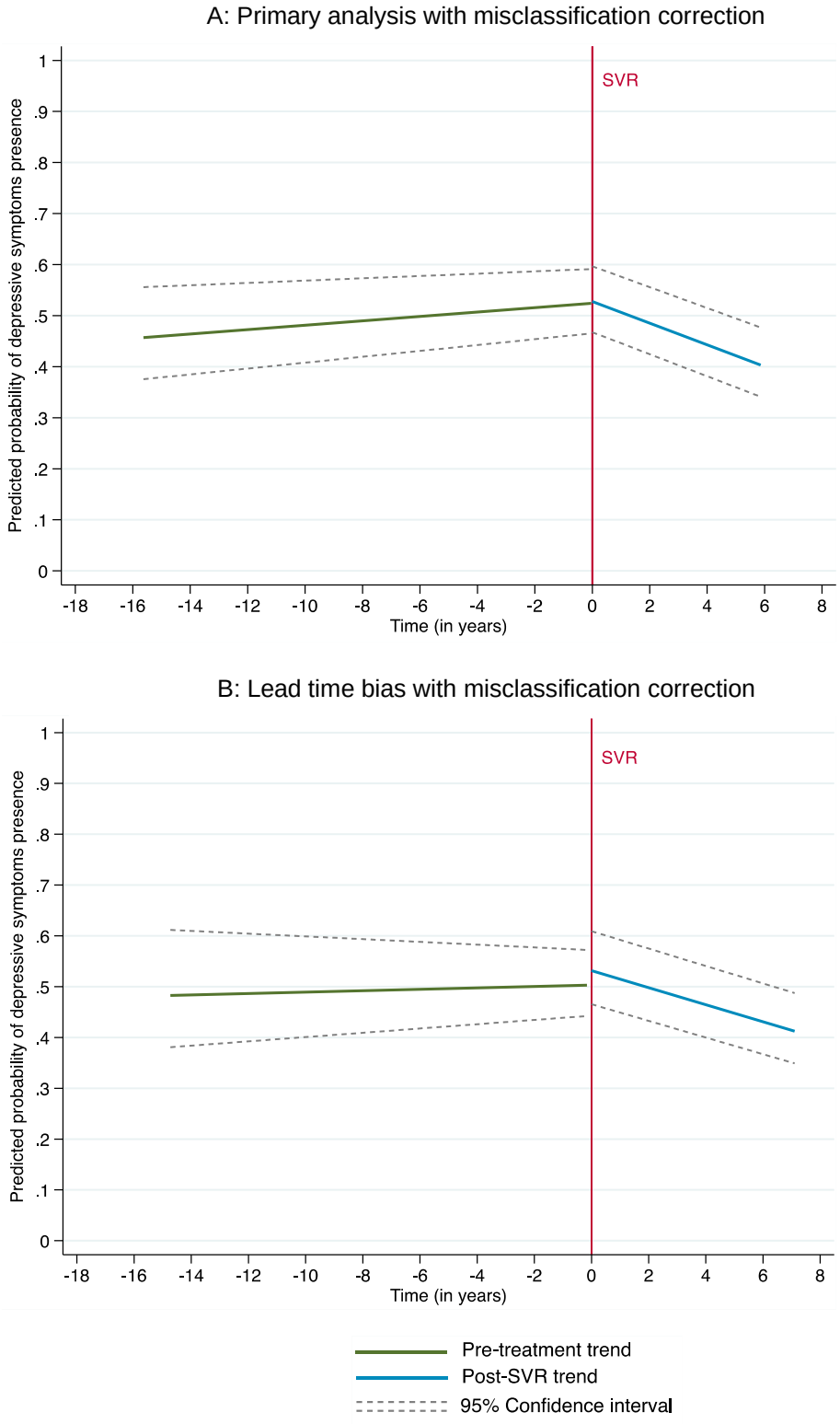

Figure Description: A. Results of the primary analysis model with outcome misclassification correction - The graph shows that pre-treatment the probability trend for presence of depressive symptoms was stable over time. There was no evidence of immediate change at SVR, however the probability trends post-SVR indicate a gradual decline in depressive symptoms over time. B. Results of the sensitivity analysis model to assess lead time bias with outcome misclassification correction - In this model, we lagged SVR by one year to assess possibility of lead time bias. The graph shows a stable pre-treatment trend like the primary analysis. The increase in the immediate level of depressive symptoms prevalence one-year pre-SVR, provides evidence for no lead time bias in this analysis, meaning depressive symptoms did not seem to improve in anticipation of the cure.

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Ethics approval: This study was approved by the Research Ethics Board of the McGill University Health Centre (2021-6985). The CCC and the FS Sub-Study were approved by the Research Ethics Board of the McGill University Health Centre (2006-1875, BMB-06-006t, 2013-994) and the research ethics boards of participating institutions. The study was conducted according to the Declaration of Helsinki.

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

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6.3. Manuscript 3: Appendix

Appendix A: Random Forest algorithm for depressive symptoms prediction

Appendix B: Causal diagram

Appendix C: Segmented modified Poisson model

Appendix D: Sensitivity analysis - non-linearity

Appendix E: Subgroup analyses

Appendix F: DAA non-responders

Appendix A: Random Forest algorithm for depressive symptoms prediction

Depression screening was not performed in the Canadian Co-infection Cohort (CCC) and hence a measure of depressive symptoms was not available. Thus, in previous work, we developed an algorithm to predict the presence of depressive symptoms indicative of risk of depression using data from a sub-study within the CCC, the Food Security and HIV-HCV co-infection study (FS sub-study) [1, 2]. In the FS sub-study, depression screening was conducted using the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) [3, 4]. The CES-D-10 is a 10-item Likert scale questionnaire that assesses presence and severity of depressive symptoms in the past week, with a total score range of 0-30. We dichotomized the score at 10 to create the CES-D-10 classes (0/1), as a score ≥10 is widely considered to be indicative of being at risk for major depression with clinically relevant depressive symptoms [4]. Both the scale and the dichotomization at 10 have been validated in HIV populations in Canada [5].

We used the supervised machine learning technique of Random Forests (RF), an ensemble learning approach which uses bootstrap aggregation of multiple decision trees, combining predictions from these many trees [6-10]. We developed probability machines to estimate the CES-D-10 class probabilities at each visit and then determined the CES-D-10 class [11]. The algorithm used 137 candidate predictors available in the CCC, selected based on the literature and subject matter expertise. Predictors fell into one of five major categories: questions related to mental health, health related quality of life, sociodemographic, behavioral, and clinical characteristics. To develop the algorithm, we split the analytical sample into training and testing data, using the recommended 80:20 split. The algorithm was then developed by 10-fold cross-validation using only the training

data and RF hyperparameters (i.e., various RF settings like number of decision trees) were tuned to maximize accuracy. The final tuned algorithms were implemented in the testing data, which was not used in the development stage. To assess the ability to distinguish between classes (discrimination), we plotted receiver operating characteristic (ROC) and estimated the area under the ROC curve (AUC) We used the default probability threshold of 0.50 for classification and at this threshold, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) measures were then estimated with the 95% confidence intervals (CI). The performance evaluation characteristics of the algorithm are shown in table S1. The algorithm performed well, with an 82% (95% CI: 78-86) chance of distinguishing between the two CES-D-10 classes.

Table 6.4: Supplementary table - Performance evaluation measures for the RF algorithm

Evaluation measures (95% CI)	**RF Algorithm (x=137)**
AUC	0.82 (0.78-0.86)
Sensitivity	0.77 (0.70-0.83)
Specificity	0.73 (0.66-0.79)
PPV	0.74 (0.68-0.80)
NPV	0.76 (0.69-0.82)
LR +	2.8 (2.2-3.6)
LR -	0.3 (0.2-0.4)

Abbreviations: CI: Confidence interval; AUC: Area under the Receiver Operating Characteristic curve; PPV: Positive predictive value; NPV: Negative predictive value; LR +: Positive likelihood ratio; LR -: Negative likelihood ratio

Appendix B: Causal diagram

Figure 6.3: Supplementary figure - Causal Diagram

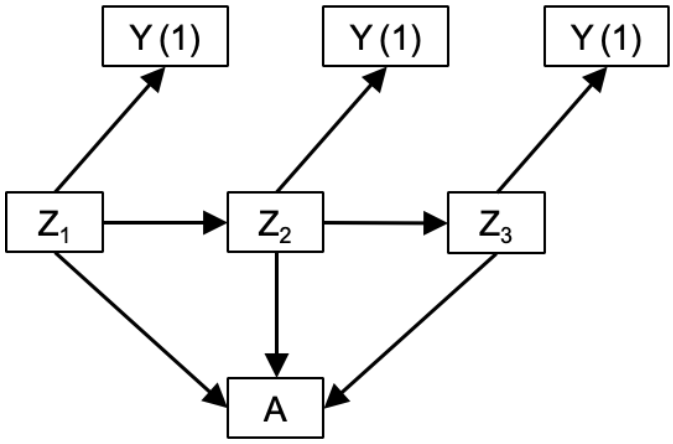

Figure Description: A: Exposure - SVR, Y: Outcome - Depressive symptoms; Z: Time varying confounders - advanced fibrosis/cirrhosis, HIV viral load, low CD4 cell count, current injection drug use, current alcohol use, recent incarceration, and antidepressant use

Appendix C: Segmented modified Poisson model

$$\log(P(\text{CES-D-10} = 1)) = \beta_0 + \beta_1 \text{time} + \beta_2 \text{pre-post} + \beta_3 \text{time} * \text{pre-post} + \beta_4 x$$

time = time in years pre-SVR and post- SVR

pre-post = indicator of pre and post SVR, *pre-post* = 0 if pre-SVR and *pre-post* = 1 if post-SVR

x = time-varying confounders

β_0 = log probability of CES-D-10 class = 1

β_1 = Pre-SVR CES-D-10 class 1 probability trends

β_2 = immediate level change in probability trend post-SVR (level change)

β_3 = impact of DAAs on post-SVR probability trends (slope change)

Appendix D: Sensitivity analysis - non-linearity

In order to assess the possible non-linearity of the relationship between the outcome, presence of depressive symptoms and time, we developed two types of non-linear models.

1. **With cubic polynomials:** In this model, we included squared and cubic polynomials of time and their interaction with pre-post to explore this possible non-linear relationship. The model we used is as follows:

$$log\ (P(CES-D-10=1)$$
$$= \beta_0 + \beta_1\ pre-post + \beta_2\ time + \beta_3\ pre-post * time + \beta_4\ time^2$$
$$+ \beta_5 time^2 * pre-post + \beta_6\ time^3 + \beta_7 time^3 * pre-post + + \beta_8\ x$$

2. **With restricted cubic splines:** We also developed a non-linear model using a spline function for time, which are piecewise polynomials, i.e., polynomials within intervals of the variable, time in our case [12]. We included restricted cubic splines or natural splines because they are smooth and can better fit a curve than linear splines. Restricted cubic splines also have benefits compared to cubic splines as they are linear at the tails and estimate fewer parameter [12]. We developed the restricted cubic spline with 5 knots for time, positioned at the 5th (-7.1 years), 27.5th (-2.2 years), 50th (-0.2 years), 72.5th (0.7 years) and 97.5th (3.4 years) percentile. We used mkspline in Stata v.17 for this analysis [13].

We then selected the model using the quasi-likelihood under the independence model criterion (QIC), a statistic applicable to Generalized estimating equations (GEEs) [14-16]. The model selection is based on the lowest QIC, and thus, the linear models were selected in this analysis.

Table 6.5: Supplementary table - Model selection using QIC

Models	**QIC**
Linear	885.9
Cubic polynomial	893.3
Restricted cubic splines	892.8
Selected model (Lowest QIC)	Linear

Appendix E: Subgroup analyses

Table 6.6: Supplementary table - Subgroup analyses - models without outcome misclassification correction

Subgroups	No. of participants	Adjusted risk ratios (95% CI)		
		Pre-treatment trends per year	Level change at SVR	Post-SVR trends per year
Gender				
Male	321	1.02 (0.99-1.04)	0.99 (0.90-1.11)	0.95 (0.89-0.99)
Female	144	1.03 (0.99-1.06)	1.04 (0.92-1.17)	0.86 (0.80-0.93)
Race				
White	323	1.01 (0.99-1.04)	0.96 (0.87-1.1)	0.94 (0.89-0.98)
Indigenous	107	1.06 (1.01-1.09)	1.10 (0.96-1.26)	0.83 (0.75-0.93)
Employment				
Not employed	317	1.01 (0.99-1.02)	1.04 (0.96-1.13)	0.92 (0.88-0.97)
Employed	129	1.12 (1.06-1.20)	0.85 (0.68-1.05)	0.87 (0.78-0.98)
Liver disease				
No liver disease	343	1.01 (1.00-1.04)	1.04 (0.95-1.14)	0.92 (0.87-0.97)
With liver disease	90	1.04 (0.97-1.11)	0.92 (0.76-1.10)	0.89 (0.81-0.98)

Appendix F: DAA non-responders

Table 6.7: Supplementary table - Sensitivity analysis model for DAA non-responders

No. of participants	Adjusted risk ratios (95% CI)		
	Pre-treatment trends per year	Level change at SVR	Post-SVR trends per year
19 (245 visits)	1.00 (0.95-1.10)	0.98 (0.65-1.50)	1.20 (1.01-1.35)

Figure 6.4: Supplementary figure - Impact of non-response on depressive symptoms in DAA non-responders

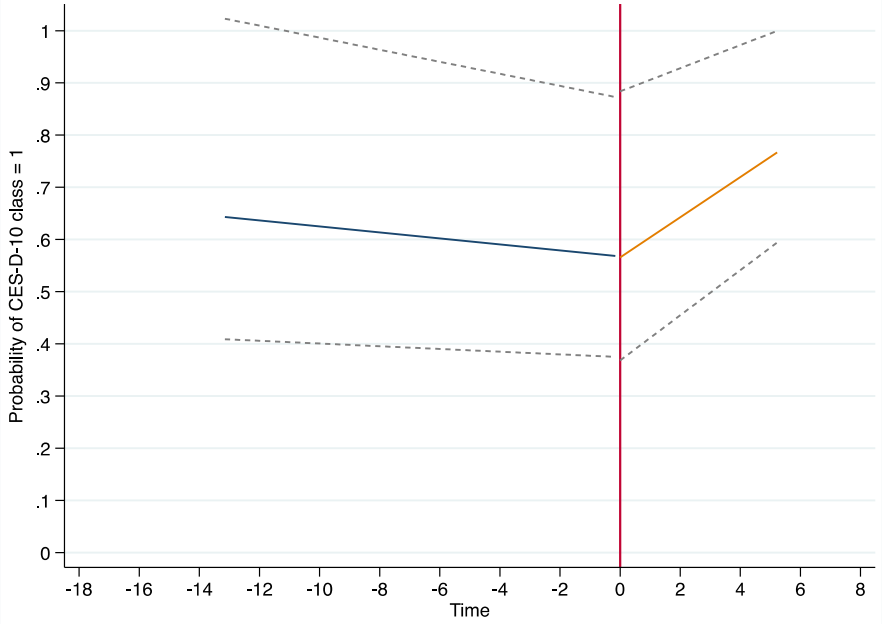

Figure Description: The graph shows that pre-treatment the probability trend for presence of depressive symptoms was stable over time. There was no evidence of immediate change at date of no-response ascertainment. However, the probability trend post-no-response indicates a gradual increase in depressive symptoms over time.

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7. CHAPTER 7: EFFECT OF DEPRESSIVE SYMPTOMS ON HEALTH SERVICES UTILIZATION

7.1. Preface to Manuscript 4

In this chapter, I aimed to assess the effect of depressive symptoms on HSU. HSU is defined as the "quantification of the use of services by persons for the purpose of preventing and curing health problems, promoting maintenance of health and wellbeing, or obtaining information about one's health status and prognosis" (114). It can be measured in several ways, including number of services used in a given period of time or percentage of a population using a certain service in a given time (114). Generally, a higher HSU is an indication of lower health status and leads to higher individual as well as societal economic burden (115).

There is evidence that suggests HSU is high among PLWH as compared to those without an HIV infection and this is even higher among those co-infected with HCV (116-118). This could be explained by increased co-morbidities, including psychiatric illness. Additionally, the literature regarding health services among people with chronic HCV suggests that cure or SVR may lead to lower HSU among people infected with HCV alone as well as co-infected with HIV (119, 120). However, studies quantifying the impact on HSU of specific psychiatric illnesses including depression are scarce. It would also be of interest to assess this impact of depressive symptoms on HSU in the light of the available treatment options and cure for HCV in the co-infected population in the second-generation DAA era. With Manuscript 3 indicating a gradual decline in depressive symptoms over time after SVR, it would also be interesting to study whether HCV cure impacts the

relationship between depressive symptoms and HSU in the HIV-HCV co-infected population.

In this manuscript, I assessed the effect of depressive symptoms and SVR on HSU in the co-infected population in the second-generation DAA era (2013-2020).

This manuscript will be submitted for publication as a short report at Epidemiology.

This analysis is accepted for poster presentation at the following conferences/seminars:

1. 24th International AIDS conference (AIDS 2022), Hybrid, Montreal Canada - July 2022

7.2. Manuscript 4: Effect of depressive symptoms on health services utilization in the HIV and Hepatitis C co-infected population in Canada

Title: Effect of depressive symptoms on health services utilization in the HIV and Hepatitis C co-infected population in Canada

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Running head: Depressive symptoms and health services utilization

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Ethics approval: This study was approved by the Research Ethics Board of the McGill University Health Centre (2021-6985). The CCC and the FS Sub-Study were approved by the Research Ethics Board of the McGill University Health Centre (2006-1875, BMB-06-006t, 2013-994) and the research ethics boards of participating institutions. The study was conducted according to the Declaration of Helsinki.

Consent to participate: Informed consent was obtained from all individual participants included in the study

Abstract

People living with HCV and HIV experience many co-morbid conditions including depression, contributing to high health services utilization (HSU). Successful HCV treatment may however have an impact. We examined the relationship between depressive symptoms and HSU and whether it was affected by sustained virologic response (SVR) in the HIV-HCV co-infected population. We used data from the Canadian Co-infection Cohort and predicted depressive symptoms using a random forest classifier and corrected for misclassification. Outcomes were number of inpatient and outpatient visits in the past 6 months. We restricted attention to the direct acting antiviral era and included all HCV-RNA+ participants. We fitted a zero-inflated negative binomial regression model. We included 1,153 participants, 530 were treated and 504 (95%) achieved SVR. Among those without SVR, inpatient visits were 16% higher and outpatient visits were 5% higher among those with depressive symptoms than those without, while among those with SVR, this association disappeared. SVR itself was associated with 24% fewer inpatient visits, but no change in outpatient visits. In conclusion, depressive symptoms were associated with a modest increase in HSU among those remaining HCV infected, indicating it contributes to poorer health outcomes. SVR was associated with substantial reduction in inpatient visits and an attenuated impact of depressive symptoms.

Background

Chronic HCV infection can result in end stage liver disease such as cirrhosis, its complications and hepatocellular carcinoma. It is also associated with many extrahepatic manifestations such as cryoglobulinemia, type 2 diabetes, and chronic kidney disease[1]. People living with HIV are also disproportionately affected by cardiovascular disease, chronic kidney disease, osteoporosis, and cancer[2]. People co-infected with HCV and HIV, thus, are faced with several co-morbid conditions which may result in increased health services utilization (HSU), i.e., the use of health care services for prevention, treatment, and management of health problems. Such problems may increase both inpatient hospitalizations and outpatient medical visits such as physician, emergency room or walk-in visits[3-8]. Greater HSU is an indicator of lower health status and has health economic implications.

Neuropsychiatric manifestations, particularly depression[9,10] represent a common and potentially burdensome co-morbidity associated with HCV and HIV infections. Among people living with HIV, studies have shown a prevalence of depression of between 20-30% and as high as 24% among those with chronic HCV [1,9,11,12]. Depression prevalence is reported to be even higher in the in the co-infected population[13]. Mechanisms may be both biological via immune activation within the central nervous system and psychosocial through social stresses caused by stigma, discrimination, lack of support, and substance use[9,14-17].

Studies assessing HSU and depression have shown evidence of an increase in the use of health services and hospitalizations among those with depression[18-20]. In a retrospective cohort study of people living with HIV in British Columbia, the interaction between co-infection with HCV and mental health disorders was assessed in relation to acute care hospitalizations. The presence of both co-infection and mental health disorders led to a larger number of hospitalizations than presence of either one [21]. There are however limited studies looking at depressive symptoms specifically and their effect on HSU in the co-infected population. HCV cure has been shown to have a number of health benefits both with respect to liver disease and related mortality and non-liver related comorbidities which could reduce HSU. Additionally, in the Canadian Co-infection Cohort (CCC), we have shown that SVR could lead to a gradual decline in depressive symptoms over time. However, it has not been examined if SVR may hence also have an impact on this relationship between depressive symptoms and HSU in the co-infected population.

Thus, in this study, we examined the effect of presence of depressive symptoms on HSU, both inpatient and outpatient healthcare visits and how it is affected by SVR in the HIV-HCV co-infected population in Canada.

Methods

We used data from the CCC, an open multicentre prospective cohort study, ongoing since 2003. The study has been described in detail elsewhere[22]. Briefly, the CCC recruits from 18 HIV centres across six Canadian provinces. Eligibility criteria include ≥16 years of age,

documented HIV infection, and evidence of HCV infection (HCV RNA positive and/or HCV seropositive). The study had recruited 2018 participants as of July 2020. Participants are followed longitudinally every 6 months and sociodemographic, behavioural, and clinical data are collected by a standardized self-administered questionnaires and chart reviews. We also used data from an associated sub-study, the Food Security and HIV-HCV co-infection study (FS sub-study). Participants for the FS sub-study were recruited from the CCC (n=725) between 20212-15. The sub-study is fully described in detail elsewhere[23], Depression screening was performed in the sub-study using the Center for Epidemiologic Studies Depression Scale-10 (CES-D-10) to assess the presence and severity of depressive symptoms in the past week[24]. We obtained a measure of depressive symptoms in the full CCC using a random forest (RF) classifier. The CES-D-10 class (cut-off ≥10 for presence of depressive symptoms indicative of a risk of depression) was predicted for each CCC visit [25,26].

In the final analytical sample, we included all participants who were HCV RNA positive in the second generation DAA era, i.e., after November 25, 2013, when the first 2nd generation DAA, Simeprevir, was approved for use by Health Canada. We followed the HCV RNA positive participants until death, withdrawal, or end of study period (July 2020). We considered participants to have achieved SVR if they were treated with 2nd generation DAAs and had undetectable HCV viral load at 12 weeks post-end of treatment.

We developed zero-inflated negative binomial (ZINB) models and obtained the incidence rate ratios (IRR) with 95% confidence intervals (CI). The exposure was the RF predicted

CES-D-10 class for presence of depressive symptoms at each included CCC visit. We addressed possible exposure misclassification using a predictive value-based record-level correction method[27]. We applied the positive predictive value (PPV) and negative predictive value (NPV) estimated for the RF algorithm; PPV: 0.70 (95% CI: 0.63-0.76) and NPV: 0.69 (95% CI: 0.62-0.76). The two HSU outcomes were: 1. Self-reported number of inpatient visits (overnight hospital stays and emergency room visits) in the past 6 months and 2. Self-reported number of outpatient visits (general practitioner, HIV clinic, specialist, and walk-in clinic visits) in the past 6 months. ZINB models accounted for the over-dispersion and excess zeroes in these HSU outcomes (Figure 7.1). We used a clustered sandwich estimator for standard errors in order to account the intragroup correlation. We included an interaction term for those who achieved SVR. We adjusted for confounders including - baseline: age, gender, race/ethnicity, education level, immigration, and province, employment, monthly income, injection drug use, incarceration, fibrosis stage, HIV viral load and CD4 count; time-varying: HCV RNA status. We conducted multiple imputation by chained equations (MICE) to address the missing data in the confounders and created five imputed datasets [28,29].

Results

We included 1,153 CCC participants who were HCV RNA positive. Of the 530 participants who initiated treatment, 504 (95%) achieved SVR. The participants were predominantly male (70%) with a median baseline age of 45 years (interquartile range (IQR): 38-51); 29% were Indigenous, 66% were unemployed, 73% had no post-secondary education, and 38% were current injection drug users. Thus, the participants were vulnerable and

possibly could face numerous potential barriers to HCV treatment and mental health care[30]. At baseline, 61% had predicted CES-D-10 scores ≥10. The median number of inpatient visits in the past 6 months was 0 (interquartile range (IQR): 0-1) and for outpatient visits was 3 (IQR: 1-6) (see Figure 7.1).

The model results are shown in table 7.1. The models indicate that among those who had not achieved SVR, the number of inpatient visits were 17% higher in those with depressive symptoms compared to those without (IRR: 1.17; 95% CI: 1.06-1.29) and outpatient visits were 5% higher (IRR: 1.05; 95% CI: 1.02-1.08). In contrast, among those who achieved SVR, the models showed no difference in inpatient and outpatient visits with respect to predicted depressive symptoms. SVR was associated with a considerable reduction in inpatient visits with 24% fewer visits (IRR: 0.76; 95% CI: 0.70-0.84) compared to those without SVR; however, no effect of SVR was observed on the number of outpatient visits (IRR: 1.00; 95% CI: 0.97-1.02).

Discussion

Depressive symptoms were associated with a modest increase in HSU, indicating a greater burden on both individuals and the health systems. SVR was associated with a substantial reduction in inpatient visits, and SVR appeared to attenuate the effect of depressive symptoms on HSU.

Depressive symptoms have been associated with increased HSU in the co-infected population in previous studies. Similarly, SVR has been reported to reduce HSU among

people infected with HCV alone as well as those co-infected with HCV and HIV [31,32]. From our studies, it appears however that the overall improvement in health due to SVR may not only directly lead to lower healthcare use for serious HCV associated comorbidities, but also for depressive symptoms themselves (e.g., lowering of severity of depressive symptoms [33]). Thus, indirectly, a better state of general health/reduced hospitalisation after SVR may also help people experiencing depressive symptoms to manage their depressive symptoms without needing to access acute healthcare resources. This possible lowering of burden on health systems due to HCV cure could be indicative of major system-level economic benefits, beyond the patient level improved outcomes.

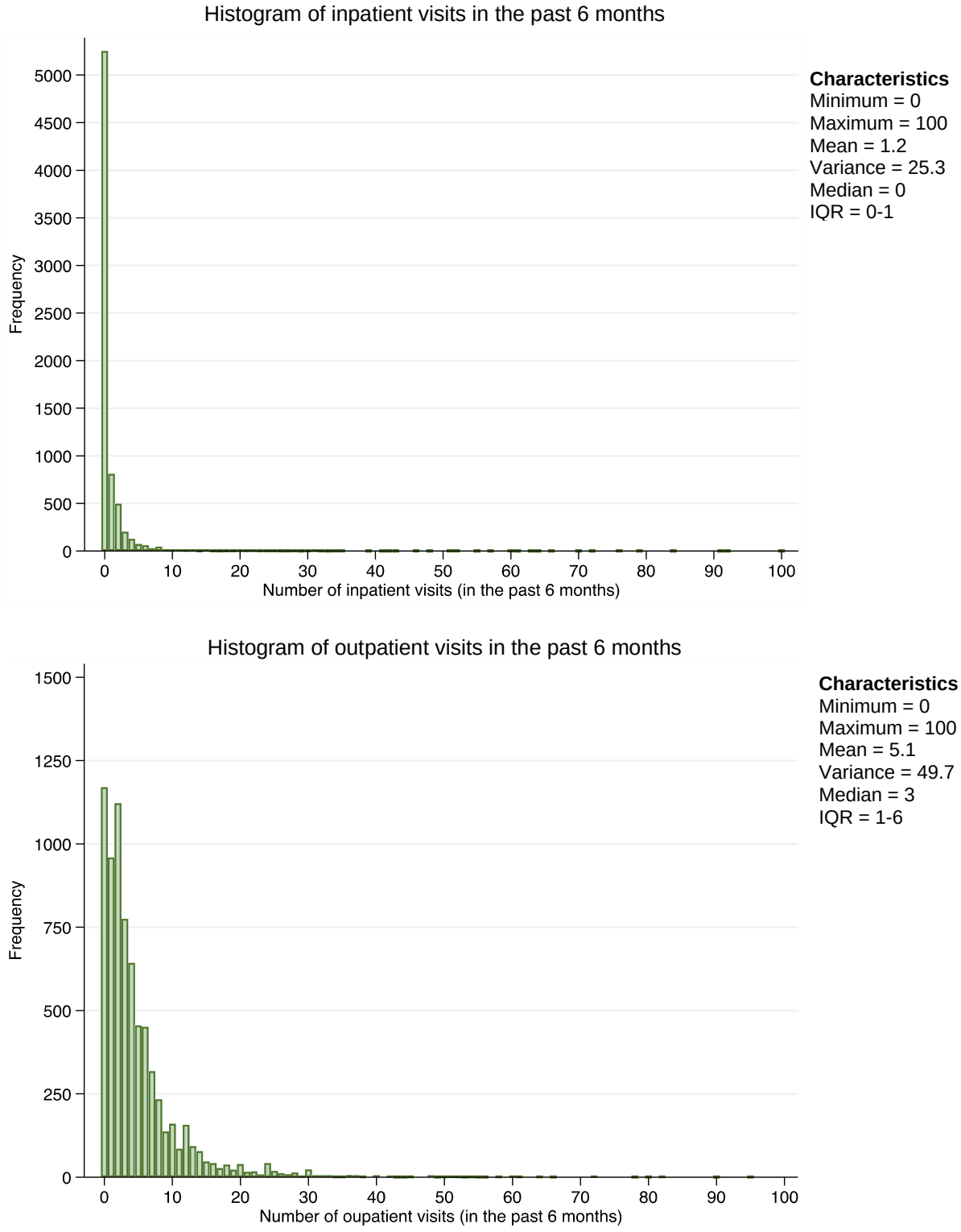
Our results are thus, consistent with these prior findings, but in addition provide evidence that there could be a modifying effect of SVR in the relationship between depressive symptoms and HSU. Interestingly, SVR reduced inpatient visits including hospitalizations, but not outpatient visits. One possible explanation in people with HIV-HCV co-infection could be continued engagement in care for HIV and for other co-morbid conditions that are not affected by HCV cure.

This study has several strengths. We used longitudinal data collected over the last 18 years in many diverse patients. Our estimates are generalizable to HIV-HCV co-infected patients engaged in care in Canada because the CCC recruits participants from primary and tertiary care clinics in urban and semi-urban areas across six provinces in Canada and includes 16% of the co-infected population in Canada. The study provides a real-world learning example of skewed distributions as seen in the HSU outcome, and

modeling methods that can be used in case of excess zeroes and overdispersion. The study, however, does have some limitations. The depressive symptoms were predicted via a random forest algorithm, and not measured directly in the cohort. Thus, misclassification was expected and therefore we corrected for potential misclassification in our analysis. We predicted the depressive symptoms based on a screening questionnaire, CES-D-10, and not a major depression diagnosis. Thus, this study does not provide an effect estimate for depression but rather for depressive symptoms that are indicative of a depression risk.

In conclusion, our study shows that depressive symptoms are associated with increased HSU and if treated for HCV this could be reduced, further supporting the benefits of universal treatment of HCV among people co-infected with HCV and HIV.

Figure 7.1: Distribution of number of self-reported inpatient and outpatient visits in the past 6 months recorded at each participant visit (n = 1,153)



Abbreviations: IQR: Interquartile range

Table 7.1: Effect of depressive symptoms and SVR on HSU in the HIV-HCV co-infected population; all IRRs are relative to those without depressive symptoms and without (or prior to) SVR

Outcomes	Depressive symptoms - Among those who had not achieved SVR		SVR		Depressive symptoms - Among those who achieved SVR	
	IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Inpatient visits	1.17	1.06-1.29	0.76	0.70-0.84	1.03	0.89-1.19
Outpatient visits	1.05	1.02-1.08	1.00	0.97-1.02	1.01	0.97-1.05

Abbreviations: SVR: Sustained virologic response; HSU**:** Health services utilization; IRR: Incidence rate ratio; CI: Confidence interval

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8. CHAPTER 8: DISCUSSION

8.1. Summary of findings

Depression is common in the HIV and HCV co-infected population and was a major side effect of the IFN-based HCV treatment regimen. Thus, treatment was relatively contraindicated in people with past or current psychiatric illness. With advent of the safer and more effective DAA regimens, HCV treatment is now more accessible. However, in spite of the overall increase in treatment uptake, there are still many patient- and system-level barriers. Depression is one such barrier which could have an effect on clinical and other outcomes in people living with HIV and HCV. Thus, in this dissertation, I investigated depressive symptoms in the HIV and HCV co-infected population in Canada.

In Manuscript 1, I aimed to predict presence of depressive symptoms indicative of being at risk for major depression in the CCC, since depression screening was only done in a subset of participants in the FS sub-study. I developed two random forest algorithms using predictor data from the CCC and the CES-D-10 screening tool data from the FS sub-study - one with all candidate predictors and the second with a reduced subset of predictors. Both algorithms had good accuracy. I found that the most important predictors were the health-related quality of life indicators, employment, HIV clinical stage, revenue source, BMI, and education. This is the first study which used machine learning algorithms for predicting presence of depressive symptoms in the HIV-HCV co-infected population. The reduced algorithm that used fewer than half of the predictors of the full algorithm still had acceptable accuracy. Thus, it could be useful in other studies without direct measures of depressive symptoms, after external validation to rule out overfitting.

I was able to use these algorithms to predict the CES-D-10 class at each CCC visit; this was then used as a measure of depressive symptoms in the next thesis objectives. I corrected for possible misclassification using a predictive value-based record level correction method, using the estimated positive and negative predictive values of the algorithm.

The aim of Manuscript 2 was to assess the effect of depressive symptoms on HCV treatment initiation in the IFN (2003-2011) and the second-generation DAA (2013-2020) eras. I observed an overall increase in HCV treatment initiation rates from the IFN to the DAA era and the percentage of eligible participants initiating HCV treatment increased from 21% to 50%. There was lower HCV treatment initiation among those with depressive symptoms compared to those without in the IFN era, but higher initiation among those with depressive symptoms in the DAA era.

In Manuscript 3, my goal was to evaluate the impact of SVR on presence of depressive symptoms over time. I observed that depressive symptoms changed very little over time in the lead up to DAA treatment and there was no evidence of immediate improvement at SVR. There was a gradual decline in depressive symptoms over time post-SVR among patients co-infected with HIV. The improvement after cure may reflect changes in biological pathways and/or improved general physical health.

Finally, Manuscript 4 aimed to assess the effect of depressive symptoms and SVR on HSU in the Canadian HIV-HCV co-infected population. I found that depressive symptoms

were associated with a modest increase in HSU, indicating that these symptoms contribute to poor health outcomes. SVR was associated with a substantial reduction in inpatient visits. Additionally, SVR appeared to attenuate the effect of depressive symptoms on HSU. This analysis provides a real-world learning example of modeling methods that can be used in case of excess zeroes and overdispersion to address the highly skewed distributions typical of HSU.

8.2. Strengths and limitations

The major strength of this thesis is that the CCC has high quality longitudinal data which is generalizable to the HIV-HCV co-infected population engaged in care in Canada. This is because the study recruits from a variety of clinical settings (outreach, primary, and tertiary care clinics in urban and semi-urban areas across the country) and includes approximately 16% of the HIV-HCV co-infected population in Canada. The CCC began in 2003 and thus I was able to leverage 19 years of longitudinal data and answer important questions with advanced analytical methods.

In Manuscript 1, I was able to use data from a sub-study within the CCC about food security to develop a prediction algorithm for depressive symptoms in the CCC, as the FS sub-study sample was generalizable to the parent CCC (see Table 4.7). I used the ensemble machine learning method of random forests, which is non-parametric, highly accurate, and relatively robust to outliers and noise. In addition, the predictor importance plots provided some insight regarding predictors that play a major role classification.

Random forests have safeguards against overfitting and thus improve chances of applicability beyond the data used to develop the classifier. Nevertheless, external validation is needed before application in other cohorts and research to mitigate the risk of overfitting.

However, there are also several limitations for Manuscript 1. I used the screening tool of CES-D-10 to assess the presence of depressive symptoms, which may be indicative of being at risk for major depression, as we did not have clinical diagnosis via a gold standard interview such as the SCID-5. Thus, I cannot make any of the conclusions in this thesis for depression, but for the specific construct of depressive symptoms that is measured by the CES-D-10 scale, as described in the section 2.7 of chapter 2. Further, I categorized the CES-D-10 to create the binary classes, and thus may have lost some information by not predicting the unit CES-D-10 scores and the validity of the cut-off of 10 could not be assessed directly in this sample, although this threshold has been assessed in HIV populations in Canada in a previous study (99). In fact, I did develop a regression algorithms to predict the continuous CES-D-10 scores in additional analysis E, but with a R-squared between 0.3-0.5, these algorithms could only explain a small portion of the variability in the outcome and were not able to predict the CES-D-10 score at a unit level with high accuracy. The sample size in this study was small for prediction models. Finally, some predictors described in other studies such as childhood trauma and food insecurity among others, were not available for the full CCC.

In the next thesis manuscripts, the clinically relevant depressive symptoms were predicted using the full random forest algorithm from Manuscript 1, and not measured directly in the cohort. Thus, misclassification was expected and therefore I needed to correct for potential misclassification in all three manuscripts, for which I used a record-level correction method using positive and negative predictive values of the algorithm.

The major strength of Manuscript 2 was that I applied robust methods to account for time-dependent confounding, competing risks and conducted multiple secondary analyses. Manuscript 4 provides a real-world example of methods taking into consideration the skewness of the data. A limitation of both Manuscripts 2 and 4 is that they do not provide an effect estimate for major depression but rather for these (predicted) clinically relevant depressive symptoms and further research with clinical diagnosis of depression using a structured interview like SCID-5, which is the gold standard for major depression diagnosis, is crucial.

In Manuscript 3, using the quasi-experimental analytic design of ITS, I was able to obtain robust marginal effect estimates of the impact of SVR on depressive symptoms in the co-infected population. I conducted multiple sensitivity analyses to account for possible issues such as lead time bias and non-linearity and adjusted for time-varying confounders in the model. However, the crucial assumption of the ITS design that the extrapolated pre-exposure trend is considered the counterfactual trend, makes it vulnerable to unmeasured time-varying confounding. With no available appropriate comparison group, I tackled this issue by adding known time-varying

confounders to the model; however, some residual confounding could still be possible. Another limitation to consider is that the median post-SVR follow-up time was 1.7 years, so the durability of the observed effect still needs to be explored with additional data.

8.3. Implications and future directions

I investigated several different questions in this thesis which are important in strengthening the available literature base regarding depressive symptoms in this highly vulnerable population of HIV-HCV co-infected individuals. First, I found that it is possible to use machine learning algorithms like the ones I developed in this thesis to accurately predict depressive symptom classes based on screening tools like the CES-D-10. Depression being a common neuropsychiatric disorder in the co-infected population, it is important to understand its impact overall as well as on specific outcomes. I used predictors, especially in the reduced algorithm, which may be routinely collected in longitudinal or cross-sectional studies in this population. Thus, this provides a basis for use of such algorithms in research studies that may not have previously screened for depression, but have rich demographic, behavioural, and clinical data. These studies can retrospectively predict presence of depressive symptoms and explore their impact in this study population in different settings. In terms of future directions, it is important to externally validate the algorithms in other datasets which have the same measured predictors, in order to rule out overfitting and assess generalizability.

As described in the introduction, depression has been part of the discussion in this population not only due to its high prevalence but also as a side effect of the IFN-based HCV treatments. The overall increase in treatment uptake was observed from the IFN to the DAA era. This is a step in the right direction, however further improvement is essential to improve treatment uptake and reach the elimination goals set by the Canadian blueprint for HCV elimination and WHO (2, 29). I found that depression may no longer be a barrier to HCV treatment initiation in the second generation DAA era in Canada in the HCV-HIV co-infected population. This study is the first to quantify this effect of depressive symptoms on HCV treatment initiation in the co-infected population and also show the difference between the DAA era and IFN era. It was observed that people with depressive symptoms were initiating treatment more than those without in the DAA era. As described earlier, one of the explanations for this improvement in treatment initiation among people with depressive symptoms could be that patients for whom IFN-based treatments were contraindicated, or were not tolerated, are now accessing treatment, i.e., a warehousing effect.

The warehousing effect has been described in the HCV literature as one where the near-term prospect of availability of DAAs with better cure rates and improved side-effects led to deferring treatment at a later date when DAAs became widely available (121). Thus, individuals with past or current psychiatric illness, as well as those harder to treat or more susceptible to side effects with IFN like those with cirrhosis and hepatocellular carcinoma, were deferred treatment. Thus, this warehousing effect is likely to have played a role in this observed increase in

treatment initiation among those with depressive symptoms following the availability of DAA. In an attempt to further understand if this effect could persist or plateau over time, in a crude analysis, we looked at treatment initiations among those with baseline depressive symptoms comparing early and the later years of the second-generation DAA era in the CCC. We observed that 65% of the people with baseline depressive symptoms initiated DAAs between 2015-2017 and comparatively lower number of people (31%) initiated between 2018-2020, which provides some evidence for possible plateauing over time. However, overall treatment rates have also been reported to have fallen once those waiting for treatment were cured (122). Hence, further analysis with extended follow-up is important to assess the durability of the observed effect using methodology for incorporating a time-varying exposure definition for depressive symptoms.

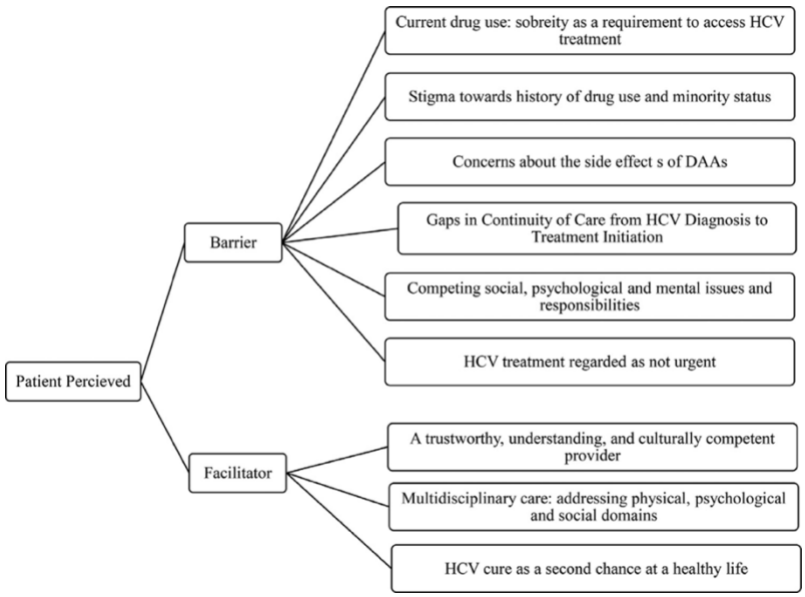

Figure 8.1: Patient perceived barriers and facilitators to DAA treatment uptake

Reproduced from Int J Drug Policy 96, Amoako A. et.al. Patient and provider perceived barriers and facilitators to direct acting antiviral hepatitis C treatment among priority populations in high income countries: A knowledge synthesis, 103247 (2021)

Depression and other mental health issues are still widely described as patient-level barriers to linkage to care in this population. There can be many reasons for this, including lack of diagnosis and treatment and that real-world health systems are unable to deal with multiple co-morbid conditions. A recent qualitative study by Amoako et.al., which included published and grey literature (post-2014), examined patient perceived barriers and facilitators of DAA treatment uptake in key priority populations including PWID, gbMSM, and Indigenous people (123). The various barriers and facilitators found are shown in figure 8.1. The patient level barriers still included competing social, psychological, and mental health issues. They discussed the literature showing that high toxicity and side-effects of IFN-based therapy still casts a shadow leading some patients as well as providers to fear initiating treatment in the presence of competing health issues. In an article by Ortiz-Paredes et. al., they conducted focus groups to determine barriers and facilitators for DAA uptake in the HIV co-infected population in Canada and found that multidisciplinary care fostering a strong supportive network and intrinsically motivated patients along with HCV education emerged as key facilitators (124).

There is growing discussion in the HIV and HCV literature about syndemics, which is defined as a “population-level clustering of social and health problems”, i.e., health conditions, and social, behavioral and structural determinants interact synergistically, leading to excess burden of disease in the affected population (125). Syndemics were described by Tsai et. al. (2017) as “a multi-level phenomena with three underlying concepts, disease concentration, disease interaction, and large-scale social forces” (126). The consideration of syndemics in relation to HIV and HCV include mental health

and substance use; efforts need to be taken in terms of integration of care in order to deal with the individual as well as joint effects of these conditions (127-129). Thus, despite evidence from my analysis in Manuscript 2 of depressive symptoms no longer being a barrier to treatment initiation quantitatively, depression could still have an impact overall on linkage to care post-cure and on other health outcomes. Screening, and possible treatment after clinical diagnosis are therefore essential for improving treatment uptake and linkage to care. This might be achieved by integration of mental health education, screening, and treatment as a part of routine care for HIV-HCV co-infected people.

In the next manuscripts, I found that SVR seems to have a direct effect on depressive symptoms over time leading to a gradual decline and that depressive symptoms lead to an increase in HSU, but this is reduced among those who had achieved SVR. Thus, SVR or HCV cure are shown here to have led to improvement in patient outcomes beyond liver outcomes and mortality. This provides further rationale for increasing treatment access and supporting adherence to treatment in all people chronically infected with HCV. Further research will be essential using longitudinal data over a longer follow-up post-SVR to assess the durability of these effects. Additionally, outcomes such as liver disease, mental health issues including depression and overall HSU add tremendous economic burden on both individuals and health systems (115, 130-133). DAAs are infamously known for their access-limiting high costs (134), although prices have steadily declined. Many studies have, however, shown DAAs to be cost-effective and sometimes cost saving in a number of settings and populations with different co-morbid conditions (135-137). As this thesis provides further evidence of advantages of DAA beyond

improved liver disease outcomes, we need to consider possible lowering of mental illness and other HSU-related costs in future work assessing the cost-effectiveness of treating all chronically infected persons with DAA regimens.

8.4. Conclusions

With the advent of the DAA regimens, the HCV landscape changed dramatically with possible elimination on the horizon. Depression was a major side effect and barrier to HCV treatment in the IFN era, so my aim was to understand the current role of depressive symptoms in the co-infected population in this DAA era. I observed that, first, depressive symptoms are no longer a barrier to HCV treatment initiation in the DAA era and second, the health benefits of curing HCV extend beyond improving liver disease, to improving mental health symptoms and reducing health service use which provides further rationale for treating HCV in all chronically infected persons.

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