IMPACT OF PUBLIC PRESCRIPTION DRUG COVERAGE ON NEWER HEPATITIS C MEDICINES IN BRITISH COLUMBIA

by

HARRIET HO

Bachelor of Commerce (Honours), The University of British Columbia, 2015

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

The Faculty of Graduate Studies and Postdoctoral Studies

(Population and Public Health)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

November 2017

Abstract

Background

Sofosbuvir and ledipasvir-sofosbuvir are breakthrough direct-acting antiviral agents (DAAs) for the treatment of hepatitis C virus (HCV) infection. These drugs were very expensive at initial listing with a price of around $60,000 CAD. However, the cure rates and side effect profiles showed drastic improvements compared to interferon-based treatments. Given limited real-world data on adherence to DAAs, this study examined adherence to sofosbuvir and ledipasvir-sofosbuvir, and identified factors associated with adherence. It also examined the impact of public prescription drug coverage (PharmaCare) on adherence, treatment uptake, and expenditure.

Methods

This study used data from the British Columbia Hepatitis Testers Cohort. Adherence was measured as proportion of days covered (PDC), calculated from prescription drug data. I used multivariable logistic regression to examine the impact of various factors on full adherence (PDC=100%). I also used interrupted time series analysis to examine the impact of PharmaCare coverage on adherence, treatment uptake, and public and private expenditure over time.

Results

Of 3,730 treatments initiated, 2,760 were eligible for analysis; 786 were treated with sofosbuvir, 1,974 were treated with ledipasvir-sofosbuvir, and 14 were treated with both. Mean PDC across both drugs, sofosbuvir, and ledipasvir-sofosbuvir were 96.17%, 95.35%, and 96.50% respectively. In the multivariable logistic regression model, several factors were statistically significant. Major mental illness, longer treatment durations, moderate socioeconomic status, and being of white ethnicity were all associated with lower proportions of individuals with full adherence. Having PharmaCare coverage and being over the age of 60 were associated with higher proportions of individuals with full adherence. In the interrupted time series analysis, the availability of PharmaCare coverage for sofosbuvir and ledipasvir-sofosbuvir did not impact trends in adherence, but did increase treatment uptake of both drugs. Furthermore, public expenditure increased after the policy change, crowding out some of the private expenditure.

Conclusion

Given the high cost of these drugs, the high adherence rates found are encouraging. Strategies to target those with major mental illness and longer treatment durations should be explored. Payers should also be prepared for increased treatment uptake and public expenditures following the availability of public coverage.

Lay Summary

Sofosbuvir and ledipasvir-sofosbuvir are newer medicines for the treatment of hepatitis C virus (HCV) infection. Although they are very expensive, cure rates and side effect profiles show drastic improvements compared to older treatments. Ensuring high adherence, meaning how closely a patient takes medication following their physicians' instructions, is one way to maximize value for money. This study examined adherence to sofosbuvir and ledipasvir-sofosbuvir, and identified factors associated with adherence. It also examined the impact of public prescription drug coverage (PharmaCare) on adherence, treatment uptake, and expenditure. Given the high cost of these drugs, the high adherence rates found in this study are encouraging. Strategies to target those with major mental illness and longer treatment durations should be explored. Payers should also be prepared for increased treatment uptake and public expenditures following the availability of public coverage.

Preface

The work contained in this thesis was conducted by Harriet Ho, under the supervision of Dr. Michael Law, with assistance from members of the thesis committee (Drs. Mark Harrison, Naveed Janjua, and Kimberlyn McGrail). The data used in this study came from the British Columbia Hepatitis Testers Cohort (BC-HTC) at the British Columbia Centre for Disease Control, led by Dr. Naveed Janjua. Members of the BC-HTC team offered insights and helped in the preparation of data for this study.

This study was part of a larger project that was granted ethics approval by the University of British Columbia Research Ethics Board: 2011-8100 ("Assessment of the Burden of Hepatitis C to Support Appropriate Prevention, Care and Treatment Using a Comprehensive Dataset of HCV and HIV Testers in British Columbia").

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ANOVA   Analysis of variance

BC   British Columbia

BCCDC   British Columbia Centre for Disease Control

BC-HTC   British Columbia Hepatitis Testers Cohort

BC-PHMRL   BC Public Health Microbiology and Reference Laboratory

BOC   Boceprevir

CADTH   Canadian Agency for Drugs and Technology in Health

CHSPR   Centre for Health Services and Policy Research

CI   Confidence interval

DAA   Direct-acting antiviral

DAD   Discharge abstract database

DIN/PIN   Drug identification number/product identification number

HBV   Hepatitis B virus

HCC   Hepatocellular carcinoma

HCV   Hepatitis C virus

HIV/AIDS   Human immunodeficiency virus/acquired immunodeficiency syndrome

ICD   International Statistical Classification of Diseases and Related Health Problems

IDU   Injection drug use

ITS   Interrupted time series analysis

LED/SOF   Ledipasvir-sofosbuvir

MEMS	Medication event monitoring system
MoH	Ministry of Health
MPR	Medication possession ratio
MSP	Medical services plan
OR	Odds ratio
OST	Opioid substitution therapy
PegIFN	Pegylated interferon
pCPA	Pan-Canadian Pharmaceutical Alliance
PDC	Proportion of days covered
PHN	Personal health number
PWID	People who inject drugs
RBV	Ribavirin
RNA	Ribonucleic acid
SIM	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virologic response
US	United States

Acknowledgements

First, I would like to thank my graduate supervisor, Dr. Michael Law, for his guidance and mentorship throughout my studies, and support for my personal and professional growth. I am truly grateful that he saw potential in my abilities, and helped inspire my interest in health policy.

Thank you to Dr. Naveed Janjua for providing me with the opportunity to work with the BC-HTC team. Without his expertise and the resources at the BCCDC, this study would not have been possible. In addition, I am grateful for all the support I have received from the BC-HTC team.

I would also like to thank Drs. Mark Harrison and Kimberlyn McGrail for their helpful insights, feedback, and encouragement throughout this process.

Thank you to all the wonderful people who have supported me throughout this journey. First, I would like to thank my family for their support and patience. Second, I would like to thank all the faculty, staff, and students I have met at the School of Population and Public Health who have enriched my learning experience.

1   Introduction

1.1   Background

1.1.1   Specialty pharmaceuticals: sofosbuvir and ledipasvir-sofosbuvir

Specialty pharmaceuticals are a designation of drugs that are considered high-cost.[1] Spending on specialty pharmaceuticals is expected to grow in the coming years and is projected to constitute 50 percent of health plans' overall drug spending by 2019, making them a major issue for both public and private payers.[2] Sofosbuvir (Sovaldi) and ledipasvir-sofosbuvir (Harvoni) are two newer direct-acting antiviral (DAA) agents that treat hepatitis C (HCV) and are considered specialty pharmaceuticals. The high costs of these two therapies have been very controversial, with a once-a day, eight- to 24-week course of treatment costing, on average, $60,000 per patient.[3]

Because this is a heavily debated topic, I aimed to provide real-world evidence on adherence, treatment uptake and expenditure to contribute to this discussion. In this thesis, I examined medication adherence to these drugs, the relationship between patient factors and adherence, and the impact of public prescription drug coverage on treatment uptake, adherence rates, and expenditures. The recent development of sofosbuvir and ledipasvir-sofosbuvir provides a unique opportunity to evaluate real-world adherence and shape future decisions on public coverage of specialty pharmaceuticals.

1.1.2   Hepatitis C

Hepatitis C (HCV) is a blood-borne disease that affects the liver.[4] The total health care cost of HCV in Canada was estimated at $161.4 million in 2013 and is projected to increase to $258.4 million in 2032, with the cost increase driven by cirrhosis and advanced liver disease.[5] There are approximately 50,000 people diagnosed with HCV in British Columbia (BC),[6] and BC's rate of new HCV cases identified per year is approximately 50% higher than the Canadian rate,[7] with 2,208 new cases identified in BC in 2015.[7] Individuals at high risk for HCV include people who inject drugs (PWIDs), those who received blood transfusions or blood products before 1992, and organ transplants recipients in Canada before 1990.[8] In BC, approximately 35% of HCV cases are PWIDs.[9]

While 25% of those with acute HCV infection clear the virus naturally, the remainder live with chronic HCV infection.[10] If left untreated, chronic HCV can lead to fibrosis, cirrhosis, and end-stage liver disease (with a natural history of decompensated cirrhosis, hepatocellular carcinoma (HCC)) when liver transplant may be needed.[11] Among those with chronic HCV, approximately 10-20% develop cirrhosis over the course of 20-30 years.[11] Those with cirrhosis have a 1-5% annual risk of HCC and 3-6% annual risk of decompensation.[11] After an episode of decompensation, individuals have a 15-20% risk of death in the next year.[11] Thus, treatment of HCV infection is needed to prevent complications related to liver disease.

HCV has several genotypes, and each genotype has variations in treatment regimen and effectiveness in regards to DAA used, duration, cure rate, and need to combine DAAs with interferon and ribavirin.[12] In BC, 61.4% of individuals with HCV had genotype 1, 12.6% had genotype 2, 24.3% had genotype 3, 1.1% had genotypes 4, 5 or 6, and 0.6% had mixed genotypes.[13]

1.1.3   Comparison of old and new therapies
Older therapies

Previously, treatments for HCV involved pegylated interferon, which resulted in severe side effects for many patients. Approximately 75% of patients who were treated with interferon reported one or more side effects, including depression, headaches, and visual disturbances.[14] As shown in Tables 1, 2 and 3, older treatments had durations of 12 to 24 weeks, with cure rates ranging from 52% to 84%. In these older treatments, patients who were former PWIDs or were on methadone substitution were more likely to discontinue treatment in the first three months.[15] Furthermore, former PWIDs had a greater risk of developing side effects of depressive symptoms, and thus side effect management was recommended in order to improve adherence.[15,16]

Newer therapies

Recent advances in pharmacotherapy have allowed for interferon-free direct acting antiviral (DAA) treatments for HCV that are more effective, often require a shorter treatment duration, and have a much better side effect profile. Health Canada first approved sofosbuvir in December

2

2013,[17] and ledipasvir-sofosbuvir in October 2014.[18] Each drug is taken as a once-a-day single tablet over the course of eight to 24 weeks depending on virus genotype.[19] Early data on cure rates suggested ledipasvir-sofosbuvir is on the order of 90% or higher, as shown in clinical trials and observational studies.[20] There was greater discrepancy in cure rates for sofosbuvir: over 80% in clinical trials,[21] and between 66-79% in the real-world on an intention-to-treat basis.[22] The most common adverse effects were fatigue and headache for both sofosbuvir[23] and ledipasvir-sofosbuvir.[24] In summary, DAAs have revolutionized the treatment of HCV compared to interferon-based treatments in terms of efficacy, tolerability and duration, making widespread treatment of HCV a reality.

Tables 1.1, 1.2, and 1.3 compare the old (contains pegylated interferon and ribavirin) and new (sofosbuvir-based) therapies that are covered under PharmaCare (discussed in section 1.1.4). To be eligible for all of these treatments, patients must have chronic HCV with liver fibrosis stage F2, an early stage of liver scarring, or greater.[25–29] Re-treatment requests are not permitted.[25–29] Since PharmaCare does not cover sofosbuvir and ledipasvir-sofosbuvir for genotypes 4, 5, and 6, they are not listed below. Boceprevir and simeprevir are older generation DAAs.

Sustained virologic response (SVR), measured 12 weeks after the end of treatment, is a validated clinical endpoint to demonstrate that HCV RNA is undetectable and treatment was successful in curing HCV.[30] As shown in Tables 1.1, 1.2, and 1.3, the new treatments tend to have higher SVR rates. In other words, they are more effective, better tolerated, and show effects faster, all of which are likely to improve adherence.

Table 1.1   Old and new HCV treatments for genotype 1

Genotype 1	New[25,26]	SVR%[21]	Old[28,29]	SVR%
Treatment naïve w/o cirrhosis	8 - 12 weeks LED/SOF	94-95	24 weeks BOC + PegIFN/RBV and 20 weeks only PegIFN/RBV	67[31]
	12 weeks SOF + PegIFN/RBV	92	12 weeks SIM + PegIFN/RBV and 12-36 weeks only PegIFN/RBV	84[21]
Treatment naïve w/ cirrhosis	12 weeks LED/SOF	94-100	44 weeks BOC + PegIFN/RBV	52[a 31]
	12 weeks SOF + PegIFN/RBV	80	12 weeks SIM + PegIFN/RBV and 12-36 weeks only PegIFN/RBV	60[21]
Treatment experienced w/o cirrhosis	12 weeks LED/SOF	94	32 weeks BOC + PegIFN/RBV and 12 weeks only PegIFN/RBV	64[32]
			12 weeks SIM + PegIFN/RBV and 12-36 weeks only PegIFN/RBV	79[21]
Treatment experienced w/ cirrhosis	24 weeks LED/SOF	100	44 weeks BOC + PegIFN/RBV	77[32]
			12 weeks SIM + PegIFN/RBV and 12-36 weeks only PegIFN/RBV	74[21]

[a] Fibrosis F4 or cirrhosis

Table 1.2   Old and new HCV treatments for genotype 2

Genotype 2	New[25]	SVR%[21]	Old[21,27]	SVR%[21]
Treatment naïve	12 weeks SOF + RBV (with contraindication to IFN)	97	24 weeks PegIFN/RBV	78
Treatment experienced (PegIFN/RBV)	12 weeks SOF + RBV	86-90	unavailable	-

Table 1.3   Old and new HCV treatments for genotype 3

Genotype 3	New[25]	SVR%[21]	Old[21,27]	SVR%[21]
Treatment naïve	24 weeks SOF + RBV (with contraindication to IFN)	94	24 weeks PegIFN/RBV	63
Treatment experienced (PegIFN/RBV)	24 weeks SOF + RBV	87	unavailable	-

1.1.4 PharmaCare coverage

Through the Common Drug Review process, the Canadian Association for Drugs and Technologies in Health (CADTH) provides reimbursement recommendations on drugs approved in Canada to federal, provincial, and territorial public drug plans, except Quebec.[33] CADTH recommended that sofosbuvir be reimbursed for patients with genotypes 2 and 3 who have compensated liver disease, and patients with genotype 4 who have not been previously treated and do not have cirrhosis.[34] CADTH recommended that ledipasvir-sofosbuvir be reimbursed for patients with genotype 1 if the drug is initiated with a physician who is experienced in treating chronic HCV and the cost of treatment does not exceed that of other interferon-free HCV treatments.[35]

PharmaCare is the public insurance plan for BC residents that partially or completely reimburses the costs of eligible prescription drugs and certain medical supplies and pharmacy services.[36] Coverage is available under many plans, including the standard high deductible plan (Plan I), a plan for individuals receiving social assistance (Plan C), and other specific plans.[36] Under Plan I, households generally have to pay out-of-pocket until they spend a household-level deductible between 3% and 4% of household income.[37] Under PharmaCare, the Limited Coverage Drug (LCD) program covers drugs that are not the first therapy that will be given to patients, or have more cost-effective options available.[38] Patients must meet certain criteria and have their physicians submit Special Authority requests in order to be approved for coverage.[38] The patient's coverage depends on the details of their PharmaCare plan and they will need to pay any necessary deductibles.[38]

PharmaCare began coverage for sofosbuvir and ledipasvir-sofosbuvir in March 2015[39] for individuals with HCV with fibrosis at stage F2 or higher.[3] Fibrosis, which is liver scarring as a result of HCV disease progression, ranges on a scale from F0 (no fibrosis) to F4 (cirrhosis), with F2 meaning moderate fibrosis.[40] This first phase covered approximately 3,800 individuals from March 2015 to December 2016.[41] BC's eligibility criteria of fibrosis stage F2 or greater in its initial coverage of sofosbuvir and ledipasvir-sofosbuvir was consistent to the policies in most of the other provinces.[3] In February 2017, after the deal between the pan-Canadian Pharmaceutical Alliance (pCPA) and drug manufacturers was reached on HCV drugs, both BC and Ontario

committed to expanding coverage to all patients with HCV, regardless of disease severity.[41,42] This expanded program will cover six HCV drugs, including sofosbuvir and ledipasvir-sofosbuvir.[41] With the expansion, BC was one of the first provinces to adopt less stringent eligibility criteria in Canada.

The first phase of this expansion began on March 2017; individuals who have a fibrosis score lower than F2 are now eligible for treatment if they also meet certain criteria, such as co-infection with human immunodeficiency virus (HIV) or hepatitis B, post-organ transplant, or women who are intending to become pregnant in the next 12 months.[43] The Ministry of Health has not announced its plans for further expansion leading up to the fully expanded program in 2018-19. Prior to public coverage, patients could only access sofosbuvir and ledipasvir-sofosbuvir through out-of-pocket payment or through private insurance coverage.

New HCV treatments drove almost two thirds of the growth in drug spending in Canada in 2015.[44] The list price of HCV treatment is between $45,000 to over $100,000 for a course of treatment, as published in an announcement by the BC Ministry of Health.[41] These prices, however, do not account for rebates paid by the manufacturer that have been negotiated between the provinces and drug manufacturers, as they are confidential.[41] Based on the Ministry's numbers of an average list price of $72,500 with a population of 50,000 British Columbians with HCV,[6] funding HCV treatment for all HCV patients would cost around $3.6 billion at list price. Even if the negotiated price were half of list price, the program would still cost the province around $1.8 billion. If these drugs were all delivered in the same year at this cost, this would comprise almost half of the $3.8 billion (2016) spent annually on public drugs in BC.[45] This raises challenges in resource allocation in the public healthcare system.

1.1.5 Medication adherence

Medication adherence is defined as the degree to which patients take their medications as their health care providers prescribed,[46] and is crucial to the effectiveness of treatment, especially for DAAs, to obtain maximum response to treatment, avoid treatment failure and prevent resistance to DAAs.[47] With the high cost of sofosbuvir and ledipasvir-sofosbuvir, ensuring that treatment achieves the best outcomes through high adherence is one way to maximize value for money. To

date, there has been very little study of patient adherence to new DAAs outside of clinical trials.[48–51]

1.2   Research Objectives

My thesis aimed to examine adherence with new DAAs in the real world. There is currently a lack of real-world evidence on adherence rates of DAAs, and adherence rates for specific groups, such as PWIDs.

1.2.1   Overall adherence to newer DAAs

As with other drugs an optimal level of adherence is essential to achieve treatment success. Treatment success for HCV is defined by achieving SVR, meaning virus levels are undetectable in blood 12 weeks following end of treatment. Given that adherence is important for achieving high SVR by DAAs, this study will provide evidence on real-world effectiveness. In addition, with the high cost of DAAs, ensuring high adherence is crucial for cost-effectiveness of the therapies. Thus, in the first objective of this thesis, I will examine the following research question:

(1) What is overall adherence with new direct acting antiviral agents?

1.2.2   Relationship between patient factors and adherence to newer DAAs

Since PWIDs comprise a large proportion of HCV cases, concerns have been raised about their likelihood to adhere with therapy.[52] Healthcare providers were less likely to discuss treatment options with PWIDs,[53] and were often unwilling to treat them.[54] In a recent phase 2 trial by Petersen et al., it was found that medication adherence to sofosbuvir and ledipasvir-sofosbuvir was high among inner city patients, but drug use was a risk factor for non-adherence in longer treatment durations.[47] This study took place as part of a clinical trial and may have limited generalizability, as typically, adherence rates are much higher in clinical trials,[46] and trials have more intense patient engagement and follow-up. Current approaches suggest that effective management of hepatitis C in PWIDs with DAAs requires additional attention and care, such as multidisciplinary clinics, peer support and case management.[55]

I will then examine PWID status as well as other variables to see if they impact adherence rates. These other variables of interest include comorbidities, disease severity (cirrhosis), mental illness, opioid substitution therapy, and socioeconomic status. My second research question is:

    (2)   What factors are associated with low adherence?

1.2.3 Impact of PharmaCare coverage on adherence, treatment uptake, and private expenditures

There is mixed evidence on whether public or private drug plans encourage better adherence rates, as seen in analyses of other prescription drugs, and the effect seemed to vary based on the nature of the plans.[56–58] One study found that public plans were associated with higher adherence as they often required lower deductibles and co-payments, while private plans were associated with lower adherence as they often required payment of the full cost of the drug at the pharmacy with delayed reimbursement.[56] Another study found the opposite: private plans were associated with higher adherence as they tended to have lower deductibles and co-payments.[57] A further study found no difference in adherence between publicly and privately insured groups.[58] However, these studies were performed in Quebec, which has a substantially different public drug plan design from BC.[59] In Quebec, those who are unable to obtain private drug insurance must enrol in a public drug plan.[59] Moreover, the costs of these previously studied drugs are much lower than those of sofosbuvir and ledipasvir-sofosbuvir. Further evidence from this proposed study is required to validate this in BC with higher cost drugs and plan characteristics specific to PharmaCare.

Cost can be a barrier to adherence. Depending on income, many patients in BC under PharmaCare would still need to pay income-based deductibles.[37] Cost-related nonadherence for prescription drugs in general is higher in BC compared to the rest of Canada.[60] Patients without prescription drug insurance also report greater nonadherence;[60] thus, patients who purchased sofosbuvir and ledipasvir-sofosbuvir before March 2015 without any coverage may have lower adherence rates. The third research question examines the impact of PharmaCare coverage on adherence:

    (3)   What impact did the start of PharmaCare coverage have on adherence to sofosbuvir and ledipasvir-sofosbuvir, treatment uptake, and public and private expenditure?

1.3 Thesis Outline

This thesis is structured in four chapters. This first chapter describes sofosbuvir and ledipasvir-sofosbuvir, medication adherence, and PharmaCare coverage and provides an outline of this thesis. The second chapter explores the first and second objectives, examining overall adherence rates and the relationship between patient factors and adherence. The third chapter addresses the third objective, studying the impact of PharmaCare coverage on adherence, treatment uptake, and public and private expenditure. The fourth and final chapter summarizes the findings from this thesis, and further discusses the implications of the results.

1.4 Disclaimer Statement

All inferences, opinions, and conclusions drawn in this thesis are those of the author, and do not reflect the opinions or policies of the Ministry of Health Data Stewards.

2 Adherence to sofosbuvir and ledipasvir-sofosbuvir in British Columbia

2.1 Introduction

As discussed in Chapter 1, adherence can play a key role in clinical effectiveness. Chapter 2 will examine adherence rates of sofosbuvir and ledipasvir-sofosbuvir in British Columbia, and the relationship between patient factors and adherence.

Medication adherence is crucial to achieving SVR and treatment success, and avoiding DAA resistance in patients.[47] Not only would adherence ensure the cost is not wasted on sofosbuvir and ledipasvir-sofosbuvir, high adherence has been linked to lower hospitalization risk and lower health care costs in the future.[61] Adherence could be improved by using treatments that have shorter durations, lower pill burdens, fewer adverse effects,[62] as seen in sofosbuvir and ledipasvir-sofosbuvir, and lower out-of-pocket costs.[63,64]

One phase 2a clinical trial found high adherence to DAAs (specifically ledipasvir-sofosbuvir) in an inner-city population.[47] They measured adherence using medication event monitoring system (MEMS) caps, pill counts, and patient reports, with adherence defined by whether the drug was taken within two hours of the expected time. Adherence was higher when the pill burden was one pill per day rather than three, and higher in the first four weeks of treatment versus the last four weeks of treatment.[47] This suggests that a shorter course of treatment with lower pill burden may improve adherence.

2.1.1 Measures of adherence

Since it is not always possible to directly observe adherence to medication, as in this study, adherence can be calculated indirectly from administrative data, which aims to reflect real-world behaviour. Prescription drug dispensation data provide information such as dispensation date, quantity of medication dispensed, and days supply, which can be used in adherence calculations. There are several common methods to calculate medication adherence from administrative data in the literature. Each method may yield slightly different results:

Proportion of days covered (PDC)[65] – PDC measures the percentage of days that medication is available and is capped at 100%. The total number of days evaluated can either be the treatment duration or a defined study period (e.g. 30 days, 90 days) for a chronic disease treatment.

$$PDC = (total\ days\ supply/total\ number\ of\ days\ evaluated) \times 100\%$$

Medication possession ratio (MPR)[66] – MPR calculates the sum of all quantities dispensed divided by the number of days in the study period, which, can either be the treatment duration or a defined period (e.g. 30 days, 90 days) for a chronic disease treatment.

Gaps[66] – Gaps measure the number of days between the end of supply for one fill and the start of the next fill. If an individual had multiple fills, one can find the mean or median gaps across these fills.

Persistence[66] – Persistence indicates whether the length of an individuals' treatment meets or exceed a certain threshold. For example, if the threshold were 90 days, a length of 91 days would be persistent, while a length of 89 days would not.

Length[66] – Length is the number of days between the start of the first fill and the end of the supply after the last fill.

2.1.2   Adherence studies to date

Currently, the literature on adherence to DAAs is still limited. To date, studies have shown that adherence to DAAs appears to be higher than adherence to interferon-containing therapies. However, few studies have used administrative data to assess adherence to sofosbuvir and ledipasvir-sofosbuvir in larger populations.

In an analysis of phase 3 clinical trial data, Younossi et al. found that the average among the lowest adherence rate across all drugs used by each patient was 77.6% for treatments containing interferon and ribavirin (n = 657), 91.3% for treatments containing ribavirin (n = 2,528), and 97.5% for interferon-free and ribavirin-free treatments (n = 1,493).[67] Sofosbuvir and ledipasvir-sofosbuvir were used with some of the treatments. In this study, all pills dispensed and returned were recorded. Then, adherence was calculated by dividing the number of pills used by the number expected to be taken. In another study for interferon-containing therapies, Lo Re et al. examined adherence using a MPR. Median adherence for pegylated interferon treatment was

104% and for ribavirin was 103% (n = 188).[68] A systematic review by Lieveld et al. found that mean adherence for interferon-containing treatments ranged from 74 to 100%, and adherence over or equal to 80% ranged from 27 to 96%.[69] In summary, adherence rates in interferon-containing therapies was high, spanning above 70% to over 100% across different methods of measuring adherence.

Adherence rates to DAAs were all above 90% in clinical trials.[47,67,70] However, it has been widely noted that adherence in clinical trials often exceeds that experienced in the community. In the real world, some studies on adherence to DAAs using administrative data have been published. A study by Kamble et al. in 2015 found high adherence rates in a large managed care organization. PDC ranged from 92.1 to 93.8% (n = 577) depending on the combination of sofosbuvir with other medication. However, this study did not contain any individuals who were treated with ledipasvir-sofosbuvir. The authors found that 14% of individuals were non-adherent, with PDC lower than 85%.[48]

Butt et al. used administrative data from Veteran Affairs to examine treatment completion, as in the percentage of the treatment course prescribed that was taken.[49] Both sofosbuvir and ledipasvir-sofosbuvir treatments were included. The percentage of individuals who completed a full course of treatment depended on the drugs used concurrently with sofosbuvir, with treatment completion of 53.62% for sofosbuvir and simeprevir (n = 1,050), 64.89% for sofosbuvir and ledipasvir-sofosbuvir (n = 974), 90.04% for sofosbuvir, interferon and ribavirin (n = 519), and 91.40% for sofosbuvir and ribavirin (n = 663).

Other studies have found higher adherence rates. Louie et al. found that in Kaiser Permanente Southern California, a large integrated health care delivery system, adherence to sofosbuvir was high, with 95.7% of individuals achieving MPR of 80% or higher (n = 213).[50] Trombatt et al. retrospectively reviewed clinical assessment forms and prescription records from a national specialty pharmacy database and found MPR was approximately 97% for sofosbuvir (n = 196).[51]

In summary, previous studies on adherence to HCV therapies show variable estimates for adherence. Furthermore, the populations in most of the studies available were not representative of the broader population. Populations were often small and specific, such as in clinical trials, where the population characteristics and study settings may not be generalizable to the real

world. Furthermore, even for studies with larger populations, the characteristics of the participants may be specific; for example, in Veteran Affairs populations, the individuals are mostly male. Thus, to fill these gaps, population based studies are needed with data from a more general population.

2.1.3 Patient factors

To provide evidence to help identify patients who are at risk of lower adherence, previous studies have examined the relationship between various patient factors and adherence rates. Below, I have highlighted some literature on several factors that will be examined in this study:

Drug use

Since PWIDs comprise a large proportion of HCV cases, concerns have been raised about their likelihood to adhere therapy.[52] In the United States (US), many PWIDs lack health insurance, and if they are insured, they would rely on public sources of insurance as they are often denied by private insurers.[71]

In the pre-DAA era, there was less uptake in HCV treatment among PWIDs.[6,72] This could be attributed to barriers at the systems, practitioner, and patient levels.[54] At the systems level, there were challenges in providing screening, testing, assessment, and treatment.[54] At the practitioner level, practitioners had sub-optimal knowledge about treatment of HCV, and often withheld treatment for perceived reasons, such as poor adherence and risk of re-infection.[54] At the patient level, patients had misconceptions about HCV and its treatment, and since HCV infection often does not have noticeable symptoms, many people had a low perceived need for treatment.[54]

With the higher tolerability of DAAs compared to interferon-based treatments, DAAs have helped remove treatment barriers and scale up HCV treatment in PWIDs.[73] It is suggested that the removal of interferon and shorter duration of DAA treatments can help improve adherence among PWIDs.[74] Although adherence to DAAs among PWIDs has been comparable to non-PWIDs, efforts should be made to prevent reinfection, and offer retreatment if reinfection occurs.[75] As a research priority, Grebely et al. suggested that treatment completion and adherence to DAAs be evaluated for PWIDs in the real world.[73]

In a recent study, Petersen et al. found that medication adherence to sofosbuvir and ledipasvir-sofosbuvir was high among inner-city patients, but both drug use (including marijuana, heroin, cocaine) within six months prior to starting therapy and alcohol abuse were risk factors for non-adherence in 12-week (p = 0.01) treatment durations, though not six-week durations (p = 0.19, 0.28).[47] This study took place as part of a clinical trial with a sample size of 60 patients and may have limited generalizability, as typically, adherence rates are much higher in clinical trials.[46] In a study of patients from a community-based agency that provides harm reduction and treatment (n = 127), Morris et al. found that adherence at or above 90% based on self-report was 92%.[76] In a community-based program in Toronto, Mason et al. found that high adherence to DAAs among people with a history of drug use (n = 74) based on self-report. There were no missed doses in 89% of treatment weeks, and 59% of patients had no missing doses throughout the course of treatment.[77]

Based on recent studies, the effect of drug use on adherence to DAAs was mixed. However, these studies were in small populations, and further research should be performed in larger populations.

Opioid substitution therapy (OST)

Opioid substitution therapy (OST), typically methadone or buprenorphine, is used for the management of opioid dependence.[78] In a post hoc analysis of phase 3 trials for ledipasvir-sofosbuvir, Grebely et al. found no statistically significant difference in treatment completion (97% for OST vs 98% for non-OST, p = 0.40) and ≥ 80% adherence (93% vs 92%, p = 1.00) among OST (n = 70) and non-OST groups (n = 1,882).[78]

In another post hoc analysis of phase 3 trials for sofosbuvir/velpatasvir, Grebely et al. found a statistically significant difference, although a small clinical difference, in treatment completion (96% for OST vs 99.7% for non-OST, p = 0.02) and no statistically significant difference in ≥ 90% adherence (90% vs 96%, p = 0.06) among OST (n = 51) and non-OST groups (n = 984).[79]

Overall, OST did not seem to impact adherence to DAAs, and when the effect on treatment completion was statistically significant, the clinical difference was small.

Mental health

The stigma of mental illness may create barriers for patients to seek treatment, providers to prescribe them, and payers to cover them.[80] In the DAA area, management of psychiatric or neuropsychiatric side effects, previously induced by interferon in older treatments, is no longer necessary.[80] However, there may still be other barriers to adherence, such as patients forgetting to take their pills every day, especially since HCV is asymptomatic.[80]

Overall, there were mixed results on whether mental health impacted adherence. In the same study of a clinical trial by Petersen et al., psychiatric disease did not impact adherence in either six-week or 12-week treatment arms.[47] Younossi et al. found that history of depression was significantly associated with adherence $\geq$ 80% (p = 0.0047), while cirrhosis (p = 0.86), history of type 2 diabetes (p = 0.54), and history of anxiety (p = 0.53) were not.[67]

Mason et al. evaluated a community-based program that provided DAA treatment to participants with history of drug use (n = 74).[77] Adherence was measured based on the number of weeks with self-reported missed doses. In a bivariate analysis, the following factors were associated with lower adherence: non-injection drug use (IDU) in the past 30 days (p = 0.01), moderate to heavy drinking in the past 30 days (p = 0.002), depression in the past 30 days (p = 0.03), treatment with an agent other than sofosbuvir/ledipasvir, and later week of treatment (p = 0.003). Gender, education, housing status, IDU in the past 30 days, OST, cognitive impairment, and social support were not associated with lower adherence. However, in a multivariate analysis, only heavy alcohol use was associated with lower adherence (odds ratio (OR) = 2.9, p = 0.05), adjusted for the other factors.

Based on the above studies on mental health and adherence to DAAs, the impact of mental health in general on adherence was mixed. Depression and alcohol use were associated with lower adherence. Psychiatric disease, when examined generally, or history of anxiety did not impact adherence. However, there is a dearth of evidence on the relationship between mental health and adherence to DAAs in larger study populations.[48–51]

Summary of patient factors

In summary, previous studies have found mixed findings on the association between IDU or mental illness with low adherence. There were statistically significant findings on the association between depression and alcohol use with lower adherence. Of the studies examined, the relationship between OST and adherence was either statistically insignificant or had small clinical significance.

2.1.4 Contributions of this study

There have been few studies published on adherence to DAAs, most of which were small studies that did not have sufficient power to detect differences, and mixed results on what factors are associated with adherence. To my knowledge, this is the first study that examines adherence to sofosbuvir and ledipasvir-sofosbuvir in a general population, rather than specific populations, such as individuals in clinical trials and insurance plans. I will also be able to assess adherence in specific population groups such as PWIDs.

2.2 Methods

2.2.1 Study context

BC's health care system consists of a single-payer system for physician and hospital services, with a mix of public and private payers for prescription drugs dispensed outside of hospitals.[59] Under PharmaCare, BC's public drug insurance program, BC residents can enrol in one of several plans, the largest of which is the income-based Fair PharmaCare plan.[36] PharmaCare coverage of sofosbuvir and ledipasvir-sofosbuvir was announced in March 2015,[39] prior to which these drugs could be accessed by private insurance plans or out-of-pocket payments by individuals.

This study examined data starting from January 23, 2014 when the first prescription of sofosbuvir was filled in BC. During the 15 months before PharmaCare coverage of sofosbuvir and ledipasvir-sofosbuvir, for treatments initiated between January 2014 and March 2015, payments came only from private insurance and out-of-pocket. The analysis also included 14

months in the post-period from April 1, 2015 to May 31, 2016, where PharmaCare coverage of these drugs was available. Figure 2.1 shows the time period of analysis. Although sofosbuvir was approved in December 2013, the first dispensation of the drug did not occur until January 2014. The first dispensation of ledipasvir-sofosbuvir occurred in November 2014. Since the longest treatment length was 168 days (24 weeks), I implemented a review period to ensure that the last patient available for assessment had the maximum 24-week follow-up time prior to the May 31, 2016 study end date. Thus, the last possible date for an individual to initiate treatment in my population was December 15, 2015.

Figure 2.1 Study timeline
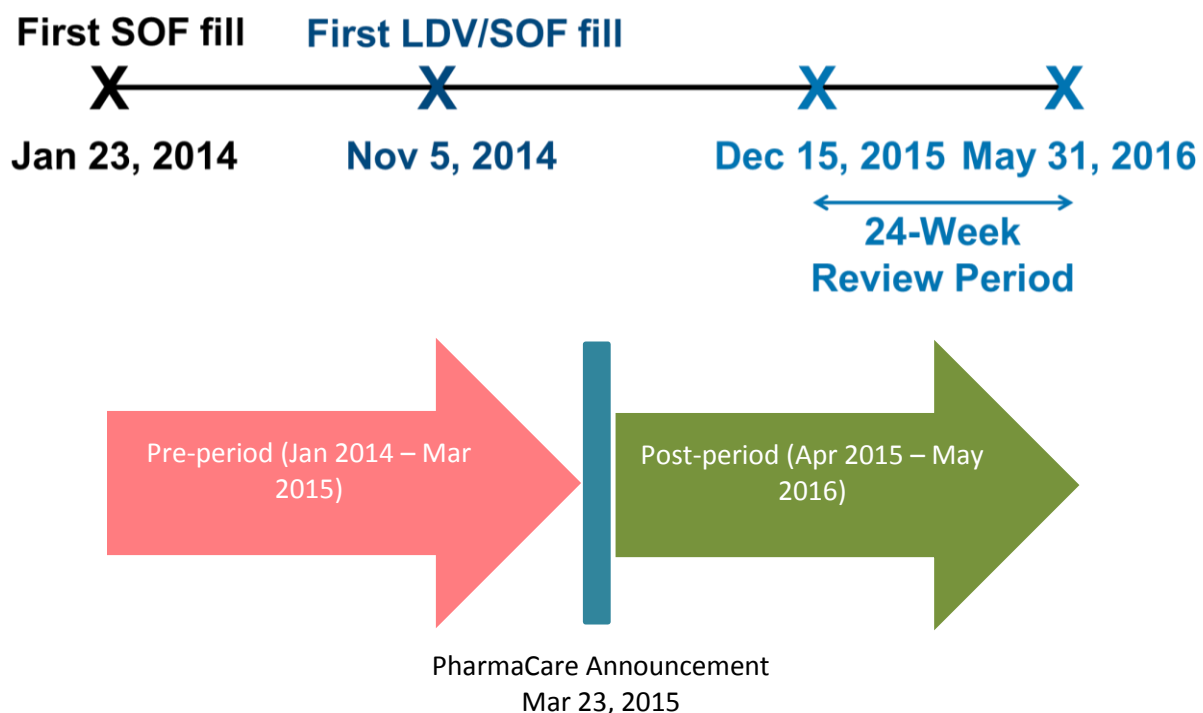
2.2.2 Data sources

This analysis is based on the BC Hepatitis Testers Cohort (BC-HTC), which is housed at the BC Centre for Disease Control (BCCDC). The BC-HTC includes all individuals in BC who have been tested for HCV or HIV, or reported a case of hepatitis B (HBV), HCV, HIV or active tuberculosis in BC from 1990 to February 2016.[13] Through personal health numbers, the data is linked to medical visits, hospitalizations, prescription drugs, the cancer registry and mortality data (Appendix 2).[13]

The data for the BC-HTC comes from comprehensive sources that capture nearly all British Columbians. The BC Ministry of Health gathers data on various public health system usage, including diagnoses, medical and surgical procedures, prescription drugs dispensations for residents under provincial jurisdiction.

Prescription drug data came from PharmaNet, which is a network run by the BC Ministry of Health and the College of Pharmacists of BC.[81] PharmaNet provides comprehensive data on all prescription drugs dispensed through community pharmacies, community health practices, and hospital outpatient pharmacies in BC.[82] It is the most comprehensive data source for prescription drug data, as all drugs dispensed in BC, regardless of payer, are registered in the PharmaNet system. However, prescription drugs dispensed inpatient at hospitals were excluded from this data set,[82] which is a limitation of my study. If any courses of sofosbuvir or ledipasvir-sofosbuvir were dispensed in hospital, those individuals may have been excluded from my study population.

2.2.3   Study population

Appendix 1 illustrates the number of individuals included and excluded in each stage of the process to make the final data set. In this study, I first included all individuals who were dispensed sofosbuvir and ledipasvir-sofosbuvir in the PharmaNet system up to May 31, 2016.

24-Week review period

Inclusion and exclusion in the final data set was determined by a 24-week review period prior to the study end date of May 31, 2016. Since the longest treatment duration is 24 weeks (168 days), excluding all individuals who started treatment in the review period provided a conservative method of ensuring that all individuals should have completed treatment before May 31, 2016.

First treatment

I ensured that only the first treatment of the same drugs was included. However, 14 individuals were treated with both sofosbuvir and ledipasvir-sofosbuvir, and they were included in the data set as these were the first instances of each respective drug.

Removal of individuals with treatment lengths over 168 days

I removed those with treatment lengths over 168 days as I assumed this would mean these individuals had initiated a second course of treatment.

Discontinued therapies

Previous studies by Kamble et al.[48] and Butt et al.[49] excluded those who discontinued therapy, defined as having a gap of over 14 days between fills. In this study, I chose not to exclude any possible discontinued patients as it would more accurately portray PDC. Excluding discontinued individuals could potentially inflate PDC.

2.2.4   PharmaNet variables

I used the following variables from PharmaNet in this study:
1. Study identification number
2. DIN/PIN (Drug Identification Number/Product Identification Number)
3. Date of service
4. Quantity dispensed – the amount of medication (e.g. number of pills) given to a patient during a fill date
5. Days supply – the number of days that the medication dispensed will last
6. Total amount paid by claims – the amount paid by PharmaCare, which covers all or part of the sum of drug cost and professional services fee
7. Drug cost claimed – the cost of the drug itself that was submitted to PharmaCare
8. Professional services fee claimed – the fee that pharmacies charged for dispensing the medication that was submitted to PharmaCare

2.2.5   Medication adherence

Although there is no gold standard for the best measure of medication adherence,[83] proportion of days covered (PDC) tends to provide more conservative estimates than other methods, such as the medication possession ratio (MPR), because it avoids double counting pills on overlaps of

refill periods.[84] Thus, I used PDC as measure of adherence in this study. Furthermore, given that the treatment periods for DAAs are short, PDC was more appropriate for my study than other measures such as persistence and gap analysis, which would have been more useful under a longer time frame of observation.

I considered PDC = 100% as full adherence to treatment and PDC < 100% as not complete adherence. This measured secondary adherence, which demonstrated that a patient completed a course of therapy properly.

I used a modification of existing methods to calculate the PDC.[85] This method adjusted for overlapping days supply, so that if an individual picked up medication early, that fill date would be shifted to after the days supply of the previous fill was finished. Figure 2.2 illustrates an example of this shift in days supply:

Figure 2.2 Adjustment of overlapping days supply in PDC calculation
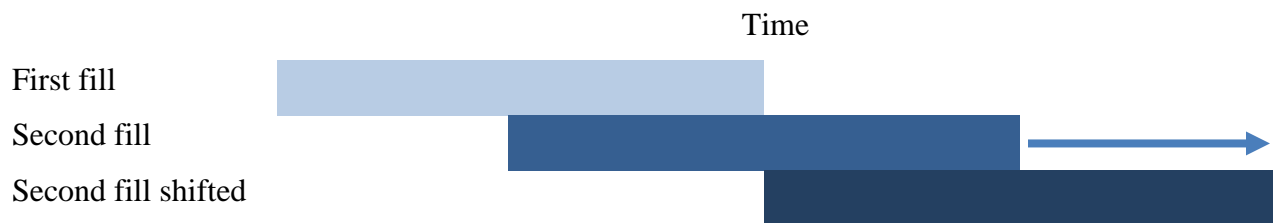
Treatment completion

I also examined treatment completion, which measured whether an individual picked up all the recommended number of pills, regardless of the time period in which the drugs were dispensed. Thus, it is possible for an individual to have treatment completion over 100% if they were dispensed more pills than the maximum number covered by PharmaCare. Pills taken beyond the PharmaCare maximum would not be publicly covered.

Treatment completion = (total days supply/total recommended treatment days) × 100%

PDC provides a more conservative measure of adherence than treatment completion. For example, an individual with a treatment period of 84 days picks up an initial 10 days of supply. They then wait 100 days after the first day of dispensation to pick up their next supply, and eventually, they pick up 84 days of supply in total. This means that treatment completion would equal 100% (84 days supply dispensed / 84 days of recommended treatment). However, since the coverage period is 84 days after the first date of dispensation, PDC would equal 11.9% (10 days supply dispensed in period of coverage / 84 days in period covered), which is much lower than the treatment completion percentage.

Treatment period

Since both sofosbuvir and ledipasvir-sofosbuvir are once-a-day pills, days supply is equivalent to quantity dispensed. Thus, in this study, quantity dispensed and days supply were used interchangeably. The recommended treatment periods of 56, 84, 112, or 168 days were based on the maximum treatment durations that PharmaCare covered during the study period (Tables 1.1, 1.2, and 1.3). Although 112 days is not listed on PharmaCare page as a maximum treatment duration, after a review of the data prior to analysis, many individuals were in this treatment group. It is still a plausible treatment duration as it is under the maximum coverage period of 168 days.

Treatment duration varies by factors such as HCV genotype, cirrhosis status, and whether an individual was previously treated. Since the data did not indicate the days supply prescribed by the physician, the treatment duration needed to be inferred from the data. To determine treatment duration, I examined the total quantity dispensed, which was the sum of quantities dispensed across all fill dates.

I proposed two scenarios to find treatment duration for use in adherence calculations. Table 2.1 summarizes the range of treatment days:

- *Optimistic*: I rounded up all pills dispensed to the next highest treatment duration. For example, an individual who was dispensed 57 days would be rounded up to the 84-day treatment category. An individual who was dispensed 83 days would also be rounded up to this category.

- *Pessimistic*: If the total quantity dispensed was within seven days below one of the recommended treatment durations, I categorized that individual under the closest treatment duration. All individuals with dispensation quantities outside of these ranges were grouped with the longest treatment length of 168 days. Although, this was an unlikely scenario, it provided a conservative measure as a precaution against inflation of PDC. For example, an individual who was dispensed 77 days would be categorized as having an 84-day treatment length, while an individual who was dispensed 76 days would be categorized as having a 168-day treatment length. If the individual who was dispensed 76 days was classified with an 84-day treatment length in the optimistic scenario, they would have a higher PDC than if they were classified with a 168-day treatment length in the pessimistic scenario. If this individual's actual prescribed treatment course was 112 days, then the 84-day optimistic scenario would inflate PDC, while the 168-day pessimistic scenario would deflate PDC, which would be more conservative.

Table 2.1   Range of days dispensed for treatment duration calculations in optimistic and pessimistic scenarios

	Optimistic	Pessimistic
Sofosbuvir		
84 days	$0 \leq$ days dispensed ≤ 84	$77 \leq$ days dispensed ≤ 84
112 days	$85 \leq$ days dispensed ≤ 112	$105 \leq$ days dispensed ≤ 112
168 days	$113 \leq$ days dispensed ≤ 168	$161 \leq$ days dispensed ≤ 168 (+ out-of-range individuals < 168)
Ledipasvir-sofosbuvir		
56 days	$0 \leq$ days dispensed ≤ 56	$49 \leq$ days dispensed ≤ 56
84 days	$57 \leq$ days dispensed ≤ 84	$77 \leq$ days dispensed ≤ 84
168 days	$85 \leq$ days dispensed ≤ 168	$161 \leq$ days dispensed ≤ 168 (+ out-of-range individuals < 168)

2.2.6 Patient factor variables

I used a combination of existing patient factor variables and variables I created for this study. Table 2.2 outlines the patient variables employed in this study. Variables created by the BC-HTC team have been described in previous studies[6,9] and are indicated below with an asterisk (*). Full description of the codes used to create these variables are included in Appendix.3.

Table 2.2 Patient factor variables

Variable	Definition
Sex	"Male" or "female." Used as is.
Age	I grouped individuals into several age categories that had a balanced number of individuals: below age 50, ages 50 to 60, and above age 60.
Ethnicity*	Since most of the individuals were white, I made ethnicity a binary variable, grouping individuals who were not white as "non-white," and keeping individuals who were originally classified as white as "white."
PharmaCare	The binary PharmaCare variable was constructed by determining whether the total amount paid by claims was above $0. If total amount paid was $0, then an individual was classified as belonging to the non-PharmaCare group. If total amount paid was over $0, then an individual was classified as belonging to the PharmaCare group.
Material deprivation*	The BC-HTC team used the deprivation index proposed by Pampalon et al., which was developed to help monitor social inequalities for health planning.[86] The authors described material deprivation as poverty or lack of financial resources, and social deprivation as lack of social capital. This index was previously employed in other studies with the BC-HTC.[6,9] The formula for the index uses client postal codes, thus in this study, individuals' socioeconomic status assignments were based on the neighbourhood or community they resided in, rather than their individual situation. In my population, 77 individuals were not assigned a deprivation index value; they either did not have a fixed

Variable	Definition
	address, and thus, lacked a postal code, or resided in a postal code that was suppressed in census data. I categorized these individuals as "Unknown/Missing." Although the authors suggest that deprivation includes both material and social dimensions, I only included material deprivation in my multivariable logistic regression model. I chose the material deprivation variable as I wanted to focus on the impact of poverty on adherence. According to the index, deprivation was divided into five quintiles, with the first quintile (Q1) being the most privileged and the fifth quintile (Q5) being the least privileged. In my model, I further grouped these quintiles into low (Q1 and Q2), moderate (Q3), and high (Q4 and Q5) deprivation.
Elixhauser comorbidity index*	Comorbidities were measured using the Elixhauser Comorbidity Index. The index uses International Classification of Diseases (ICD) diagnosis codes from administrative data to identify whether individuals had diagnoses in any of 31 comorbidity categories.[87] For each category that an individual had a diagnosis, their score would increase by one; thus, if an individual had 14 comorbidities, their Index would be 14. Most individuals had a low Index. Thus, to have balanced categories, I grouped the scores as follows: 0, 1, and 2 and above.
Cirrhosis*	If a patient had hospitalizations or medical service visits related to cirrhosis any time before the start of HCV treatment.
Diabetes*	If a patient had hospitalizations, medical service visits, or drug dispensations related to diabetes any time before the start of HCV treatment.

Variable	Definition
Hepatitis B (HBV)*	If a patient had hospitalizations, medical service visits, or drug dispensations related to HBV any time before the start of HCV treatment.
Hepatocellular carcinoma (HCC)*	If patient had an HCC diagnosis any time before the start of HCV treatment.
Major mental illness*	If patient had hospitalization or medical service visit related to major mental illness any time before the start of HCV treatment.
Injection drug use (IDU) *	Recent injection drug use was determined by whether an individual had medical service visits or hospitalizations related to drug use within one year prior to the start of HCV treatment.
Opioid substitution therapy (OST) *	Whether an individual was classified as being on OST was determined by whether they had medical service visits or drug dispensations for OST within the HCV treatment period.
Problematic alcohol use *	If a patient had hospitalizations or medical service visits related to alcohol use any time before the start of HCV treatment.
Treatment type	I categorized individuals by treatment type based on DINPIN: 2418355 for sofosbuvir and 2432226 for ledipasvir-sofosbuvir.
Treatment duration	Calculated based on total quantity of medication dispensed. The categories of treatment lengths are outlined in Table 2.1.

2.2.7   Relationship between patient factors and adherence

Bivariate analyses

I performed initial bivariate analyses to determine whether there was an effect of patient factors on PDC in both drugs. I used two-sample t-test for patient factor variables with two levels, and analysis of variance (ANOVA) for variables with more than two levels. I reported the mean PDC in each group, as well as the p-value to determine if there was a statistically significant difference between the means of each group. These analyses were also used to provide insights on the best method to build a logistic regression model in the next step.

Multivariable logistic regression model

Previous studies have used 80% as a threshold for adherence.[67] However, since in my study, average PDC was high, I used full adherence as the outcome variable: PDC < 100% was assigned as 0, and PDC = 100% was assigned as 1.

Fourteen individuals were treated with both sofosbuvir and ledipasvir-sofosbuvir, and thus, appeared in the data twice. To ensure independent observations, I removed the second treatment initiation from this analysis.

I built a multivariable logistic regression model, including all patient factor variables available, so that I could observe the effect of each variable on full adherence, adjusted for all the other variables. I incorporated fixed effects, creating a dummy variable for each year, to control for any changes in adherence over time. Since there were only two years, I only kept the 2014 dummy variable in the model, with '0' indicating 2015 and '1' indicating 2014. I also performed a sensitivity analysis using quarter fixed effects, instead of year, for a total of 8 quarter dummy variables.

2.2.8 Analysis

The analyses for this study were performed on SAS software, Version 9.4 of the SAS System for Windows, R Version 3.3.2, and RStudio Version 1.0.136.

2.3 Results

2.3.1 Study characteristics

As shown in Appendix 1, I included 786 observations for sofosbuvir and 1,974 observations for ledipasvir-sofosbuvir for a total of 2,760 observations. However, since 14 individuals received both treatments, there were only 2,746 unique individuals.

Appendix 4 presents a summary of the participant profile of each treatment with those 14 individuals only appearing once in the treatment they received first. Overall, the distributions of patient characteristics were similar across both treatment types. However, ledipasvir-sofosbuvir had a larger proportion of PharmaCare-covered individuals (78.06%) compared to sofosbuvir

(41.09%), which was reasonable given that sofosbuvir was available months early than ledipasvir-sofosbuvir when PharmaCare coverage was not yet available.

Across both drugs, 84 days was the most common treatment duration, with 52.93% of individuals for sofosbuvir and 52.30% of individuals for ledipasvir-sofosbuvir. However, most of the remainder of sofosbuvir-treated individuals had a treatment length of 168 days (41.09%), while for ledipasvir-sofosbuvir, treatment length was distributed to 56 days (22.96%) and 168 days (24.74%).

2.3.2 Adherence in the optimistic scenario

Proportion of days covered

Overall, PDC was high in the optimistic scenario (Table 2.3). Mean PDC for both drugs, sofosbuvir, and ledipasvir-sofosbuvir were 96.17%, 95.35%, and 96.50% respectively. Across both drugs, 89.89% of individuals achieved PDC of over 90%. For sofosbuvir, 87.53% of individuals achieved PDC of over 90%, while for ledipasvir-sofosbuvir, 90.83% of individuals achieved PDC of over 90%. Figures 2.3, 2.5, and 2.7 illustrate the distribution of PDC.

Since adherence rates were so high, I also compared the proportions of those who were 100% adherent (PDC = 100%) versus those who were not (PDC < 100%). I found that 70.36% were 100% adherent, while 29.64% were not.

Table 2.3 Summary of the number of individuals in each treatment group and adherence rates in the optimistic and pessimistic scenarios

Treatment duration (days)	Number of individuals (%)	
	Optimistic	Pessimistic
Sofosbuvir		
84	416 (52.93)	395 (50.25)
112	47 (5.98)	37 (4.71)
168	323 (41.09)	354 (45.04)
Total	786	786
Mean PDC (%)	95.35	94.40
PDC ≥ 90% (%)	87.53	87.28
Ledipasvir-sofosbuvir		
56	450 (22.80)	433 (21.94)
84	1,028 (52.08)	1,017 (51.52)
168	496 (25.13)	524 (26.55)
Total	1,974	1,974
Mean PDC (%)	96.50	96.07
PDC ≥ 90% (%)	90.83	90.83

2.3.3   Adherence in the pessimistic scenario

Proportion of days covered

I found that adherence rates, even in the pessimistic scenario, were quite high (Table 2.3). Mean PDC for both drugs, sofosbuvir, and ledipasvir-sofosbuvir were 95.59%, 94.40%, and 96.07% respectively. Across both drugs, 89.82% of individuals achieved PDC of over 90%. For sofosbuvir, 87.28% of individuals achieved PDC of over 90%, while for ledipasvir-sofosbuvir, 90.83% of individuals achieved PDC of over 90%. Figures 2.4, 2.6, and 2.8 illustrate the distribution of PDC.

Since adherence rates were so high, I also compared the proportions of those who were 100% adherent (PDC = 100%) versus those who were not (PDC < 100%). I found that 70.36% were 100% adherent, while 29.64% were not, which were identical to the findings in the optimistic scenario.

When the pessimistic scenario was applied, 97.86% of individuals remained in the same treatment length category as in the optimistic scenario, and 2.14% were classified in a different category.

Figure 2.3 Adherence in the optimistic scenario for both treatments

Sofosbuvir and Ledipasvir-sofosbuvir - PDC Distribution (n = 2,760)
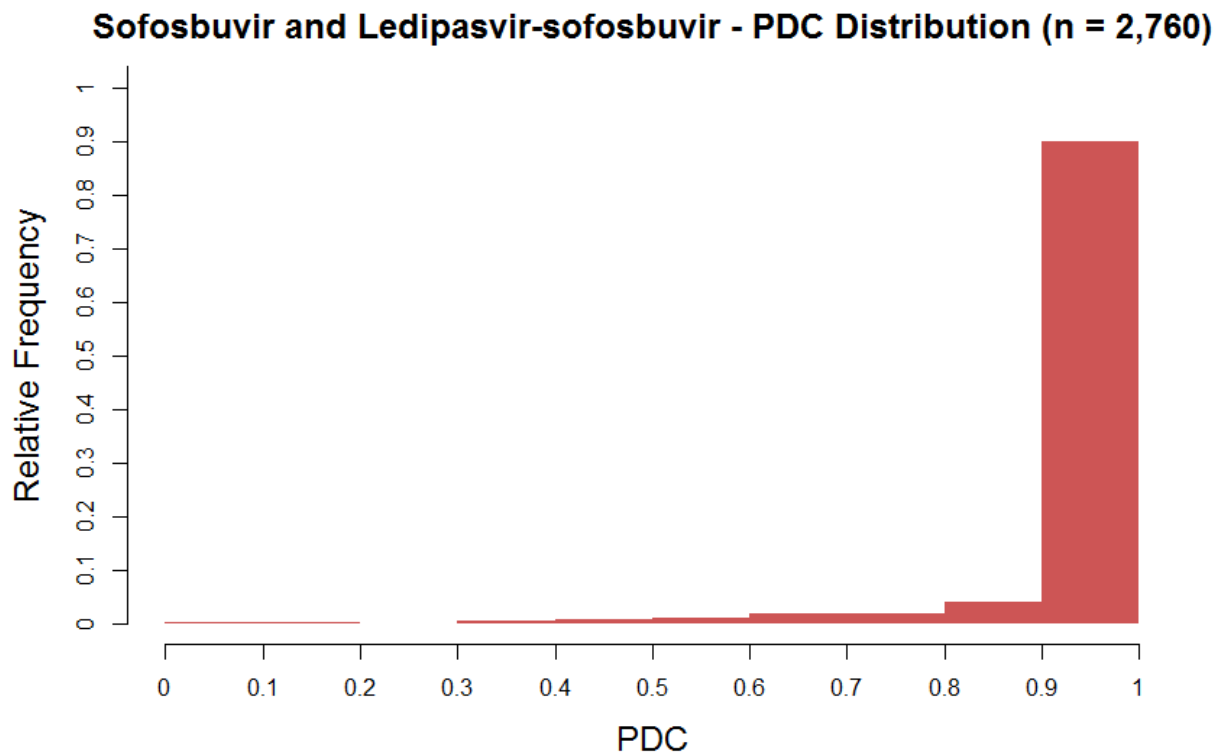
Figure 2.4   Adherence in the pessimistic scenario for both treatments

Sofosbuvir and Ledipasvir-sofosbuvir - PDC Distribution (n = 2,760)
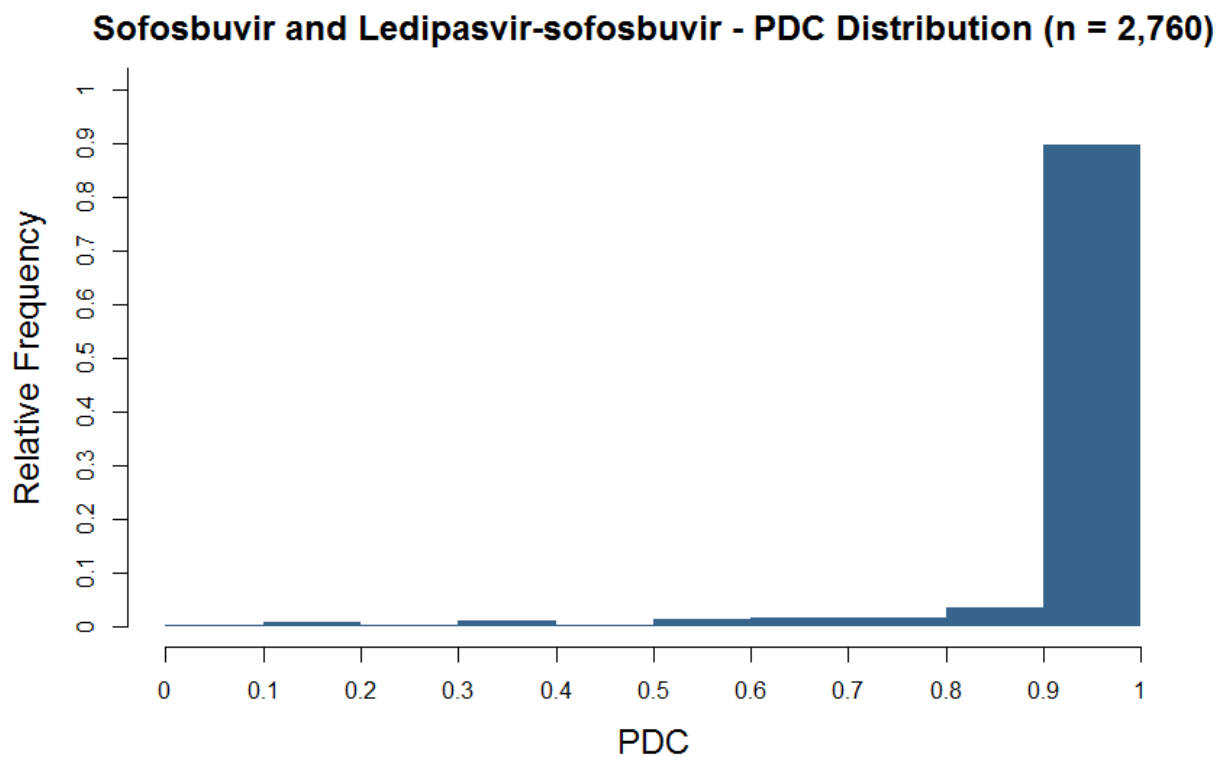
Figure 2.5 Adherence in the optimistic scenario for sofosbuvir
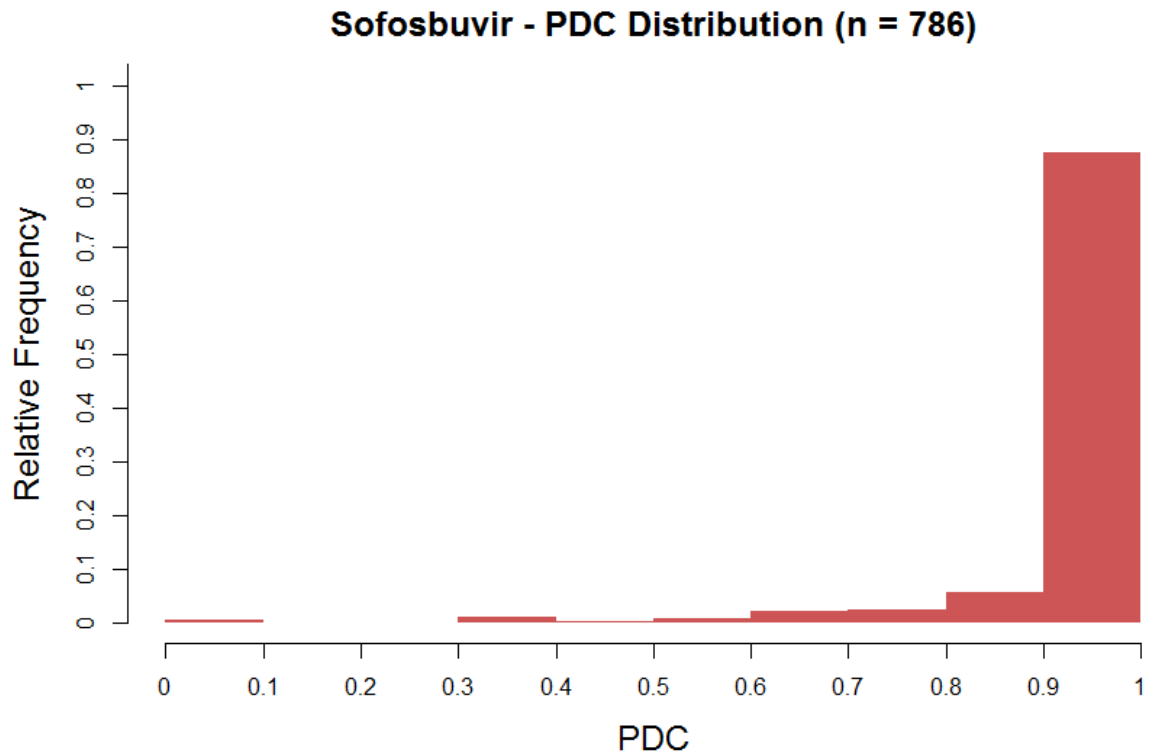
Figure 2.6 Adherence in the pessimistic scenario for sofosbuvir
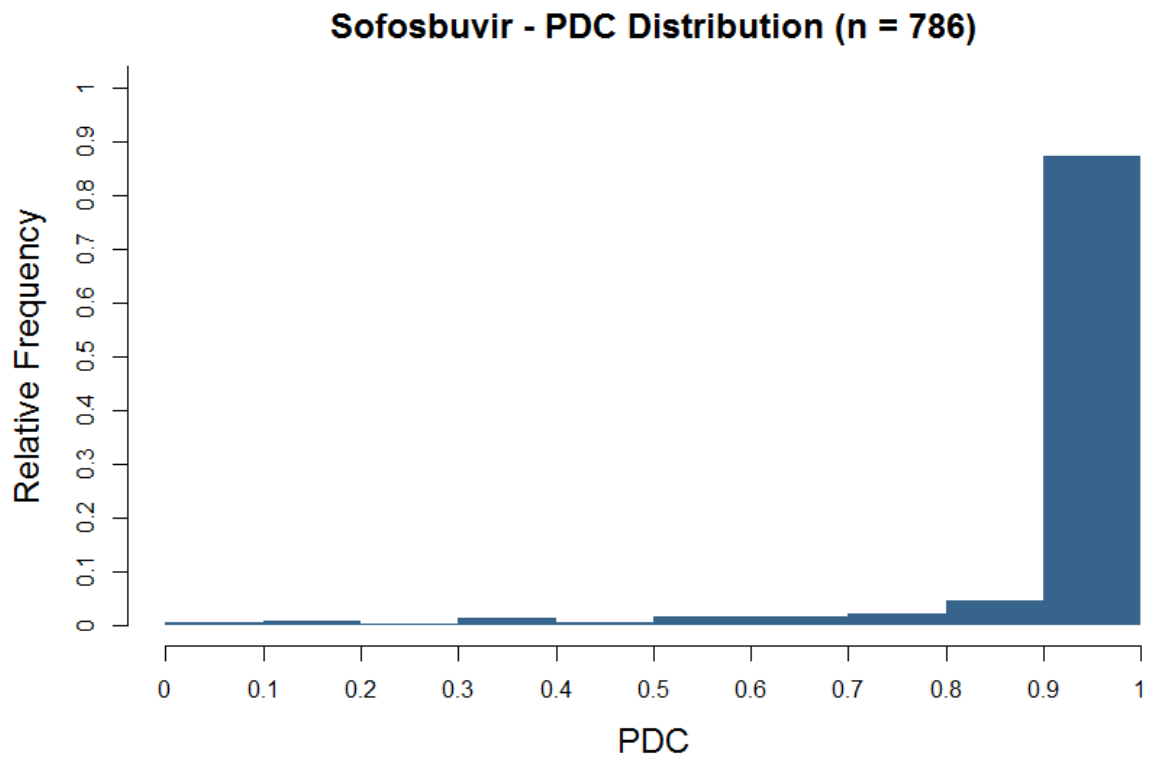
Figure 2.7 Adherence in the optimistic scenario for ledipasvir-sofosbuvir
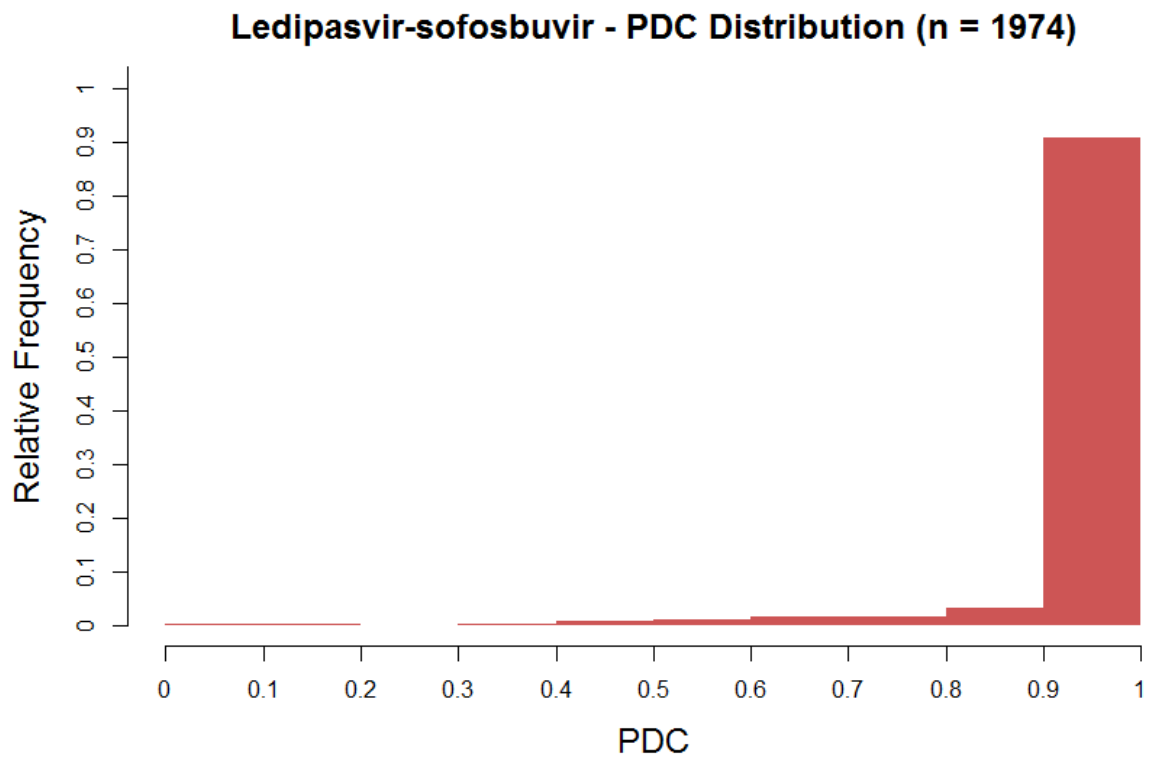
Figure 2.8 Adherence in the pessimistic scenario for ledipasvir-sofosbuvir
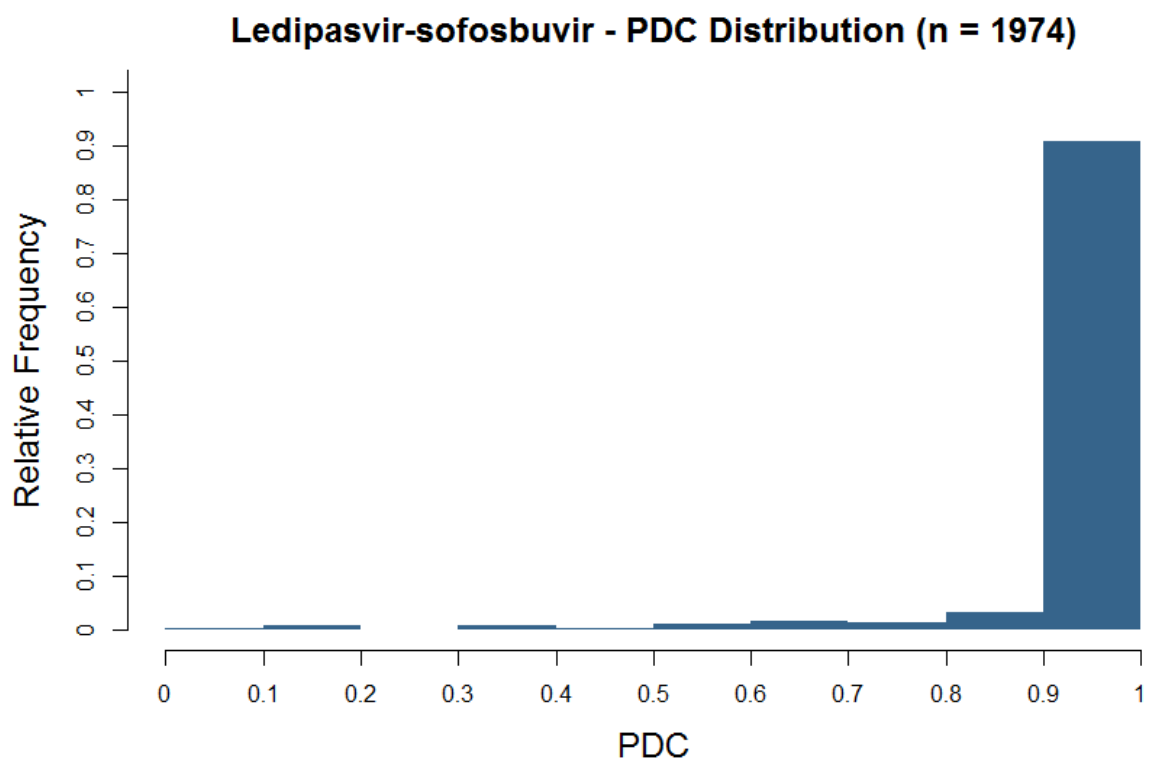
2.3.4 Checking for inflated PDC

Given that the treatment durations are short, it is possible that the first fill date could inflate PDC. For example, if an individual, who was supposed to received 84 days of treatment, was dispensed 84 days supply in the first fill, their PDC would be 100%. This would not be a good indicator of adherence, as there were no subsequent fills to further investigate an individual's behaviour over time. However, this did not seem to be a major concern. Of my sample, only 11 (1.40%) individuals for sofosbuvir, 35 (1.77%) individuals for ledipasvir-sofosbuvir were dispensed their complete treatment course in the first and only fill.

Even for the rest of the individuals who had more than one fill, the first fill could have also inflated PDC. For example, an individual, who was recommended 84 days of treatment, was dispensed 28 days of supply in the first fill. They did not pick up their second and subsequent fills until over 100 days since the date of the first fill. Their calculated PDC would be 0.33; however, it is possible that this individual only adhered to their medication for the first few days, or not at all, and thus, their actual PDC would be much lower.

To examine this issue, I removed the individuals who only had one fill, and examined the dispensation behaviours for the rest of the data set:

Sofosbuvir

I removed 11 individuals who had only one fill date out of 786 people in total. Within the 775 left, 669 (86.32%) refilled on time.

Ledipasvir-sofosbuvir

I removed 35 individuals who had only one fill date out of 1,974 people in total. Within the 1,939 left, 1,703 (87.83%) refilled on time.

Based on the above findings, it did not appear that PDC inflation was a concern as most of the individuals treated were early or on time with their second fill. This suggests that they were likely adherent in the first fill, and that PDC was unlikely inflated.

2.3.5 Treatment completion

Treatment completion was also very high (Table 2.4). For both therapies, 95.72% of patients completed over 90% of the treatment.

Table 2.4 Summary of treatment completion rates

	Both (%)	Sofosbuvir (%)	Ledipasvir-sofosbuvir (%)
Optimistic			
Mean completion	98.35	98.00	98.49
Completion ≥ 90%	95.80	94.66	96.25
Pessimistic			
Mean completion	97.74	96.99	98.04
Completion ≥ 90%	95.72	94.40	96.25

Looking at completion, 1.73% of individuals for sofosbuvir and 1.56% for ledipasvir-sofosbuvir completed over 100% of their treatments, meaning they received more pills than required.

Given the high rates of adherence and treatment completion in the pessimistic scenario, I used treatment duration from the optimistic scenario for the remainder of my calculations. Furthermore, there was a small difference in the number of individuals with different treatment durations between the two methods.

2.3.6 Impact of patient factors on adherence

Although adherence was high in the entire cohort, I used a multivariable logistic regression model to see whether any patient factors were associated with adherence. In a sensitivity analysis, the model with the quarter dummy variables (Appendix 6) showed similar results to the model with the year dummy variable (Table 2.5). Thus, I selected the more parsimonious model with the year dummy variable.

Table 2.5   Multivariable logistic regression model with year fixed effects for factors associated with full adherence

Variable	Estimate	SE	p-value	Adjusted OR (95% CI)
Sex – Male	-0.98	0.095	0.30	0.91 (0.75, 1.09)
Age (reference: < 50)				
50-60	0.15	0.13	0.24	1.16 (0.90, 1.50)
> 60	0.29	0.13	0.026*	1.34 (1.03, 1.74)
Ethnicity – White	-0.38	0.19	0.047*	0.69 (0.47, 0.99)
PharmaCare	0.27	0.12	0.021*	1.31 (1.04, 1.65)
Material deprivation (reference: most privileged)				
Moderately privileged	-0.25	0.12	0.035*	0.78 (0.62, 0.98)
Least privileged	-0.13	0.099	0.19	0.88 (0.72, 1.07)
Unknown/missing	0.15	0.28	0.58	1.17 (0.69, 2.04)
Elixhauser comorbidity index (reference: 0)				
1	-0.16	0.12	0.17	0.85 (0.67, 1.07)
≥ 2	-0.08	0.12	0.50	0.92 (0.73, 1.17)
Cirrhosis	0.045	0.12	0.70	1.05 (0.83, 1.32)
Diabetes	-0.12	0.11	0.26	0.88 (0.71, 1.10)
Hepatitis B (HBV)	0.046	0.16	0.77	1.05 (0.77, 1.45)
Hepatocellular carcinoma (HCC)	0.77	0.40	0.056	2.17 (1.03, 5.14)
Major mental illness	-0.34	0.10	0.0011*	0.71 (0.58, 0.87)
Injection drug use (IDU) diagnosis	0.044	0.20	0.83	1.04 (0.71, 1.56)
Opioid substitution therapy (OST)	-0.23	0.14	0.11	0.79 (0.60, 1.06)
Problematic alcohol use	-0.15	0.11	0.16	0.86 (0.70, 1.06)
Ledipasvir-sofosbuvir (reference: sofosbuvir)	0.22	0.11	0.05	1.25 (1.00, 1.55)
Treatment duration (reference: 56 days)				
84 days	-0.17	0.14	0.22	0.85 (0.64, 1.10)
112 days	-0.88	0.34	0.0091*	0.41 (0.21, 0.81)
168 days	-0.70	0.15	< 0.001*	0.49 (0.37, 0.66)
Year fixed effect (reference: 2015)				
2014	-0.15	0.16	0.33	0.86 (0.63, 1.17)

* $p < 0.05$

Age

Being over the age of 60 was associated with higher odds of perfect adherence. The odds of full adherence among individuals over the age of 60 were 1.34 (95% CI: 1.03, 1.74) times the odds of full adherence among individuals under the age of 50, adjusted for the other variables ($p = 0.03$). There was no significant relationship in the odds of full adherence between those between the age of 50 and 60 and those under the age of 50 ($p = 0.25$).

Ethnicity (white)

Being white was associated with lower odds of full adherence. The odds of full adherence among white individuals 0.69 (95% CI: 0.47, 0.99) times the odds of full adherence among non-white individuals, adjusted for the other variables ($p = 0.047$).

PharmaCare

Being covered by PhamaCare was associated with higher odds of full adherence. The odds of full adherence among PharmaCare-covered individuals were 1.31 (95% CI: 1.04, 1.65) times the odds of full adherence among non-PharmaCare-covered individuals, adjusted for the other variables ($p = 0.021$).

Material deprivation

Being moderately privileged was associated with lower odds of full adherence. The odds of full adherence among those who were moderately privileged were 0.78 (95% CI: 0.62, 0.98) times the odds of full adherence among the most privileged individuals, adjusted for the other variables ($p = 0.035$). However, there was no significant relationship in the odds of full adherence between those who were the least privileged and those with unknown SES, with the most privileged individuals ($p = 0.19, 0.58$).

Major mental illness

Having a history of major mental illness was associated with lower odds of full adherence. The odds of full adherence among those with major mental illness were 0.71 (95% CI: 0.58, 0.87) times the odds of full adherence among those without major mental illness, adjusted for the other variables ($p = 0.0011$).

Treatment length

Receiving 112 and 168 days of treatment was associated with lower odds of full adherence. The odds of full adherence among those who were treated for 112 days and 168 days were 0.41 (95% CI: 0.21, 0.81) and 0.49 (95% CI: 0.37, 0.66) times respectively the odds of full adherence among those who were treated for 56 days, adjusted for the other variables (p = 0.0091, < 0.001). However, there was no significant relationship in the odds of full adherence between those who were treated for 84 days and those who were treated for 56 days (p = 0.22).

Other variables of interest

Notably, I found no statistically significant relationship between IDU, OST, and problematic alcohol use and full adherence. The estimated OR for IDU was 1.04 (95% CI: 0.71, 1.56), suggesting that the difference in full adherence between IDU and non-IDU patients was also not clinically significant. If the results were statistically significant, the estimated OR for OST and problematic alcohol use would have been more clinically significant, at 0.79 (95% CI: 0.60, 1.06) and 0.86 (95% CI: 0.70, 1.06) respectively.

2.4   Discussion

2.4.1   Overview of findings

Adherence

The adherence rates found in this study aligned with the results found in previous studies using administrative data. PDC in my study, as well as in others that used administrative data, were above 90%.[48–51] Given the large sample size, my findings add strong support for high adherence rates for sofosbuvir and ledipasvir-sofosbuvir in the literature.

The use of administrative data provided an opportunity to observe adherence in the real world. In a clinical trial setting, patients may be closely monitored, and thus their behaviour may not be reflective of the real world. Therefore, my findings provide greater generalizability on adherence.

Patient factors

Given that there were mixed findings on the association between IDU or mental illness with low adherence, my findings contributed to the literature, showing that there was no significant association between IDU and adherence. I found a significant association between mental illness and low adherence, which aligned with the limited previous evidence that psychiatric disease and depression was associated with low adherence. However, I did not find an association between problematic alcohol use and adherence, which did not align with previous findings. My findings aligned with other findings in the literature that OST was not associated with adherence.

2.4.2 Strengths

The data came from a general population in a real-world scenario, which allowed me to capture insights that are generalizable to a broad population. From my knowledge, this is the first study that examined adherence in a general population for sofosbuvir and ledipasvir-sofosbuvir. In previous studies, such as clinical trials, the study setting and method for participant follow-up were likely to have been different from the real world, limiting the generalizability of the results. Even in real-world studies, they have been performed on specific populations, such as members of insurance plans or managed care organizations. Patients may need to meet certain criteria to be enrolled, and thus they may not be representative of the broader population. Although there were specific criteria to be eligible for PharmaCare coverage, my population included both PharmaCare and non-PharmaCare individuals.

Furthermore, using administrative data to calculate PDC helped reduce self-report bias, compared to measures of adherence that used patient-reported data. This further improves the generalizability of the findings by measuring adherence with a method that reflects close to real world behaviour.

Using administrative data allowed me to classify individuals under various patient factors, which also helped reduce self-report bias. In previous studies where self-report was used, individuals may under-report certain factors, such as injection drug use, and over-report other factors, such as income.

2.4.3 Limitations

Measuring adherence

My study still had a few limitations. Ultimately, my study lacked the ability to directly observe the behaviours of individuals' adherence. Although calculating PDC from administrative data provided a more conservative measure than others, there are still several possibilities that PDC may not be able to accurately measure adherence behaviour. For example, PDC assumes that if an individual has picked up 7 days supply of pills and then picks up their next seven days supply early or on time, they would be adherent for 14 days. However, it is possible that they skipped a few days or did not take any of the pills at all, even if they picked them up. Administrative data is still widely used to calculate adherence as it is convenient and inexpensive[65] and these measures also have high agreement with other adherence measures, such as self-report.[88] In addition, my data did not include information on the course of treatment prescribed by physicians, so this needed to be inferred from the data. This is one limitation of PharmaNet data and detailed prescription information may be available under more direct observation methods. However, the strengths of having a general population from PharmaNet data still outweigh the limitations.

There may have been some limitations to using full adherence (PDC = 100%) as an outcome variable in the multivariable logistic regression model. If I chose a different threshold, for example PDC = 80% or 90%, the coefficient estimates for variables in my logistic regression model may have been different, depending on the distribution of adherence rates for each variable. Ultimately, the best threshold for adherence would need to be determined by clinical effectiveness. Further studies should link adherence to SVR to determine the best PDC threshold to be used for research as well as in a clinical setting.

Patient characteristics

The individuals in this first stage of PharmaCare coverage of sofosbuvir and ledipasvir-sofosbuvir may not be similar to the patients who will be covered under the expanded program in 2018-19. Thus, the predictive power of my logistic regression model may not be generalizable to the future larger scale program.

Furthermore, some of the classifications of patient factors may not be completely representative of the individuals' status at the time of treatment. I used histories of cirrhosis, diabetes, HBV, HCC, major mental illness, and problematic alcohol use. Although, once diagnosed, an individual's status with any of these diagnoses would unlikely change, it was still possible that their status may have changed. However, this was unlikely, and if there were any changes, they would probably affect few individuals, and thus, would minimally impact my results.

Clinical significance

Although the results of the logistic regression model may help clinicians identify risk factors for low adherence, ultimately, full adherence may not be a clinically significant outcome. This is especially because adherence rates are already high, and thus, the clinical differences between full and not full adherence are possibly minimal.

2.4.4 Implications for policy, practice, and research

Policy

Given the evidence found in this study, my findings assuage concerns for low adherence for sofosbuvir and ledipasvir-sofosbuvir. These encouraging results support future public coverage for sofosbuvir and ledipasvir-sofosbuvir in BC and other jurisdictions, as well as for populations, such as PWIDs, for which there are heightened concerns about adherence.

Practice

Given that there was no difference in odds of perfect adherence among those who are PWID, on OST, and have problematic alcohol use, there should not be barriers for individuals who use substances to be able to access treatment. However, physicians may need to work more closely with patients who have histories of major mental illness to help them achieve better adherence.

My findings also suggest that shorter treatment durations improve adherence rates. Clinicians should work with patients to provide shorter treatments when appropriate and possible. Furthermore, for individuals with HCV genotype 1 who can take either sofosbuvir and ledipasvir-sofosbuvir, my findings suggest that they should be treated with ledipasvir-sofosbuvir for higher adherence rates.

Research

Future studies should be performed using administrative datasets from other jurisdictions to provide further evidence to whether these findings align with other findings on adherence rates. Furthermore, a similar study should be performed after PharmaCare has fully expanded its program in BC to evaluate whether there are any differences between the results in the smaller population of this study and the broader HCV patient population who will receive treatment.

2.5   Conclusion

Given the high cost of sofosbuvir and ledipasvir-sofosbuvir, the high adherence rates found in this study are encouraging. Of the variables of interest, I found that history of major mental illness may be a risk factor for low adherence that should be considered prior to initiating treatment. However, injection drug use, using opioid substitution therapy, and problematic alcohol use were not found to be risk factors for concern.

3 Impact of PharmaCare coverage on sofosbuvir and ledipasvir-sofosbuvir in British Columbia

3.1 Introduction

3.1.1 Policy change

As described in Chapter 1, BC PharmaCare introduced public coverage for sofosbuvir and ledipasvir-sofosbuvir in late March 2015, more than a year after the first prescription of sofosbuvir was dispensed in January 2014. Although the cost of this policy amounted to over $200 million from March 2015 to May 2016, public drug coverage reduces private insurance costs and out-of-pocket costs for patients. With the future expansion of coverage of HCV treatment in BC, it is important to evaluate the implications of this policy change. As a growing number of new and expensive specialty medicines becomes available, the impact of public drug coverage becomes an important consideration for both public drug plans and employers providing private drug coverage in Canada. This chapter examines the impact of this policy change on trends in adherence, treatment uptake, and public and private expenditure in BC.

3.1.2 Impact of pubic coverage on adherence trends

From my knowledge, there have not been any studies examining trends in adherence over time for sofosbuvir and ledipasvir-sofosbuvir, as well as the impact of change in prescription drug coverage on these trends. However, some studies have examined adherence trends in other drugs. Generally, increased cost sharing has been associated with lower adherence.

In a review (n = 132) by Goldman et al., the authors found that increased cost sharing was associated with lower rates of drug treatment, lower adherence, and higher discontinuation rates.[89] They also found that there is limited evidence to support the hypothesis that lower income groups are more sensitive to cost sharing.

In a study of cardiovascular drugs using interrupted time series analysis, the elimination of copayments for statins and reduction of copayments for clopidogrel led to an immediate increase in adherence rates at Pitney Bowes, a US corporation.[90] For statins, the policy change led to a 3.1 percent immediate increase in monthly proportion of days covered (PDC) in the intervention

group (n = 2,051) compared to control (n = 38,174), but no change in trend of adherence. For clopidogrel, the policy change led to a 4.2 percent immediate increase in monthly PDC in the intervention group (n = 779) compared to control (n = 11,627), but also no change in trend of adherence.

Viswanathan et al. performed a systematic review that included examining the effect of policy interventions on adherence.[63] They found moderate-strength evidence that decreased out-of-pocket costs had a statistically significant effect on improved adherence to cardiovascular and diabetes medications. In one study, there was no effect on adherence to the respiratory medications that they examined. In two of the five studies for cardiovascular medications and two of the three studies for diabetes medications, adherence decreased over time.

For specialty drugs, Goldman et al. found that the use of these drugs was insensitive to cost sharing.[91] However, they examined specialty drugs for cancer, kidney disease, rheumatoid arthritis and multiple sclerosis, and thus the results may not be generalizable to HCV DAAs.

Since these studies examined drugs for chronic diseases that should be taken regularly and for long periods, the results may not be generalizable to DAAs with comparatively short and defined treatment lengths. Furthermore, the characteristics of the populations examined in these studies may be different from those in my study. Drug coverage in Canada is substantially different from those in other countries, and it may be the case that private drug coverage plans in Canada give access to expensive drugs, such as DAAs, even in the absence of public coverage. However, given the lack of literature on the impact of policy on adherence to DAAs, these studies suggest that the introduction of PharmaCare coverage may have an immediate positive effect on adherence, but no effect on the longer-term trend.

3.1.3   Impact of public coverage on treatment uptake and expenditure

To date, there has been limited study on the impact of public coverage of DAAs on treatment uptake and expenditure. One study conducted in the US examined the early patterns of utilization after introduction of public coverage, Medicaid, for sofosbuvir in the US.[92] In 2014, the second quarter saw an increase in number of prescriptions compared to the first quarter, with a two-fold increase in some states. By the third quarter, utilization stabilized or slowed, and fell in seven states. Overall, in the first year, there was a rapid increase in expenditure by Medicaid. Based on

these findings, Medicaid coverage of sofosbuvir increased both utilization and expenditure on the drug.

Another study examined the impact of insurer-required cost sharing (out-of-pocket cost) on index abandonment rate of sofosbuvir in a commercially insured population from 14 different plans (n = 3,991). An abandoned prescription is one that was delivered to a pharmacy, but not picked up.[93] The authors found an association between cost sharing categories over $2,500 and abandonment rate.[94] Given these findings, I hypothesized that there would be greater treatment uptake after the availability of PharmaCare coverage, given that coverage would help decrease the up-front, out-of-pocket costs for patients, particularly those without a private drug plan.

3.1.4   Contributions of this study

To my knowledge, this is the first study utilizing interrupted time series to analyze trends in adherence, treatment uptake, and expenditure for sofosbuvir and ledipasvir-sofosbuvir following a change in public coverage. This will also be the first study of its kind to evaluate trends in the use of these therapies in BC. I hypothesized that adherence would be similar after public coverage. Although PharmaCare will help decrease cost-sharing, which has typically been linked to increased adherence in the literature, I predict that a person who paid for the treatment completely out-of-pocket would also have high motivation to adhere to treatment due to the large monetary investment. Providing information on trends will be helpful for policymakers in regards to resource planning.

3.2   Methods

3.2.1   Study context, data sources and study population

This study took place in BC, and used the same data sources and study population described in Chapter 2 (Appendix 2). As shown in Figure 3.1, only private payment was available between January 2014 and March 2015. After the PharmaCare policy change, public coverage was available in late March 2015/April 2015.

Although PharmaCare coverage began on March 23, 2015, March 2015 was still classified as being in the pre-period, as only three individuals began treatment under PharmaCare in that

month. The first treatment under PharmaCare began on March 31, 2015. Thus, it was appropriate to categorize March 2015 in the pre-period as PharmaCare coverage was minimal.

Figure 3.1 Study timeline
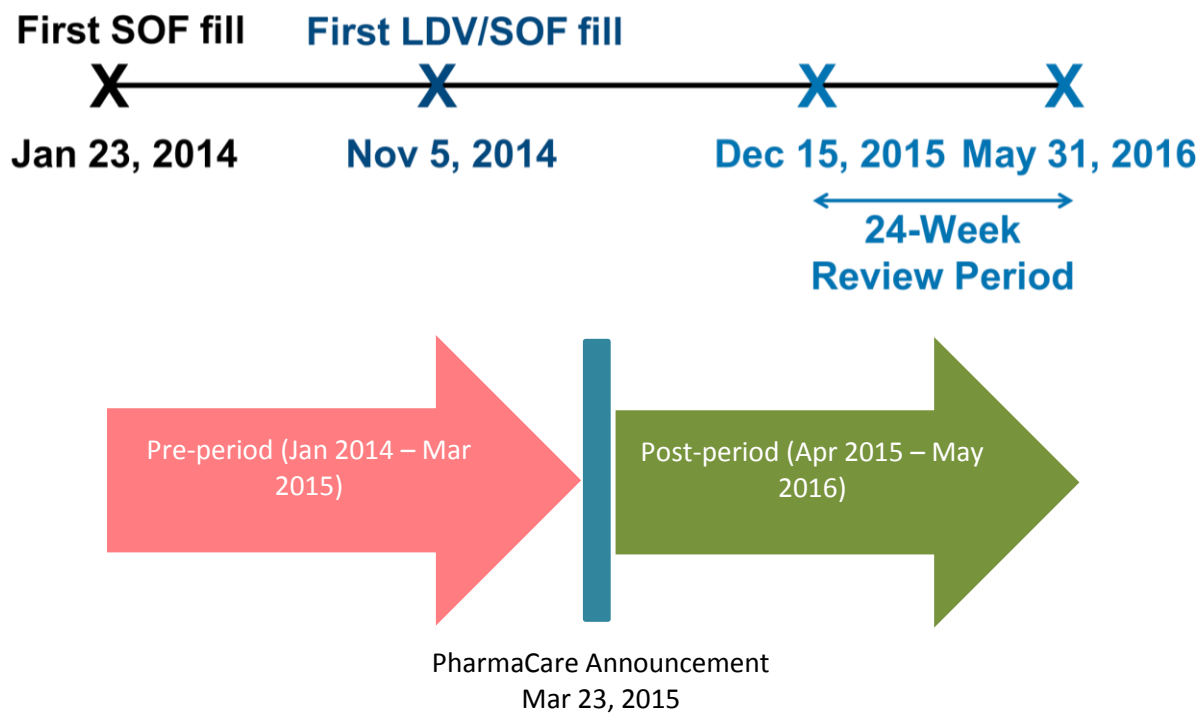
Inclusion

I included all 2,760 instances of sofosbuvir and ledipasvir-sofosbuvir treatments that were initiated from January 2014 to December 2015 as outlined in Chapter 2. For individuals who had more than one treatment – one sofosbuvir and one ledipasvir-sofosbuvir treatment – I kept both for these analyses.

3.2.2 Interrupted time series analysis

Interrupted time series (ITS) analysis is one of the most robust quasi-experimental study designs. The use of ITS in drug utilization research has been growing, and over half of studies in this area have evaluated drug policy changes.[95]

I analysed the impact of the PharmaCare policy on several outcomes using segmented regression analysis based on the following equation:[96]

$$Y_t = \beta_0 + \beta_1 * \text{Time} + \beta_2 * \text{Level} + \beta_3 * \text{Trend}$$

The following are the definitions for the variables used in the model:[96]

- **Intercept**: The intercept (β_0) represents the baseline value of the outcome at month zero.
- **Time**: This numbers the months in sequence starting from '1' in January 2014. The coefficient for time (β_1) denotes the change in the outcome per month based on the underlying trend from the pre-period.
- **Level**: '0' indicates the pre-period, from January 2014 to March 2015. '1' denotes the post-period where PharmaCare coverage was available, from April 2015 to May 2016. The coefficient for a level change (β_2) represents the change in the outcome per month immediately after the PharmaCare policy change.
- **Trend**: All months in the pre-period were marked as '0.' Trend numbers the months sequentially in the post-period, with '1' in April 2015. The coefficient for a trend change (β_3) estimates the change in the monthly trend of the outcome in the post-period compared to the pre-period.

Data points

Generally, ITS should contain a minimum of 12 time points in the pre-period and 12 time points in the post-period.[97] In my analysis, the monthly time points were the starting month of treatment for a patient.

In the study period, there were 15 data points in the pre-period and nine data points in the post-period. Since sofosbuvir dispensations spanned the entire study period, there were also 15 data points in the pre-period and nine data points in the post-period for the sofosbuvir stratified analysis. However, since the first prescription of ledipasvir-sofosbuvir occurred in November 2014, there were only five points in the pre-period and nine data points in the post-period. Since the analyses for ledipasvir-sofosbuvir may be underpowered because of the low number of

monthly data points and imbalanced number of points before and after the policy change, the findings from analyzing sofosbuvir and ledipasvir-sofosbuvir together may be more meaningful.

I examined several outcome variables (Y_t) in the ITS analyses:

Adherence

In Chapter 2, I found that PharmaCare coverage was associated with higher PDC and perfect adherence. In this chapter, I examined whether these adherence trends varied over time. I used the average PDC at each month, weighted by the number of individuals in that month.

Number of individuals treated

The total number of individuals who started treatment in each month was plotted at each time point.

Public and private expenditure

The total amounts of public and private payments in each month were separated and plotted at each time point. Public and private payment were calculated as follows:

- Public payment = total amount of claims paid (includes drug cost, professional services fee, and special services fee)
- Private payment = drug cost claimed + professional fee claimed + special services fee claimed – total claims paid
  = total cost claimed – public payment (total amount of claims paid)

Total cost claimed = drug cost claimed + professional fee claimed + special services fee claimed

The amount paid by PharmaCare (public payment) depended on the individual's plan. Private payment also included co-pay; thus, it was possible for an individual to have both public and private payment on the same dispensation.

3.2.3 Analysis

The analyses for this study were performed on SAS software, Version 9.4 of the SAS System for Windows, R Version 3.3.2, and RStudio Version 1.0.136.

3.3 Results

3.3.1 Adherence

Adherence rates in the period before public coverage were high, and remained high in the period following the coverage change. None of the findings for changes in level or trend were significant for both drugs together, nor sofosbuvir and ledipasvir-sofosbuvir stratified. Overall, this suggests that PharmaCare coverage did not impact average adherence rates.

Figure 3.2 shows a linear ITS model for sofosbuvir and ledipasvir-sofosbuvir. The trend suggested that PDC would go over one, which was impossible given the definition that maximum PDC is capped at 100%.

Figures 3.3 and 3.4 present the ITS models for sofosbuvir and ledipasvir-sofosbuvir respectively.

Figure 3.2 Interrupted time series model for the impact of PharmaCare on adherence to sofosbuvir and ledipasvir-sofosbuvir
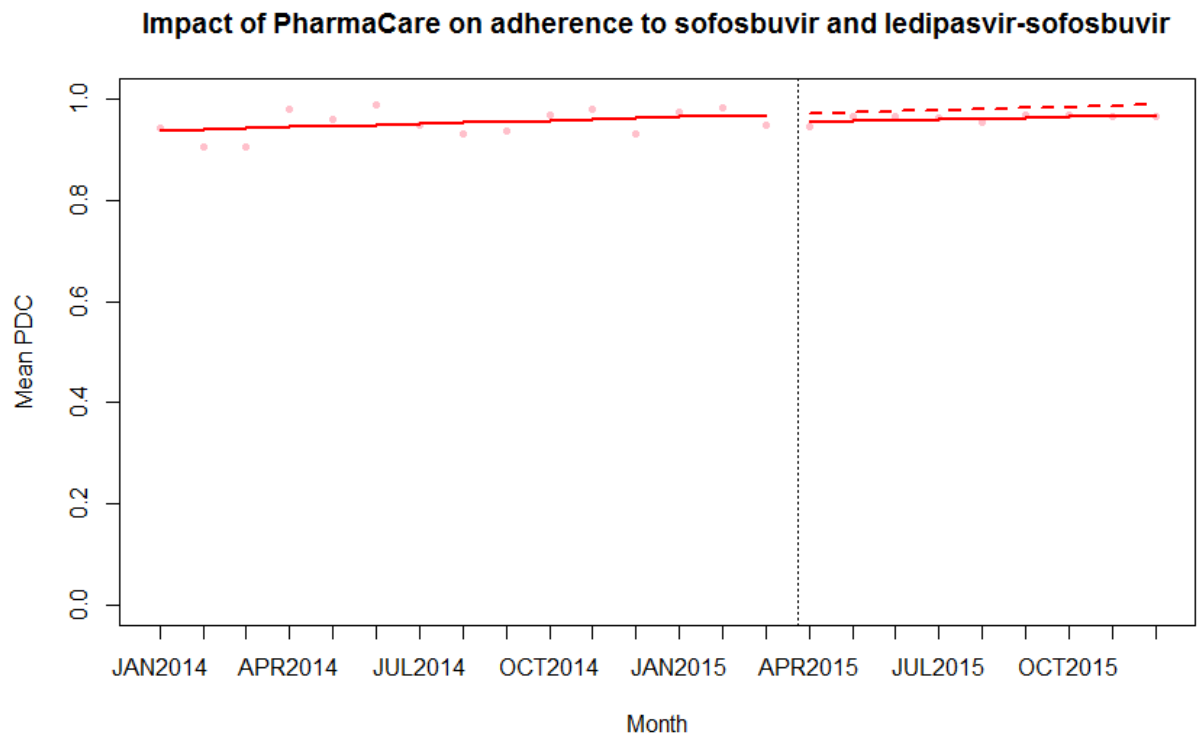
Figure 3.3 Interrupted time series model for the impact of PharmaCare on adherence to sofosbuvir

Impact of PharmaCare on adherence to sofosbuvir
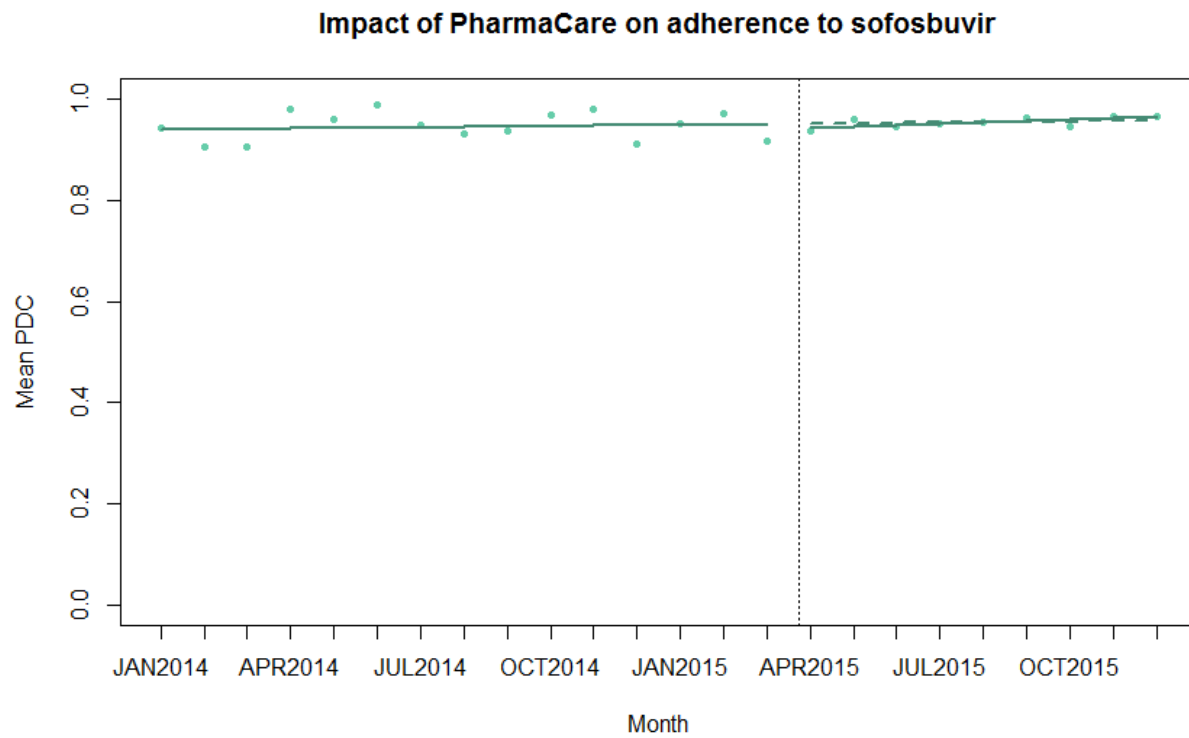
Figure 3.4 Interrupted time series model for the impact of PharmaCare on adherence to ledipasvir-sofosbuvir

Impact of PharmaCare on adherence to ledipasvir-sofosbuvir
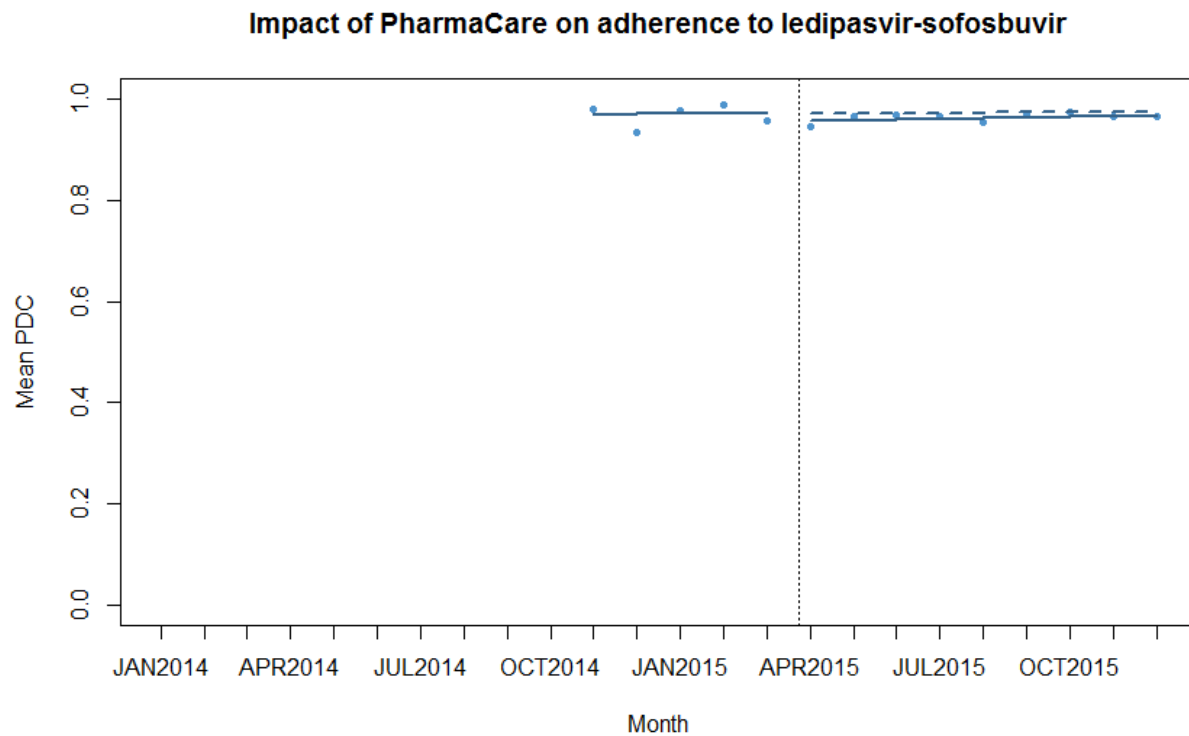
3.3.2   Treatment uptake

After the policy change, there was a sustained increase in treatment uptake per month across both drugs and ledipasvir-sofosbuvir alone, but not sofosbuvir alone. Thus, it appeared that the increase in level of treatment uptake when both drugs were analyzed together was driven primarily by ledipasvir-sofosbuvir. None of the findings for trend were significant for both drugs together, nor sofosbuvir and ledipasvir-sofosbuvir stratified.

Figure 3.5 Interrupted time series model for the impact of PharmaCare on treatment uptake of sofosbuvir and ledipasvir-sofosbuvir

Impact of PharmaCare on uptake of sofosbuvir & ledipasvir-sofosbuvir
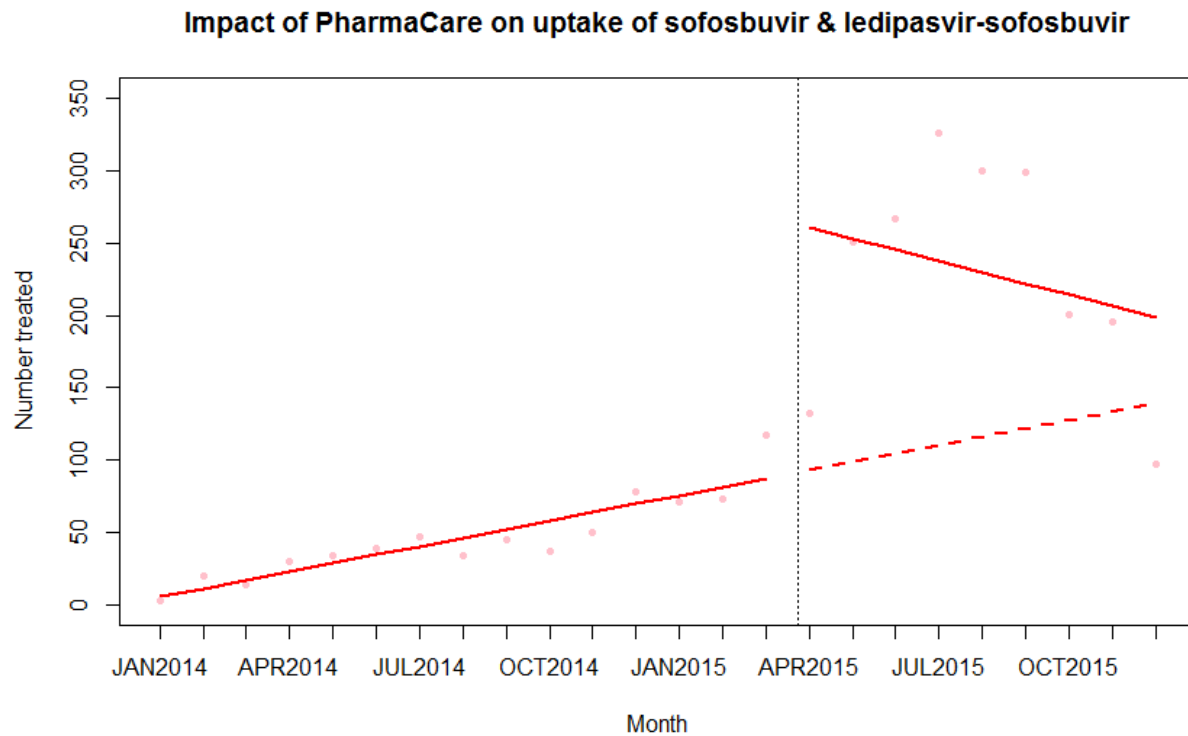
Across both drugs, after the policy change, there was a sustained increase of 182 new individuals treated per month (p = 0.0004). The decrease in treatment uptake of 14 individuals per month thereafter was not statistically significant, though it was close to significant (p = 0.07). This represents an increased uptake of 1,022 people in total from April 2015 to December 2015, compared to the counterfactual.

Figure 3.6 Interrupted time series model for the impact of PharmaCare on treatment uptake of sofosbuvir
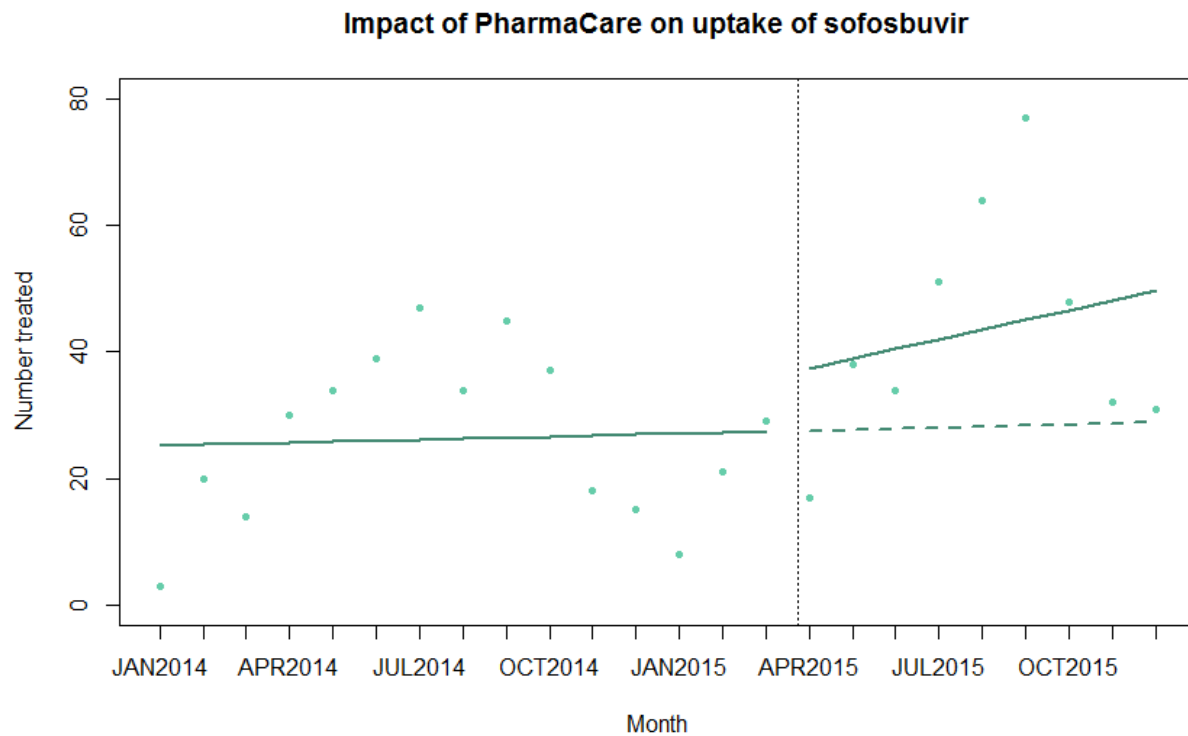
For sofosbuvir, after the policy change, the sustained increase of nine new individuals treated per month was not statistically significant (p = 0.55). The increase in treatment uptake of one individual per month thereafter was also not statistically significant (p = 0.55). This represents an increased uptake of 139 people in total from April 2015 to December 2015, compared to the counterfactual.

Figure 3.7 Interrupted time series model for the impact of PharmaCare on treatment uptake of ledipasvir-sofosbuvir

Impact of PharmaCare on uptake of ledipasvir-sofosbuvir
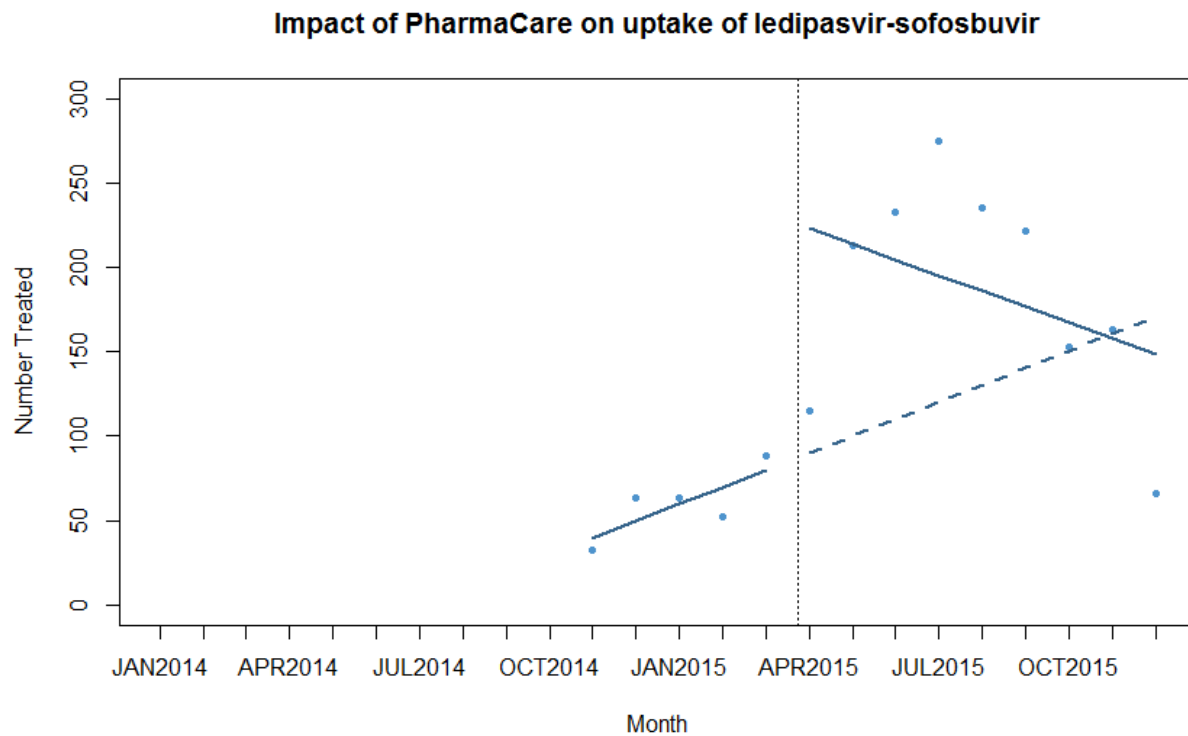
For ledipasvir-sofosbuvir, after the policy change, there was a sustained increase of 153 new individuals treated per month (p = 0.027). The decrease in treatment uptake of 19 individuals per month thereafter was also not statistically significant (p = 0.33). This represents an increased uptake of 503 people in total from April 2015 to December 2015, compared to the counterfactual.

3.3.3 Public and private expenditure

Public expenditure was $0 in the pre-period, given that PharmaCare coverage was not available. Following the start of public coverage, I observed statistically significant decreases of $1.68 million to $2.33 million in private expenditure in the post-period, as well as a statistically significant downward trend between $415,695 and $479,843 per month. Thus, it is clear that public coverage crowded out at least a portion of private payments. However, even if an individual received PharmaCare coverage, private insurance could still cover the deductible and required out-of-pocket payment as outlined by their PharmaCare plan.

Without phase in period

Figure 3.8 Interrupted time series model for the impact of PharmaCare on public and private expenditure on sofosbuvir and ledipasvir-sofosbuvir without phase in period

Impact of PharmaCare on public and private expenditure on sofosbuvir and ledipasvir-sofosbuvir
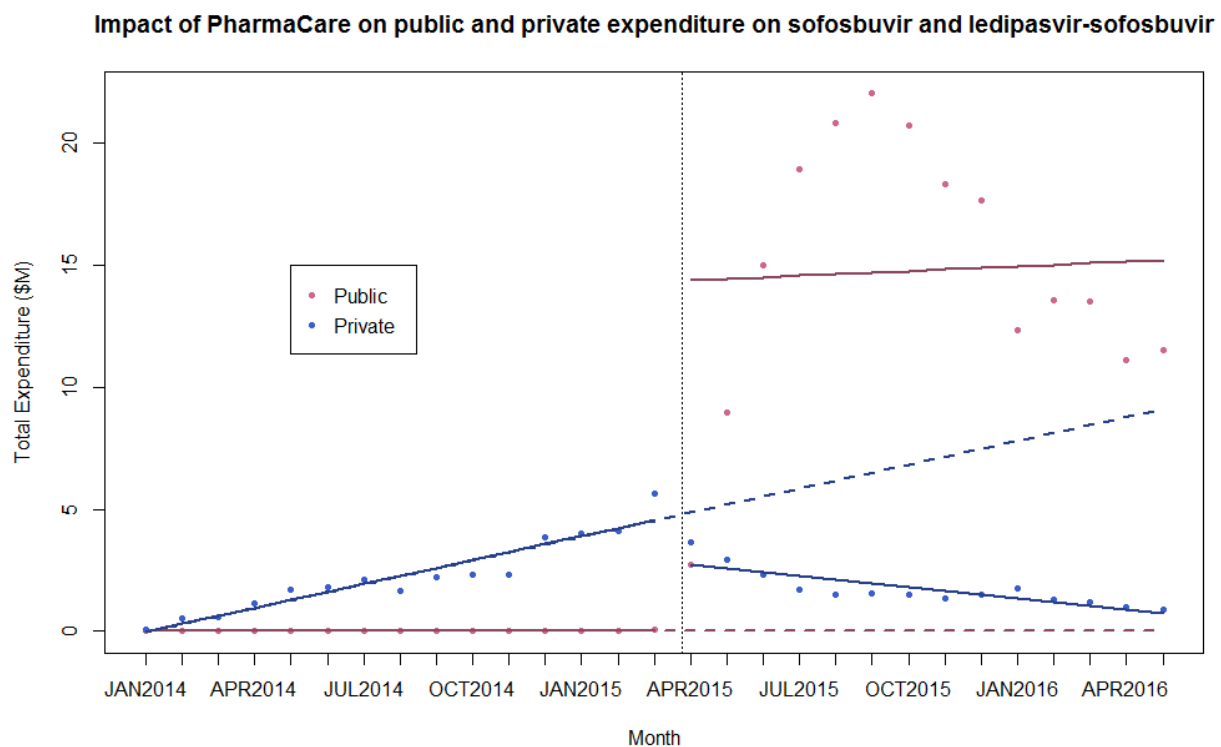
After the policy change, there was a sustained increase of $14.31 million in average monthly public expenditure (p < 0.001, 95% CI: $8.64 million, $19.99 million), and no significant change in expenditure per month thereafter (p = 0.86). After the policy change, there was a sustained

decrease of $1.68 million in average monthly private expenditure (p = 0.0001, 95% CI: -$2,37 million, -$981,865), and a $479,843 decrease per month (p < 0.001, 95% CI: -$562,812, -$396,875).

With phase in period

Figure 3.9 Interrupted time series model for the impact of PharmaCare on public and private expenditure on sofosbuvir and ledipasvir-sofosbuvir with phase in period
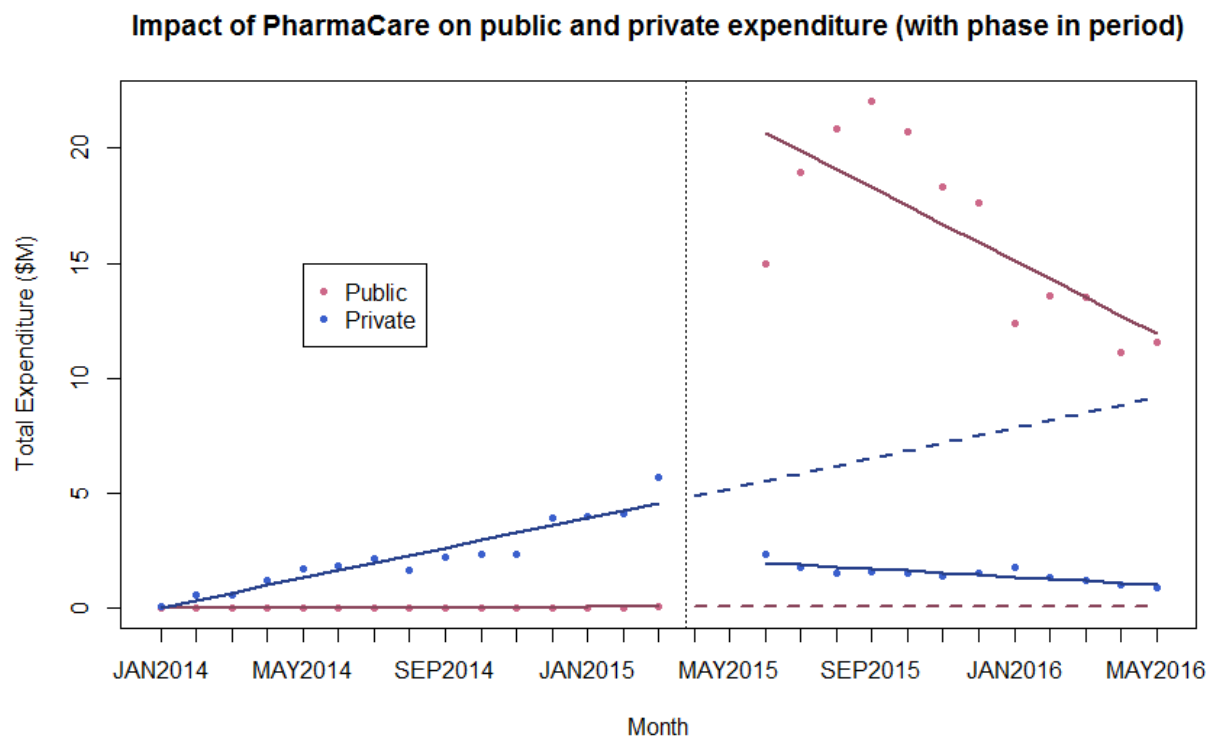
I performed further analysis to allow for a two-month phase-in period after the policy change, removing the April and May 2015 points. With the policy change, there was a sustained increase of $23.07 million in average monthly public expenditure (p < 0.001, 95% CI: $19.79 million, $26.35 million), and a decrease of $798,578 per month (p = 0.0003, 95% CI: -$1.17 million, -$428,828). After the policy change, there was a sustained decrease of $2.33 million in average monthly private expenditure (p < 0.001, 95% CI: -$3.07 million, -$1.59 million), and a $415,695 decrease per month (p < 0.001, 95% CI: -$499,154, -$332,236).

Table 3.1   Summary of output from interrupted time series analyses

Adherence	Level (PDC %) (95% CI)	p-value	Slope (PDC %) (95% CI)	p-value
Both	-1.68 (-9.70, 6.34)	0.69	-0.057 (-1.30, 1.19)	0.93
SOF	-1.19 (-5.37, 3.00)	0.58	0.22 (-0.49, 0.93)	0.55
LDV/SOF	-1.64 (-5.60, 2.33)	0.44	0.11 (-0.86, 1.09)	0.82
Treatment uptake	**Level (n persons) (95% CI)**	**p-value**	**Slope (n persons) (95% CI)**	**p-value**
Both	182 (97, 266)	0.0004*	-14 (-27, 0)	0.066
SOF	9 (-19, 36)	0.55	1 (-3, 6)	0.55
LDV/SOF	153 (37, 269)	0.027*	-19 (-57, 18)	0.33
Monthly expenditure (w/o phase-in)	**Level ($) (95% CI)**	**p-value**	**Slope ($) (95% CI)**	**p-value**
Public	14,314,560 (8,636,830, 19,992,290)	< 0.001*	62,900 (-614,019, 739,998)	0.86
Private	-1,677,682 (-2,373,498, -981,865)	0.0001*	-479,843 (-562,812, -396,875)	< 0.001*
Monthly expenditure (w/ phase-in)	**Level ($) (95% CI)**	**p-value**	**Slope ($) (95% CI)**	**p-value**
Public	23,067,920 (19,790,075, 26,345,764)	< 0.001*	-798,578 (-1,168,328, -428,828)	0.0003*
Private	-2,328,964 (-3,068,830, -1,589,098)	< 0.001*	-415,695 (-499,154, -332,236)	< 0.001*

*p < 0.05

3.4   Discussion

3.4.1   Overview of findings

Adherence

Overall, the introduction of PharmaCare coverage for sofosbuvir and ledipasvir-sofosbuvir did not impact adherence rates to these drugs. As shown in the ITS analyses, there was no statistically significant effect of PharmaCare on a level or trend change in mean monthly PDC. However, previous studies have shown that decreased out-of-pocket costs were associated with higher adherence in other drugs.[63,90] This was likely because adherence rates for sofosbuvir and ledipasvir-sofosbuvir were already high prior to the PharmaCare policy change. This may reflect the short duration of treatment and the severity of leaving HCV untreated. However, the overall high adherence rates across the pre- and post-periods were favourable, demonstrating that patients appeared to be taking the drugs for the full duration. In my study, there was no change in trend of adherence after the policy change, which aligned with Choudhry et al.'s findings.[90]

Treatment uptake

PharmaCare coverage did increase treatment uptake immediately when I examined both drugs and ledipasvir-sofosbuvir alone. I infer that some individuals, who had wanted HCV treatment in the pre-intervention period but were waiting for the government to eventually cover the drugs, received treatment immediately after the policy change and contributed to the surge in treatment uptake.

However, PharmaCare did not effect a statistically significant change in the trend of treatment uptake after the policy was implemented. The overall downward trend of uptake after the PharmaCare policy change, although not statistically significant, was expected, as there would eventually be fewer people left to be treated that fit into the current eligibility criteria. Since there were fewer points in the post-intervention period, it would be helpful to plot more points when new data is available to get a fuller picture of the trend. In the upcoming PharmaCare expansion, I would expect to see similar trends: a spike in treatment uptake when eligibility criteria become less strict, and an overall decrease in uptake over time as there are fewer people left in the treatment pool. These trends aligned with Liao and Fischer's findings for Medicaid,

where they also demonstrated a large increase in uptake in the beginning, which eventually slowed or stabilized.[92]

However, it was interesting that when the drugs were stratified, sofosbuvir showed an upward, although not significant, trend in treatment uptake after the policy change, while ledipasvir-sofosbuvir showed a downward trend. This may be because most of the individuals who benefitted from the policy change were prescribed ledipasvir-sofosbuvir. Thus, a large number of individuals received treatment soon after the policy change, and the eligible pool shrank over time as individuals were treated. It is possible that fewer individuals who benefitted from the policy change were prescribed sofosbuvir, and thus, there was no significant change in trend. The downward trend when both drugs were examined was driven primarily by ledipasvir-sofosbuvir, as there were a larger number of ledipasvir-sofosbuvir treatments than sofosbuvir.

Public and private expenditure

The increase in public expenditure also aligned with Liao and Fischer's findings for Medicaid.[92] However, after the policy change, it appeared that public expenditure was crowding out at least part of the private expenditure for sofosbuvir and ledipasvir-sofosbuvir. It was possible that those who had private insurance had already obtained treatment prior to the policy change, and thus, during the post-period, there were fewer of these individuals left to be treated, thus driving down the monthly private expenditure. It was also possible that with the introduction of PharmaCare coverage, some private plans had reduced expenditures through members surpassing their PharmaCare deductible and thus becoming eligible for public coverage. As the public drug plan acts as first payer in BC, this would have the effect of driving down private expenditures.

3.4.2 Strengths

As with the first study, another key strength of this study came from examining a general population. To my knowledge, this is the first study that used interrupted time series analysis on sofosbuvir and ledipasvir-sofosbuvir. Interrupted time series is one of the most robust quasi-experimental study designs, and has not been previously used to study the impact of public prescription drug coverage of sofosbuvir and ledipasvir-sofosbuvir.

3.4.3 Limitations

Although ITS analysis is one of the most robust quasi-experimental designs, there are some limitations to using this study design, given the available data. I had nine data points in the post-period, which was less than the general recommendation of 12 data points. Furthermore, for ledipasvir-sofosbuvir, there were only five data points in the pre-period. The low number of data points in my study may have resulted in insufficient statistical power to find true effects. There were also fewer than 100 observations in some of the data points, which may not have captured an acceptable level of variability.[96] These limitations were due to the size of the data currently available. When the PharmaCare program expands over the next two years, a larger study population will be available for analyses, which would likely resolve the limitations I faced here.

Furthermore, using a linear trend in the interrupted time series models may not have always fit the data. For example, in the PDC graphs, the counterfactual line crossed 1, which should be impossible, since PDC has a ceiling of 1. In addition, the data points in the post-period for the treatment uptake and expenditure graphs showed a parabolic shape, which was not ideal for the model used. Before finalizing the linear model, I tested a model with a quadratic term, which did not improve model fit.

The PharmaNet data lacks the ability to stratify the types of private payment available. The numbers I reported in this study included individual out-of-pocket payments (either paying for the treatment entirely on their own or co-payment) and the amount covered by private insurance. It would be useful to separate private payment into further categories to provide a clearer assessment of the impact of payment type on adherence. However, given the high cost of these medicines, I think it is likely that these amounts largely came from private insurance plans.

3.4.4 Implications for policy, practice, and research

As I found that PharmaCare coverage did not impact adherence rates, the primary motivation of this policy should not be to improve adherence rates, but rather to address other objectives, such as increasing affordability and thus availability of the treatment. Given the significant increases in treatment uptake and public expenditure immediately after the availability of public coverage, governments and other payers should carefully budget in advance to ensure that they have sufficient resources to operate the program. To treat 5,000 individuals per year at a cost of

around $55,000 per treatment, the government would need to budget $275 million per year. Although continuing to offer public coverage of HCV treatments would be costly for society, ultimately, the program advances health equity. Prior to the availability of public coverage, people of low socioeconomic status and PWIDs were less likely to receive treatment.[6,72] Furthermore, improving coverage to scale-up treatment is one way to help achieve the World Health Organization's goal to eliminate HCV worldwide by 2030.[98]

Alongside this challenge, decision makers should also consider that despite the high upfront monetary costs of sofosbuvir and ledipasvir-sofosbuvir, HCV-related health costs would likely be lower in the future, due to the decreased burden of HCV from the high effectiveness of DAAs. This would be a fruitful area for future research studies.

Furthermore, with an expected surge in treatment uptake, policymakers should also ensure that there is enough capacity of clinicians who can prescribe and provide treatment to the increased number of individuals who are seeking this care. This could mean rolling out programs in gradual phases to avoid a one-time surge in uptake and costs.

3.5   Conclusion

Overall, PharmaCare coverage increased public expenditure and resulted in more individuals being able to access treatment. However, the effect of public coverage on adherence was not significant when examined over time, likely due to high adherence rates throughout our study period. This is a promising result, as it suggests public coverage does not result in an increase in poorer adherence to these expensive medicines. With the expansion of PharmaCare coverage in BC, the government should brace for a significant increase in treatment uptake and public costs, and plan resources accordingly.

4 Conclusions

4.1 Summary of Findings

4.1.1 Introduction

With the expected growth of spending on specialty pharmaceuticals, such as sofosbuvir and ledipasvir-sofosbuvir,[2] ensuring that the drugs provide good value for money is a key concern for the public healthcare system. High adherence to treatment is one way of maximizing value for money.[47] Currently there are 50,000 people living with HCV in BC.[6] The cost of providing DAA treatment to all of these individuals at once would cost at least $1.8 billion, almost half of the annual public drug expenditure in BC.[45] Given the burden of public coverage of sofosbuvir and ledipasvir-sofosbuvir in BC, I examined adherence in this thesis to evaluate real-world use of these drugs.

My thesis aimed to address several objectives: (1) descriptive analyses of overall adherence to sofosbuvir and ledipasvir-sofosbuvir, (2) the relationship between patient factors and adherence, and (3) the impact of PharmaCare coverage on adherence, treatment uptake, and private and public expenditure. To examine these objectives, I performed two independent studies using administrative data from the BC Hepatitis Testers Cohort: the first to address objectives (1) and (2), and the second to address objective (3).

4.1.2 Adherence to sofosbuvir and ledipasvir-sofosbuvir in British Columbia

In the first study, I examined overall adherence rates and impact of patient factors on adherence. From a review of the literature, this is the first study that examined adherence rates to these drugs in a general population. This study aimed to evaluate whether sofosbuvir and ledipasvir-sofosbuvir were taken properly in the real world. Furthermore, I aimed to find factors that were associated with low adherence, which would be useful information for physicians to help identify at-risk patients and provide support to achieve higher adherence.

I reported adherence rates for eligible treatments for sofosbuvir and ledipasvir-sofosbuvir that were initiated between January 2014 and December 15, 2015. Overall, adherence rates were high, which were in line with the limited published studies; mean PDC for both drugs, sofosbuvir, and ledipasvir-sofosbuvir were 96.2%, 95.4%, and 96.5% respectively.

Second, I examined the relationship between various patient factors and full adherence (PDC = 100%) in a multivariable logistic regression model with fixed effects. I was particularly interested in examining the impact of injection drug use, opioid substitution therapy, problematic alcohol use, and major mental illness on adherence, given the controversy of treating individuals with these factors. I found that, adjusted for the other variables in the model, there was no significant difference in the proportion of individuals with perfect adherence who are IDU, receiving OST and have a history of problematic alcohol use, compared to those without.

Adjusted for the other variables in the model, I found that being white, having moderate socioeconomic status, having major mental illness, and longer treatment lengths (112 days and 168 days) were associated with a lower proportion of individuals with full adherence. I found that being over the age of 60 and receiving PharmaCare coverage were associated with a higher proportion of individuals with full adherence.

This study on adherence and patient factors provided favourable insights that adherence rates were high across the board, and that sofosbuvir and ledipasvir-sofosbuvir were taken properly in the real world. Furthermore, it provided evidence to inform policy that there should not be restrictions on coverage policies based on patient factors, such as injection drug use.

4.1.3   Impact of PharmaCare coverage on sofosbuvir and ledipasvir-sofosbuvir in British Columbia

In the second study, I examined the impact of PharmaCare coverage on adherence, treatment uptake, and public and private expenditure using interrupted time series analysis. To my knowledge, this is also the first study of its kind for sofosbuvir and ledipasvir-sofosbuvir. With more expensive, specialty drugs in the pipeline, and the imminent expansion of HCV drug coverage in BC, the insights on the impact of public drug coverage from this study will help decision makers plan for future drug coverage.

I found no significant impact of PharmaCare on adherence over time. This was likely because adherence rates were high throughout the entire study period. PharmaCare coverage did have a significant impact on treatment uptake across both drugs and ledipasvir-sofosbuvir alone. However, the implementation of PharmaCare coverage did not have a significant impact on treatment uptake on sofosbuvir alone. This was likely due to the close timing of the PharmaCare

policy change in late March 2015 and the first prescription of ledipasvir-sofosbuvir in November 2014.

PharmaCare did have a significant impact on expenditures: public spending increased around $23 million per month within two months of the March 2015 announcement, but decreased approximately $800,000 per month thereafter. This large increase in public payment crowded out at least a portion of private expenditure; private spending decreased $2.3 million per month within months of the policy change, and continued decreasing approximately $400,000 per month thereafter.

In summary, the availability of PharmaCare coverage for sofosbuvir and ledipasvir-sofosbuvir did not impact trends in adherence, but did increase treatment uptake of both drugs. Furthermore, public expenditure increased after the policy change, crowding out some of the private expenditure.

4.2   Recommendations

4.2.1   Recommendations for policy and practice

No restrictive guidelines for public coverage

My findings suggest that restrictions on coverage, such as injection drug use, opioid substitution therapy, should not be in place. Payers should not respond to political pressures to restrict coverage on these grounds. Given the high budgetary impact of sofosbuvir and ledipasvir-sofosbuvir on formularies, it is acceptable for payers to offer coverage in phases, from more restrictive to less restrictive criteria. My findings suggest that these criteria should not be based on factors related to drug use.

Identifying major mental illness as a risk factor

I noted that major mental illness was associated with a lower proportion of individuals who achieved perfect adherence. Based on this finding, I suggest that clinicians examine patients' mental health history prior to commencing HCV treatment so that additional support can be provided where it might be needed.

Prescribe lower treatment durations when possible

Furthermore, I found that longer treatment durations (112 and 168 days) were associated with lower proportion of individuals achieving full adherence. When possible, clinicians should prescribe a lower treatment duration when appropriate. For example, a genotype 1 individual who is treatment naïve and does not have cirrhosis would be eligible for either eight to 12 weeks of ledipasvir-sofosbuvir or 12 weeks of sofosbuvir plus pegylated interferon and ribavirin. If possible, I would recommend the eight- to 12-week treatment, with a shorter number of weeks if a patient has achieved a low viral load. Early evidence from a phase 2a study for genotype 1b patients without cirrhosis (n = 26) suggests that treatment could be further shortened down to three weeks for some patients.[99] This would not only be beneficial for improving full adherence as shown in my study, but also improve access to treatment due to lower direct costs.[100] However, further research needs to be performed in larger study populations before such short durations are implemented in clinical practice.[100]

In summary, my study shows that adherence to sofosbuvir and ledipasvir-sofosbuvir has been high in BC, and supports policy to provide treatment to all individuals with HCV, regardless of their characteristics. With any expansion in treatment coverage, payers should be aware of the immediate impact on budgets and resources.

4.2.2   Recommendations for research

Observational study after new PharmaCare policy change

I recommend that studies, analogous to the ones in my thesis, be performed after the expanded PharmaCare coverage of HCV treatments has been fully implemented. This would allow for a unique opportunity to evaluate the impact of not one, but two policy changes in the same jurisdiction. Furthermore, given that the first policy change was restrictive and the second policy change will remove these criteria, this future study would also evaluate whether incremental changes coverage criteria would impact adherence, treatment uptake, and expenditure. This would also provide a longer time frame of data points to use for interrupted time series analyses.

Observational study using interrupted time series with control

The findings of this study could be further strengthened by incorporating a control group into the interrupted time series models. This control group could be a comparative population in another jurisdiction where the public coverage was not introduced during the study period. Adding a control would allow for comparison of slope and trend between two populations, and help reduce potential threats to internal validity, particularly history bias. I am not aware of any external events that occurred at the same time as the PharmaCare policy change. However, by adding a control group, I would be able to mitigate any possible history bias. I would be able to see how much of the effects in BC can be attributed to the intervention itself if the control group was not affected by the same possible external events as the BC group.

Observational study in another jurisdiction

BC has the highest population of individuals with HCV in Canada. This may mean that the characteristics of the population are different from others in Canada. Further study in general populations in other jurisdictions would be useful to validate our findings. Recently, after the pCPA deal, Ontario also announced expansion in coverage,[42] so this could be a potential jurisdiction to examine.

Observational study on HCV incidence, prevalence, and outcomes

Beyond adherence, treatment uptake, and expenditures, other public health outcomes, such as HCV incidence and prevalence are also key considerations for the public healthcare system. Given that if an individual is cured of HCV, they would be less likely to transmit the infection to others, I recommend that a similar study be performed using interrupted time series analysis to examine the trends in HCV incidence and prevalence before and after the policy change. Furthermore, I also recommend a study that examines the impact of the policy on future medical outcomes (e.g. cirrhosis, hepatocellular carcinoma) and health system costs related to HCV. This could be performed by either tracking patients longitudinally or through modelling.

4.3   Final Conclusions

4.3.1   Implication of specialty pharmaceuticals

With the growing issue of specialty pharmaceuticals on budgets, payers need to devise strategies to manage future costs. The decision to expand HCV treatments in BC[41] comes with an opportunity cost of medicines for other diseases, as well as other services in the health care system. BC's strategy to gradually expand criteria for HCV treatment[43] is one way to help spread out the costs and alleviate the immediate budgetary impact. To decide on the funding of specialty pharmaceuticals, decision makers can employ tools, such as cost-benefit analyses, to determine the future health costs saved by treating all or certain groups of patients with high-cost drugs. For example, in the case of HCV treatments, decision makers can employ cost-benefit analyses to determine the future health costs associated with advanced stages of liver disease, such as cirrhosis and hepatocellular carcinoma.

However, although this expansion program was possible with the deals made with pharmaceutical companies to lower HCV treatment drug costs,[41] governments should explore further policy options that reduce costs of specialty pharmaceuticals across the board.

Bibliography

1.   Gleason PP, Alexander CA, Starner CI, et al. Health Plan Utilization and Costs of Specialty Drugs Within 4 Chronic Conditions. *J Manag Care Pharm*. 2013;19(7):542-548.

2.   Health Policy Brief: Specialty Pharmaceuticals. *Health Aff*. 2013;(November 25, 2013).

3.   Marshall AD, Saeed S, Barrett L, et al. Restrictions for reimbursement of direct-acting antiviral treatment for hepatitis C virus infection in Canada: a descriptive study. *C Open*. 2016;4(4):E605-E614. doi:10.9778/cmajo.20160008.

4.   Chen SL, Morgan TR. The Natural History of Hepatitis C Virus (HCV) Infection. *Int J Med Sci*. 2006;3(2):47-52.

5.   Myers RP, Krajden M, Bilodeau M, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. *Can J Gastroenterol Hepatol*. 2014;28(5):243-250.

6.   Janjua NZ, Kuo M, Yu A, et al. The Population Level Cascade of Care for Hepatitis C in British Columbia , Canada : The BC Hepatitis Testers Cohort (BC-HTC). *EBioMedicine*. 2016:4-10. doi:10.1016/j.ebiom.2016.08.035.

7.   BC Centre for Disease Control. *British Columbia Annual Summary of Reportable Diseases 2015*. Vancouver, BC; 2016.

8.   HealthLinkBC. Hepatitis C Virus Infection. HealthLinkBC Files. http://www.healthlinkbc.ca/healthfiles/hfile40a.stm. Published 2013. Accessed November 28, 2015.

9.   Janjua NZ, Yu A, Kuo M, et al. Twin epidemics of new and prevalent hepatitis C infections in Canada : BC Hepatitis Testers Cohort. *BMC Infect Dis*. 2016;16(334). doi:10.1186/s12879-016-1683-z.

10.   Islam N, Krajden M, Shoveller J, et al. Role of primary T-cell immunodeficiency and hepatitis B coinfection on spontaneous clearance of hepatitis C: The BC Hepatitis Testers Cohort. *J Viral Hepat*. 2017;24(5):421-429. doi:10.1111/jvh.12650.

11. Westbrook RH, Dusheiko G. Natural history of hepatitis C. *J Hepatol*. 2014;61(1 Supplement):S58-S68. doi:10.1016/j.jhep.2014.07.012.

12. Messina JP, Humphreys I, Flaxman A, et al. Global Distribution and Prevalence of Hepatitis C Virus Genotypes. *Hepatology*. 2014;61(1):77-87. doi:10.1002/hep.27259.

13. Janjua NZ, Kuo M, Chong M, Yu A, Alvarez M. Assessing Hepatitis C Burden and Treatment Effectiveness through the British Columbia Hepatitis Testers Cohort (BC-HTC): Design and Characteristics of Linked and Unlinked Participants. *PLoS One*. 2016;11(3):1-19. doi:10.1371/journal.pone.0150176.

14. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, Management, and Treatment of Hepatitis C. *Hepatology*. 2004;39(4):1147-1171. doi:10.1002/hep.20119.

15. Schaefer M, Mauss S. Hepatitis C Treatment in Patients with Drug Addiction: Clinical Management of Interferon-Alpha-Associated Psychiatric Side Effects. *Curr Drug Abuse Rev*. 2008;1(2):177-187. doi:10.2174/1874473710801020177.

16. Castera L, Constant A, Henry C, et al. Impact on adherence and sustained virological response of psychiatric side effects during peginterferon and ribavirin therapy for chronic hepatitis C. *Aliment Pharmacol Ther*. 2006;24(8):1223-1230. doi:10.1111/j.1365-2036.2006.03107.x.

17. Health Canada. Summary Basis of Decision (SBD) for Sovaldi. https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00188. Published 2016. Accessed April 24, 2017.

18. Health Canada. Summary Basis of Decision (SBD) for Harvoni. https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00249. Published 2016. Accessed April 24, 2017.

19. Marino Z, Van Bommel F, Forns X, Berg T. New concepts of sofosbuvir-based treatment regimens in patients with hepatitis C. *Gut*. 2014;63(2):207-215.

20. Younossi ZM, Park H, Gordon SC, et al. Real-World Outcomes of Ledipasvir/Sofosbuvir in Treatment-Naïve Patients With Hepatitis C. *Am J Manag Care*. 2016;22(Special Issue

No. 6):SP205-SP211.

21.   Myers R, Ramji A, Bilodeau M, Wong S, Feld J. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. *Can J Gastroenterol Hepatol*. 2015;29(1):19-34.

22.   Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Effectiveness of sofosbuvir-based regimens in genotype 1 and 2 hepatitis C virus infection in 4026 U.S. Veterans. *Aliment Pharmacol Ther*. 2015;42(5):559-573. doi:10.1111/apt.13300.

23.   U.S. Food & Drug Administration (FDA). SOVALDI® (sofosbuvir) tablets, for oral use. 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204671s004lbl.pdf. Accessed November 13, 2017.

24.   U.S. Food & Drug Administration (FDA). HARVONI (ledipasvir/sofosbuvir). 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205834s002lbl.pdf. Accessed November 13, 2017.

25.   Ministry of Health. Limited Coverage Drugs - Sofosbuvir. http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-sofosbuvir. Accessed February 10, 2016.

26.   Ministry of Health. Limited Coverage Drugs – Ledipasvir-Sofosbuvir. http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-ledipasvir-sofosbuvir. Accessed February 10, 2016.

27.   Ministry of Health. Limited Coverage Drugs - Ribavirin with Pegylated Interferon. http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-ribavirin-with-pegylated-interferon. Accessed April 16, 2016.

28.   Ministry of Health. Limited Coverage Drugs - Boceprevir. http://www2.gov.bc.ca/gov/content/health/practitioner-professional-

resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-boceprevir. Accessed April 20, 2016.

29.   Ministry of Health. Limited Coverage Drugs - Simeprevir. http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-simeprevir. Accessed April 20, 2016.

30.   Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: A cure and so much more. *Clin Infect Dis*. 2011;52(7):889-900. doi:10.1093/cid/cir076.

31.   Poordad F, McCone J, Bacon BR, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. *N Engl J Med*. 2011;364(13):1195-1206. doi:10.1056/NEJMoa1207363.

32.   Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1207-1217. doi:10.1056/NEJMoa1009482.

33.   Canadian Agency for Drugs and Techology in Health. CADTH Common Drug Review (CDR). https://www.cadth.ca/about-cadth/what-we-do/products-services/cdr. Accessed September 9, 2017.

34.   Canadian Agency for Drugs and Techology in Health. *CADTH Canadian Drug Expert Committee Final Recommendation: Sofosbuvir*.; 2016.

35.   Canadian Agency for Drugs and Techology in Health. *CADTH Canadian Drug Expert Committee Final Recommendation: Ledipasvir-Sofosbuvir*.; 2016.

36.   Ministry of Health. PharmaCare for B.C. Residents. http://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents. Accessed April 24, 2017.

37.   Ministry of Health. Fair PharmaCare Plan. http://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/fpc01.pdf. Published 2016. Accessed November 13, 2017.

38. Ministry of Health. PharmaCare Special Authority. http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority. Accessed November 16, 2015.

39. Ministry of Health. B.C covers two curative hepatitis C drugs. https://news.gov.bc.ca/stories/bc-covers-two-curative-hepatitis-c-drugs. Published 2015. Accessed April 24, 2017.

40. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, Management, and Treatment of Hepatitis C: An Update. *Hepatology*. 2009;49(4):1335-1374. doi:10.1002/hep.22759.

41. Ministry of Health. More patients to benefit from hepatitis C treatments. https://news.gov.bc.ca/releases/2017HLTH0037-000374. Published 2017. Accessed April 17, 2017.

42. Grant K. Deal reduces price of life-saving hepatitis C drugs for Canadians. *The Globe and Mail*. http://www.theglobeandmail.com/news/national/deal-reduces-price-of-life-saving-hepatitis-c-drugs-for-canadians/article34107225/. Published February 22, 2017.

43. Ministry of Health. PharmaCare Newsletter 17-004. http://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/newsletters/news17-004.pdf. Published 2017. Accessed November 13, 2017.

44. Canadian Institute for Health Information. *Prescribed Drug Spending in Canada, 2016: A Focus on Public Drug Programs*. Ottawa, ON; 2016.

45. Canadian Institute for Health Information. *National Health Expenditure Trends, 1975 to 2016*. Ottawa, ON; 2016.

46. Osterberg L, Blaschke T. Adherence to Medication. *N Engl J Med*. 2005;353(5):487-497. doi:10.1056/NEJMra050100.

47. Petersen T, Townsend K, Gordon LA, et al. High adherence to all-oral directly acting antiviral HCV therapy among an inner-city patient population in a phase 2a study. *Hepatol Int*. 2015;10(2):310-319. doi:10.1007/s12072-015-9680-7.

48.   Kamble P, Walker DR, Marx S, et al. Adherence and discontinuation rates of sofosbuvir-based regimens: modeling real-world experience in a large managed care organization. 2015.

49.   Butt AA, Yan P, Shaikh OS, Chung RT, Sherman KE. Treatment adherence and virological response rates in hepatitis C virus infected persons treated with sofosbuvir-based regimens: results from ERCHIVES. *Liver Int*. 2016;36(9):1275-1283. doi:10.1111/liv.13103.

50.   Louie V, Latt NL, Gharibian D, et al. Real-World Experiences With a Direct-Acting Antiviral Agent for Patients With Hepatitis C Virus Infection. *Perm J*. 2017;21:1-6.

51.   Trombatt WD, Koerner PH, Craft ZN, Miller RT, Kamal KM. Retrospective Analysis of the Medication Utilization and Clinical Outcomes of Patients Treated with Various Regimens for Hepatitis C Infection. *J Pharm Pract*. 2017;30(2):154-161. doi:10.1177/0897190015626008.

52.   Foster GR. Injecting drug users with chronic hepatitis C: Should they be offered antiviral therapy? *Addiction*. 2008;103(9):1412-1413. doi:10.1111/j.1360-0443.2008.02214.x.

53.   Mehta SH, Genberg BL, Astemborski J, et al. Limited Uptake of Hepatitis C Treatment Among Injection Drug Users. *J Community Health*. 2008;33(3):126-133. doi:10.1007/s10900-007-9083-3.

54.   Grebely J, Oser M, Taylor LE, Dore GJ. Breaking Down the Barriers to Hepatitis C Virus (HCV) Treatment Among Individuals With HCV/HIV Coinfection: Action Required at the System, Provider, and Patient Levels. *J Infect Dis*. 2013;207(suppl_1):S19-S25. doi:10.1093/infdis/jis928.

55.   Taylor LE, Swan T, Matthews G V. Management of Hepatitis C Virus/HIV Coinfection Among People Who Use Drugs in the Era of Direct-Acting Antiviral-Based Therapy. *Clin Infect Dis*. 2013;57(Suppl 2):118-124. doi:10.1093/cid/cit326.

56.   Cyr MC, Beauchesne MF, Lemiere C, Blais L. Comparison of the adherence and persistence to inhaled corticosteroids among adult patients with public and private drug

insurance plans. *J Popul Ther Clin Pharmacol*. 2013;20(1):26-41.

57.   Assayag J, Forget A, Kettani FZ, Beauchesne MF, Moisan J, Blais L. The impact of the type of insurance plan on adherence and persistence with antidepressants: A matched cohort study. *Can J Psychiatry*. 2013;58(4):233-239.

58.   Despres F, Perreault S, Lalonde L, Forget A, Kettani FZ, Blais L. Impact of drug plans on adherence to and the cost of antihypertensive medications among patients covered by a universal drug insurance program. *Can J Cardiol*. 2014;30(5):560-567. doi:10.1016/j.cjca.2013.11.032.

59.   Daw J, Morgan SG. Stitching the gaps in the Canadian public drug coverage patchwork? A review of provincial pharmacare policy changes from 2000 to 2010. *Health Policy (New York)*. 2012;104(1):19-26. doi:10.1016/j.healthpol.2011.08.015.Stitching.

60.   Law MR, Cheng L, Dhalla IA, Heard D, Morgan SG. The effect of cost on adherence to prescription medications in Canada. *Can Med Assoc J*. 2012;184(3):297-302. doi:10.1503/cmaj.111270.

61.   Sokol MC, McGuigan K a, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005;43(6):521-530. doi:10.1097/01.mlr.0000163641.86870.af.

62.   Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: A proof-of-concept phase 2A cohort study. *Lancet*. 2015;385(9973):1107-1113. doi:10.1016/S0140-6736(14)61228-9.

63.   Viswanathan M, Golin CE, Jones CD, et al. Interventions to Improve Adherence to Self-administered Medications for Chronic Diseases in the United States: A Systematic Review. *Ann Intern Med*. 2012;157(11):785-795.

64.   Eaddy MT, Cook CL, O'Day K, Burch SP, Cantrell CR. How Patient Cost-Sharing Trends Affect Adherence and Outomces: A Literature Review. *Pharm Ther*. 2012;37(1):45-55.

65.   Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: A proposal for standard definitions and preferred measures. *Ann*

Pharmacother. 2006;40(7-8):1280-1288. doi:10.1345/aph.1H018.

66. Fairman K, Matheral B. Evaluating Medication Adherence: Which Measure Is Right for Your Program? *J Manag Care Pharm*. 2000;6(6):499-504.

67. Younossi ZM, Stepanova M, Henry L, Nader F, Younossi Y, Hunt S. Adherence to treatment of chronic hepatitis C: from interferon containing regimens to interferon and ribavirin free regimens. *Medicine (Baltimore)*. 2016;95(28):1-8.

68. Lo Re III V, Amorosa VK, Localio AR, et al. Adherence to Hepatitis C Virus Therapy and Early Virologic Outcomes. *Clin Infect Dis*. 2009;48(2):186-193. doi:10.1086/595685.Adherence.

69. Lieveld FI, Van Vlerken LG, Siersema PD, Van Erpecum K. Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review. *Ann Hepatol*. 2013;12(3):380-391.

70. Tang LSY, Masur J, Sims Z, et al. Safe and effective sofosbuvir-based therapy in patients with mental health disease on hepatitis C virus treatment. *World J Hepatol*. 2016;8(31):1318-1326. doi:10.4254/wjh.v8.i31.1318.

71. Underhill K. Paying for Prevention: Challenges to Health Insurance Coverage for Biomedical HIV Prevention in the United States. *Am J Law Med*. 2012;38(4):607-666.

72. Janjua NZ, Islam N, Wong J, et al. Shift in disparities in hepatitis C treatment from interferon to DAA era: A population--based cohort study. *J Viral Hepat*. 2017;24(8):624-630. doi:10.1111/jvh.12684.

73. Grebely J, Bruneau J, Lazarus J V, et al. Research priorities to achieve universal access to hepatitis C prevention, management and direct-acting antiviral treatment among people who inject drugs. *Int J Drug Policy*. 2017;47(September 2017):51-60. doi:10.1016/j.drugpo.2017.05.019.

74. Gonzalez SA, Fierer DS, Talal AH. Medical and Behavioral Approaches to Engage People Who Inject Drugs Into Care for Hepatitis C Virus Infection. *Addict Disord Their Treat*. 2017;16(2):S1-S23. doi:10.1097/ADT.0000000000000104.

75. Grebely J, Hajarizadeh B, Dore GJ. Direct-acting antiviral agents for HCV infection affecting people who inject drugs. *Nat Rev Gastroenterol Hepatol*. 2017. doi:10.1038/nrgastro.2017.106.

76. Morris L, Smirnov A, Kvassay A, et al. Initial outcomes of integrated community-based hepatitis C treatment for people who inject drugs: Findings from the Queensland Injectors' Health Network. *Int J Drug Policy*. 2017;47(September 2017):216-220. doi:10.1016/j.drugpo.2017.05.056.

77. Mason K, Dodd Z, Guyton M, et al. Understanding real-world adherence in the directly acting antiviral era: A prospective evaluation of adherence among people with a history of drug use at a community-based program in Toronto, Canada. *Int J Drug Policy*. 2017;47(September 2017):202-208. doi:10.1016/j.drugpo.2017.05.025.

78. Grebely J, Mauss S, Brown A, et al. Efficacy and Safety of Ledipasvir/Sofosbuvir With and Without Ribavirin in Patients With Chronic HCV Genotype 1 Infection Receiving Opioid Substitution Therapy: Analysis of Phase 3 ION Trials. *Clin Infect Dis*. 2016;63(11):1405-1411. doi:10.1093/cid/ciw580.

79. Grebely J, Dore GJ, Zeuzem S, et al. Efficacy and Safety of Sofosbuvir/Velpatasvir in Patients With Chronic Hepatitis C Virus Infection Receiving Opioid Substitution Therapy: Analysis of Phase 3 ASTRAL Trials. *Clin Infect Dis*. 2016;63(11):1479-1481. doi:10.1093/cid/ciw579.

80. Chasser Y, Kim AY, Freudenreich O. Review Article Hepatitis C Treatment: Clinical Issues for Psychiatrists in the Post-Interferon Era. *Psychosomatics*. 2017;58(1):1-10. doi:10.1016/j.psym.2016.09.004.

81. Government of British Columbia. PharmaNet. http://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents/pharmanet. Accessed February 8, 2016.

82. Population Data BC. PharmaNet. https://www.popdata.bc.ca/data/external/PharmaNet. Published 2015. Accessed February 8, 2016.

83. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: Its importance in cardiovascular outcomes. *Circulation*. 2009;119(23):3028-3035. doi:10.1161/CIRCULATIONAHA.108.768986.

84. Zhao B, Wong EC, Palaniappan L. Pharma and Health Care Estimating Patient Adherence to Medication with Electronic Health Records Data and Pharmacy Claims Combined. *SAS Glob Forum 2013*. 2013:1-7.

85. Leslie RS. Using Arrays to Calculate Medication Utilization. In: *Proceedings of the SAS® Global Forum 2007 Conference*. Cary, NC: SAS Institute Inc.; 2007:1-5.

86. Pampalon R, Hamel D, Gamache P, Raymond G. A deprivation index for health planning in Canada. *Chronic Dis Can*. 2009;29(4):178-191.

87. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity Measures for Use with Administrative Data. *Med Care*. 1998;36(1):8-27.

88. Curtis JR, Ms AOW, Allison J, Ms AF, Kovac SH, Saag KG. Agreement and validity of pharmacy data versus self-report for use of osteoporosis medications among chronic glucocorticoid users y. *Pharmacoepidemiol Drug Saf*. 2006;15(December 2005):710-718.

89. Goldman DP, Joyce GF, Zheng Y. Prescription Drug Cost Sharing. *JAMA*. 2007;298(1):61-69.

90. Choudhry NK, Fischer MA, Avorn J, et al. At Pitney Bowes, Value-Based Insurance Design Cut Copayments And Increased Drug Adherence. *Health Aff*. 2010;29(11):1995-2001. doi:10.1377/hlthaff.2010.0336.

91. Goldman DP, Joyce GF, Lawless G, Crown WH, Willey V. Benefit Design And Specialty Drug Use. *Health Aff*. 2006;25(5):1319-1331. doi:10.1377/hlthaff.25.5.1319.

92. Liao JM, Fischer MA. Early Patterns of Sofosbuvir Utilization by State Medicaid Programs. *N Engl J Med*. 2015;373(13):1280-1281. doi:10.1056/NEJMc1508384.

93. Shrank WH, Choudhry NK, Fischer MA, et al. The Epidemiology of Prescriptions Abandoned at the Pharmacy. *Ann Intern Med*. 2010;153(10):633-640.

94.   Karmarkar TD, Starner CI, Qiu Y, Tiberg K, Gleason PP. Sofosbuvir Initial Therapy Abandonment and Manufacturer Coupons in a Commercially Insured Population. *Am J Manag Care*. 2016;22(Special Issue No. 6):SP191-SP197.

95.   Jandoc R, Burden AM, Mamdani M, Levesque LE, Cadarette SM. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. *J Clin Epidemiol*. 2015;68(8):950-956. doi:10.1016/j.jclinepi.2014.12.018.

96.   Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27:299-309.

97.   Anonymous. Module 5, time series analysis. In: Anonymous, ed. *Pharmacoepidemiology: Behavioral and Cultural Themes*. Newcastle: Center for Clinical Epidemiology and Biostatistics Australia; 2001.

98.   World Health Organization. *Combating Hepatitis B and C to Reach Elimination by 2030*. Geneva; 2016.

99.   Lau G, Benhamou Y, Chen G, et al. Efficacy and safety of 3-week response-guided triple direct-acting antiviral therapy for chronic hepatitis C infection: a phase 2, open-label, proof-of-concept study. *Lancet Gastroenterol Hepatol*. 2016;1(2):97–104. doi:10.1016/S2468-1253(16)30015-2.

100.   Aghemo A, Colombo M. Response-Guided Duration of Direct Acting Antiviral Therapy for Chronic Hepatitis C: Back to the Future? *Gastroenterology*. 2017;152(5):1238-1239. doi:10.1016/j.jhep.2016.09.001.

Appendices

Appendix 1 Flowchart of observations included and excluded in the final data set

```
┌─────────────────────────────┐          ┌─────────────────────────────┐
│         Sofosbuvir          │          │    Ledipasvir-sofosbuvir    │
│ All dispensations of the    │          │ All dispensations of the    │
│ drug                        │          │ drug                        │
│ N observations = 13,475     │          │ N observations = 32,380     │
│ N individuals = 1,021       │          │ N individuals = 2,709       │
└─────────────────────────────┘          └─────────────────────────────┘
              │                                        │
              ▼                                        ▼
┌─────────────────────────────┐          ┌─────────────────────────────┐
│ One record per service date │          │ One record per service date │
│ N observations = 8,530      │          │ N observations = 17,331     │
│ N individuals = 1,021       │          │ N individuals = 2,709       │
└─────────────────────────────┘          └─────────────────────────────┘
              │                                        │
              ▼                                        ▼
┌─────────────────────────────┐          ┌─────────────────────────────┐
│ One record per person       │          │ One record per person       │
│ N observations = 1,021      │          │ N observations = 2,709      │
│ N individuals = 1,021       │          │ N individuals = 2,709       │
└─────────────────────────────┘          └─────────────────────────────┘
              │                                        │
              ▼                                        ▼
┌─────────────────────────────┐          ┌─────────────────────────────┐
│ Remove individuals who      │          │ Remove individuals who      │
│ started in review period    │          │ started in review period    │
│ N observations = 809        │          │ N observations = 1,998      │
│ N individuals = 809         │          │ N individuals = 1,998       │
└─────────────────────────────┘          └─────────────────────────────┘
              │                                        │
              ▼                                        ▼
┌─────────────────────────────┐          ┌─────────────────────────────┐
│ Remove individuals who were │          │ Remove individuals who were │
│ dispensed > 168 days        │          │ not dispensed +/- 7 days of │
│ N observations = 786        │          │ recommended treatment       │
│ N individuals = 786         │          │ duration                    │
│                             │          │ N observations = 1,974      │
│                             │          │ N individuals = 1,974       │
└─────────────────────────────┘          └─────────────────────────────┘
              │                                        │
              ▼                                        ▼
┌─────────────────────────────┐          ┌─────────────────────────────┐
│ Ensure only one record per  │          │ Ensure only one record per  │
│ person                      │          │ person                      │
│ N observations = 786        │          │ N observations = 1,974      │
│ N individuals = 786         │          │ N individuals = 1,974       │
└─────────────────────────────┘          └─────────────────────────────┘
                    │                          │
                    ▼                          ▼
           ┌─────────────────────────────────────────┐
           │ Concatenate sofosbuvir and              │
           │ ledipasvir-sofosbuvir                   │
           │ N observations = 2,760                  │
           │ N individuals = 2,746                   │
           └─────────────────────────────────────────┘
```

Appendix 2 Criteria and Data Sources for the BC Hepatitis Testers Cohort (BC-HTC)

Criteria for Inclusion in BC-HTC

All individuals:

- tested at the centralized provincial laboratory for HCV or HIV   OR
- reported by BC public health as a confirmed case of HCV OR
- reported in BC enhanced surveillance system as a confirmed case of HIV or AIDS (all reports)   OR
- reported by BC public health as a confirmed case of HBV OR
- included in BC Enhanced Strain Surveillance System (EHSSS) as an acute HBV or HCV case
- All individuals meeting at least one the above criteria were linked internally across all their tests and case reports. Those with a valid personal health number (PHN) were then sent for deterministic linkage with province-wide Cancer and Ministry of Health (MoH) datasets

Provincial Communicable Disease Data Sources:	**Data Date Ranges:**
BC-PHMRL HIV laboratory testing datasets (tests: ELISA, Western blot, NAAT, p24, culture)	1988–2015
BC-PHMRL HCV laboratory tests datasets (tests: antibody, HCV RNA, genotyping)	1992–2017 Mar 9
HIV/AIDS Information System (HAISYS) (public health HIV/AIDS case reports)	1980–2015
Panorama (public health case reports of HCV, HBV, and TB)	1990–2015
Enhanced Strain Surveillance System (EHSSS) (risk factor data on a subset of acute HCV and acute HBV cases)	2000–2015
Cancer and MoH Administrative Data Sources:	**Data Date Ranges:**
BC Cancer Registry (BCCR) (primary tumour registry, excludes metastatic cancers)	1970–2014
Discharge Abstracts Dataset (DAD) (hospitalization records)[1]	1985–2015
Medical Services Plan (MSP) (physician diagnostic and billing data)[2]	1990–2015
PharmaCare/PharmaNet (Pharma) (prescription drug dispensations)[3,4]	1985–2016 May 31
BC Vital Statistics (VS) (deaths registry)[5]	1985–2015

The final BC-HTC comprises all individuals successfully linked on PHN to the MoH Client Roster[6] (a registry of all BC residents enrolled in the publicly-funded universal healthcare system)

Sources:

1. British Columbia Ministry of Health [creator]. Discharge Abstract Database (Hospital Separations). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2016. http://www.health.gov.bc.ca/data/
2. British Columbia Ministry of Health [creator]. Medical Services Plan (MSP) Payment Information File. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2016. http://www.health.gov.bc.ca/data/
3. British Columbia Ministry of Health [creator]. PharmaCare. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2016. http://www.health.gov.bc.ca/data/
4. British Columbia Ministry of Health [creator]. PharmaNet. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2016. http://www.health.gov.bc.ca/data/
5. BC Vital Statistics Agency [creator]. Vital Statistics Deaths. BC Vital Statistics Agency [publisher]. Data Extract. BC Vital Statistics Agency (2014). 2016.
6. British Columbia Ministry of Health [creator]. Client Roster (Client Registry System/Enterprise Master Patient Index). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2016. http://www.health.gov.bc.ca/data/

Appendix 3 Definitions of comorbid conditions for the BC Hepatitis Testers Cohort (BC-HTC)

Definition

Cirrhosis

Cirrhosis was flagged at the first occurrence of either 2 physician visit or 1 hospitalization code relevant to decompensated cirrhosis and compensated cirrhosis including esophageal varices with or without bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, ascites, and portal hypertension, chronic hepatitis failure (alcoholic/non-alcoholic), hepatic coma, unspecified hepatic failure, unspecified cirrhosis of the liver or previous cause of chronic liver disease.

Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 4562; exact codes 4560, 4561, 56723, 5722, 5723, 5724, 5712, 5728, 5715, 7895, 07044, 5713

Hospitalization Data: DAD1/ICD-9-CM diagnostic codes: starting with 4562; exact codes 4560, 4561, 56723, 5722, 5723, 5724, 5712, 5728, 5715, 7895, 07044, 5713. DAD2/ICD-10-CA diagnostic codes: starting with K703; exact codes: I850, K652, K721, K729, K766, K767, K7460, K7469, R18, I9820, I983, K704

Diabetes

Diabetes was defined at the first occurrence of 2 MSP or 1 hospitalization or 2 PharmaNet codes for diabetes-specific diagnostic codes.

Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 250

Hospitalization Data: DAD1/ICD-9-CM: starting with 250; DAD2/ICD-10-CA: starting with E10-E14

PharmaNet DIN/PIN*: 2435462, 2435470, 2448610, 2449935, 2444933, 2444941, 2449943, 2439611, 2449390, 2449404, 2190885, 2190893, 2238469, 2239474, 2238470, 2239475, 2238471, 2239476, 2361809, 2361817, 2230443, 2230444, 12599, 720941, 808741, 1900935, 1913662, 1913689, 1959360, 1987836, 2020742, 2085887, 2147548, 2224569, 2226812, 2228939, 2229596, 2230037, 2234514, 2236548, 2236734, 2242096, 2248009, 2316544, 2340771, 2345862, 2350467, 2363712, 454753, 720933, 808733, 1900927, 1913654, 1913670, 1959352, 1987534, 2020734, 2084341, 2147521, 2224550, 2226804, 2228920, 2229595, 2230036, 2234513, 2236543, 2236733, 2242095, 2248008, 2340763, 2345854, 2350459, 2363704, 2242987, 2297795, 2348578, 2405067, 2423286, 2429764, 2438658, 2356422, 2407124, 2429772, 2439328, 765996, 2155850, 2229519, 2238103, 2245247, 2248210, 2248453, 2254719, 2287072, 2294400, 2336316, 2363518, 2443635, 2443643, 2245272, 2269589, 2273101, 2273756, 2274248, 2279061, 2284545, 2295377, 2245273, 2269597, 2273128, 2273764, 2274256, 2279088, 2284553, 2295385, 2245274, 2269619, 2273136, 2273772, 2274272, 2279126, 2295393, 2313596, 2269600, 2274264, 2370921, 2351056, 2351064, 2437899, 2245438, 2245439, 2245440, 2239925, 2321483, 2354934, 2355671, 2357461, 2366355, 2373289, 2415976, 2424266, 2239926, 2321491, 2354942, 2355698, 2357488, 2366363, 2373297, 2415984, 2424274, 2239924, 2321475, 2354926, 2355663, 2357453, 2366347, 2373270, 2415968, 2424258, 12610, 1987828, 2224798, 12602, 13889, 21849, 93033, 156663, 209872, 312762, 431168, 1987542, 2224771, 1934074, 552267, 628301, 723789, 1985930, 2231095, 2236985, 2237531, 2238698, 2231096, 2236986, 15598, 2425483, 2425491, 2443937, 2443945, 314552, 2045710, 2099233, 2148765, 2162822, 2167786, 2188902, 2220628, 2223562, 2229516, 2229994, 2230026, 2230670, 2231389, 2233999, 2238827, 2239081, 2242794, 2242974, 2246820, 2246964, 2252945, 2257726, 2265575, 2268493, 2269031, 2284782, 2305062, 2314908, 2331519, 2334437, 2339110, 2341603, 2343606, 2353377, 2361264, 2364506, 2365286, 2378043, 2378116, 2378620, 2378841, 2379767, 2380196, 2380722, 2385341, 2388766, 2406020, 2408228, 2409283, 2421828, 2438275, 2162849, 2229517, 2229656, 2229785, 2230027, 2230475, 2230671, 2231058, 2239214, 2242589, 2242726, 2242783,

Definition

2242793, 2242931, 2246821, 2246965, 2252953, 2257734, 2265583, 2269058, 2284790, 2314894, 2331527, 2334445, 2339129, 2341522, 2343614, 2353385, 2361272, 2364514, 2365294, 2378051, 2378124, 2378639, 2378868, 2379775, 2380218, 2380730, 2385368, 2388774, 2406039, 2408236, 2409291, 2421836, 2438283, 2268507, 2300451, 2446065, 24708, 399302, 586773, 13730, 21350, 24716, 156728, 209937, 312711, 377937, 430986, 2244353, 2245397, 2377209, 2229704, 2229705, 2233562, 2241283, 2403412, 2271842, 2412829, 2333554, 2375842, 2242572, 2274914, 2297906, 2298279, 2301423, 2302861, 2302942, 2303124, 2303442, 2307634, 2307669, 2312050, 2320754, 2326477, 2345366, 2363232, 2374013, 2375850, 2384906, 2389290, 2391600, 2397307, 2417049, 2418002, 2421674, 2434121, 2242573, 2274922, 2297914, 2298287, 2301431, 2302888, 2302950, 2303132, 2303450, 2307642, 2307677, 2312069, 2320762, 2326485, 2339587, 2345374, 2363240, 2365529, 2374021, 2374587, 2375869, 2384914, 2389304, 2417057, 2418010, 2421682, 2434148, 2242574, 2274930, 2297922, 2298295, 2301458, 2302896, 2302977, 2303140, 2303469, 2307650, 2307723, 2312077, 2320770, 2326493, 2339595, 2345382, 2363259, 2365537, 2374048, 2374595, 2375877, 2384922, 2389312, 2417065, 2418029, 2421690, 2434156, 2279460, 2279479, 2279487, 2294346, 2417200, 2417197, 2417189, 5894, 6009, 12556, 12564, 178543, 237000, 244449, 271330, 274119, 274127, 275409, 275417, 275425, 420336, 480290, 480304, 539201, 539244, 542911, 542938, 542946, 546348, 554820, 648094, 999717, 1986791, 22303140, 45230001, 45230002, 45230003, 45230004, 45230005, 45230006, 45230007, 45230008, 45230009, 45230010, 45230011, 45230012, 45230013, 47450001, 47450002, 47450003, 47450004, 47450005, 47450006, 47450007, 66123203, 66124134, 66124135, 66124215, 66124225, 66124232, 66124582, 66127961, 513644, 2275872, 2241112, 2306166, 2307170, 2307553, 2326329, 2354144, 2354349, 2403366, 2241113, 2306174, 2307189, 2307561, 2326337, 2354152, 2354357, 2403374, 2241114, 2306182, 2307197, 2307588, 2326345, 2354160, 2354365, 2403382, 2241111, 2388839, 2388847, 2303922, 586714, 1959220, 2024233, 2024284, 2025256, 2415089, 646148, 2024241, 446580, 612278, 1934090, 446564, 612227, 1934112, 446602, 612251, 1934082, 2403277, 2403250, 2403269, 2258781, 2258803, 2258811, 446572, 612235, 1934066, 514551, 552275, 612170, 1985949, 2022249, 2275864, 612197, 632651, 632686, 1986085, 1986805, 1986813, 446610, 612219, 612189, 514535, 612162, 612359, 587737, 1959239, 2024225, 2024268, 2024403, 2241310, 2403447, 446599, 612243, 1934104, 612200, 2247087, 2357909, 2248440, 2357917, 2248441, 2357925, 2247085, 2357887, 2247086, 2357895, 2419300, 2419319, 2419327, 2419335, 2419343, 2419351, 552259, 614416, 1985957, 1985981, 2417235, 2417219, 2417227, 644358, 733075, 2024276, 2389185, 2389169, 2389177, 2265435, 2265443, 2245689, 2251930, 2276410, 2441829, 2294338, 2240294, 2240295, 2403420, 2240297, 2403439, 889121, 632694, 650935, 1986821, 2022230, 632678, 1985965, 773654, 1985973, 889113, 1962639, 2024292, 889105, 1962655, 2024306, 795879, 1959212, 2024217, 2024446, 2025248, 889091, 1962647, 2024314, 1962663, 2024322, 2416808, 2333872, 2416794, 2333856, 2416786, 2333864

Elixhauser Comorbidity Score

Using DAD ICD-9 and ICD-10 code data, we calculated a score in which any hospitalization for one of the 31 Elixhauser diagnostic groups was scored as 1.

Congestive Heart Failure, Cardiac Arrhythmia, Valvular Disease, Pulmonary Circulation Disorders, Peripheral Vascular Disorders, Hypertension Uncomplicated, Hypertension Complicated, Paralysis, Neurological Disorders, Chronic Pulmonary Disease, Diabetes Uncomplicated, Diabetes Complicated, Hypothyroidism, Renal Failure, Liver Disease, Peptic Ulcer Disease excluding bleeding, AIDS/HIV, Lymphoma, Metastatic Cancer, Solid Tumor without Metastasis, Rheumatoid Arthritis/collagen, Coagulopathy, Obesity, Weight Loss, Fluid and Electrolyte Disorders, Blood Loss Anemia, Deficiency Anemia, Alcohol Abuse, Drug Abuse, Psychoses, Depression.

Definition

Ethnicity

Individuals were assigned one of twelve ethnicities (Central Asian, White, Black, Chinese, Filipino, Japanese, Korean, Latin American, Pacific Islander, South Asian, Southeast Asian or West Asian) based on first and last name using the ONOMAP ethnicity software.

If multiple ethnicities were assigned, surname origins from the Family Education Genealogy website were applied. Remaining individuals were assigned ethnicities manually by a researcher familiar with diverse surnames and by using search tools on ancestry.ca and behindthename.com. Confidentiality guidelines were upheld at all times to ensure protection of identifiable information.

Hepatocellular Carcinoma (HCC)

Individuals were flagged at first HCC diagnosis date from the BC Cancer Registry data.

Site: C220

AND Histology: 81703, 81713, 81723, 81733, 81743, 81753

Hepatitis B

Hepatitis B was flagged at the first occurrence of a case of HBV recorded in iPHIS or PANORAMA; if none recorded, then the first occurrence of 2 MSP (2 physician visits or 2 fee items), 1 hospitalization code or 1 PharmaNet code involving acute or chronic hepatitis B diagnoses with hepatic coma and with or without delta agents; inactive carriers; or hepatitis B-specific treatment.

Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 0702, 0703 or exact code V0261; or fee item codes 90831 and 90675, 90690 and 91765

Hospitalization Data: DAD1/ICD-9-CM diagnostic codes: starting with 0702, 0703; or exact code V0261. DAD2/ICD-10-CA diagnostic codes: starting with B16, B180, B181; or exact code Z2250

PharmaNet DIN/PIN: 2247823, 2282224, 2247128, 2239193, 2288389

Injection Drug Use

Injection drug use was defined at the first occurrence of 1 MSP or 1 hospitalization diagnostic codes for major drug-related diagnoses involving addiction, dependence, and drug-induced mental disorders; illicit drug use most likely to be injectables (e.g. excluding cannabis), or illicit use of prescribed drugs including: hallucinogens, barbituates/tranquillizers, sedatives, hypnotics, anxiolytics, opioids, cocaine, amphetamine, volatile solvents; or discharge to drug rehabilitation, counselling, surveillance.

Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 292, 3040, 3042, 3044, 3046-9, 3054-7, 3059, 6483, 9650, 9697, 970

Hospitalization Data: DAD1/ICD-9-CM: starting with 292, 3040, 3042, 3044, 3046-9, 3054-7, 3059, 6483, 9650, 9697, 9700, 9701, 9708, 9709, E8500; DAD2/ICD-10-CA: starting with F11, F13-5, F18, F19, T42 or exact codes T401, T402, T404, T405, T406, T436, T438, T439, T507

Definition

Material and Social Deprivation Quintiles

The Québec Index of Material and Social Deprivation was calculated based on individuals' 6-digit postal code. The deprivation index combines six indicators related to health and welfare that represent material or social deprivation and are available by enumeration area in Canadian census data: 1) proportion of persons without high-school diploma 2) ratio of employment to population 3) average income 4) proportion of persons separated, divorced, widowed 5) the proportion of single-parent families 6) proportion of people living alone.

Major mental illness

Major mental illness was flagged at the first occurrence of either 1 hospitalization diagnostic code OR 2 MSP diagnostic codes from a psychiatrist visit for schizophrenic, bipolar, delusional, nonorganic psychotic, adjustment, anxiety, dissociative, personality and major depressive disorders

Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 295-298, 300-301, 308-309, 311, or exact code 50B

Hospitalization Data: DAD1/ICD-9-CM: starting with 295-298, 300-301, 308-309, 311; DAD2/ICD-10-CA: starting with F20-F25, F28-F34, F38-F45, F48, F60-F61

Opioid Substitution Therapy (OST)

Opioid substitution therapy was flagged at the first occurrence of either 1 MSP or 1 PharmaNet code involving methadone or buphrenorphine substitution treatment, with or without direct pharmacist interaction.

Physician Billing Data: MSP fee item 39

PharmaNet DIN/PIN: 2242963, 2242964, 999792, 66999990, 66999991, 66999992, 66999993, 66999997, 66999998, 66999999, 67000000, 2295695, 2295709

Problematic Alcohol Use

Problematic alcohol use was defined at the first occurrence of 2 MSP or 1 hospitalization codes for major alcohol-related diagnoses including alcoholic mental disorders and dependence/abuse syndromes; alcoholic polyneuropathy, myopathy, cardiomyopathy; pseudo Cushing's syndrome; or discharge to alcohol rehabilitation, counselling, or surveillance

Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 291, 303, 3050, 3575, 4255

Hospitalization Data: DAD1/ICD-9-CM: starting with 291, 303, 3050,3575, 4255; DAD2/ICD-10-CA: starting with F10, E244, G312, G621, G721, I426, Z502, Z714

Appendix 4 Participant profile for sofosbuvir and ledipasvir-sofosbuvir

Variable	Sofosbuvir n (%)	Ledipasvir-sofosbuvir n (%)
Sex		
Female	282 (35.88)	608 (31.02)
Male	504 (64.12)	1,352 (68.98)
Age		
< 50	120 (15.27)	284 (14.49)
50-60	336 (42.75)	722 (36.84)
> 60	330 (41.98)	954 (48.67)
Ethnicity		
Non-White	80 (10.18)	102 (5.20)
White	706 (89.82)	1,858 (94.80)
PharmaCare		
No	463 (58.91)	430 (21.94)
Yes	323 (41.09)	1,530 (78.06)
Material deprivation		
Most privileged	291 (37.02)	712 (36.33)
Moderately privileged	153 (19.47)	389 (19.85)
Least privileged	328 (41.73)	796 (40.61)
Unknown/missing	14 (1.78)	63 (3.21)
Elixhauser comorbidity index		
0	220 (27.99)	621 (31.68)
1	181 (23.03)	481 (24.54)
≥ 2	385 (48.98)	858 (43.78)
Cirrhosis		
No	590 (75.06)	1,590 (81.12)
Yes	196 (24.94)	370 (18.88)
Diabetes		
No	601 (76.46)	1,559 (79.54)
Yes	185 (23.54)	401 (20.46)
Hepatitis B (HBV)		
No	728 (92.62)	1,808 (92.24)
Yes	58 (7.38)	152 (7.76)
Hepatocellular carcinoma (HCC)		
No	773 (98.35)	1,929 (98.42)
Yes	13 (1.65)	31 (1.58)
Major mental illness		
No	229 (29.13)	622 (31.73)
Yes	557 (70.87)	1,338 (68.27)
Injection drug use (IDU) diagnosis		
No	741 (94.27)	1,869 (95.36)
Yes	45 (5.73)	91 (4.64)

Variable	Sofosbuvir n (%)	Ledipasvir-sofosbuvir n (%)
Opioid substitution therapy (OST)		
No	716 (91.09)	1,745 (89.03)
Yes	70 (8.91)	215 (10.97)
Problematic alcohol use		
No	606 (77.10)	1,505 (76.79)
Yes	180 (22.90)	455 (23.21)
Treatment duration		
56 days	0 (0.00)	450 (22.96)
84 days	416 (52.93)	1,025 (52.30)
112 days	47 (5.98)	0 (0.00)
168 days	323 (41.09)	485 (24.74)

Appendix 5 Bivariate analyses examining the association between individual patient factors and mean PDC and full adherence

Variable	n (%)	Mean PDC (%)	p-value	Full adherence (%)	p-value
Sex					
Female	890 (32.41)	95.70		70.67	
Male	1,856 (67.59)	96.40	0.14	70.26	0.86
Age					
< 50	404 (14.71)	95.48		66.34	
50-60	1,058 (38.53)	95.84		68.71	
> 60	1,284 (46.76)	96.66	0.082	73.05	0.011*
Ethnicity					
Non-White	182 (6.63)	98.19	9.549e-07*	76.37	
White	2,564 (93.37)	96.03		69.97	0.081
PharmaCare					
No	893 (32.52)	95.54		65.40	
Yes	1,853 (67.48)	96.48	0.043*	72.80	8.276e-05*
Material deprivation					
Most privileged	1,003 (36.53)	96.71		72.38	
Moderately privileged	542 (19.74)	96.00		67.53	
Least privileged	1,124 (40.93)	95.65		69.75	
Unknown/missing	77 (2.80)	97.99	0.066	74.03	0.19
Elixhauser comorbidity index					
0	841 (30.63)	97.16		74.44	
1	662 (24.11)	96.49		69.49	
≥ 2	1,243 (45.27)	95.33	0.00072*	68.14	0.0072*
Cirrhosis					
No	2,180 (79.39)	96.40		71.06	
Yes	566 (20.61)	95.30	0.0498*	67.84	0.15
Diabetes					
No	2,160 (78.66)	96.24		71.16	
Yes	586 (21.34)	95.92	0.53	67.58	0.10
Hepatitis B (HBV)					
No	2,536 (92.35)	96.17		70.47	
Yes	210 (7.65)	96.16	0.99	69.52	0.83
Hepatocellular carcinoma (HCC)					
No	2,702 (98.40)	96.15		70.21	
Yes	44 (1.60)	97.30	0.42	81.82	0.13
Major mental illness					
No	851 (30.99)	97.13		76.03	
Yes	1,895 (69.01)	95.74	0.00069*	67.86	1.793e-05

Variable	n (%)	Mean PDC (%)	p-value	Full adherence (%)	p-value
Injection drug use (IDU) diagnosis					
No	2,610 (95.05)	96.37		70.69	
Yes	136 (4.95)	92.17	0.0069*	64.71	0.16
Opioid substitution therapy (OST)					
No	2,461 (89.62)	96.46		71.15	
Yes	285 (10.38)	93.70	0.0034*	63.86	0.013*
Problematic alcohol use					
No	2,111 (76.88)	96.57		71.81	
Yes	635 (23.12)	94.86	0.0027*	65.67	0.0035
Treatment type					
Sofosbuvir	786 (28.62)	95.35		62.34	
Ledipasvir-sofosbuvir	1,960 (71.38)	96.50	0.019*	73.62	6.361e-09
Treatment duration					
56 days	450 (16.39)	95.84		78.89	
84 days	1,441 (52.48)	96.66		72.94	
112 days	47 (1.71)	91.62		53.19	
168 days	808 (29.42)	95.75	0.0059*	62.13	1.657e-11*

* $p < 0.05$

Appendix 6 Multivariable logistic regression model with quarter fixed effects for factors associated with full adherence

Variable	Estimate	SE	p-value	Adjusted OR (95% CI)
Sex – Male	-0.094	0.095	0.32	0.91 (0.75, 1.10)
Age (reference: < 50)				
50-60	0.14	0.13	0.27	1.15 (0.89, 1.49)
> 60	0.28	0.13	0.036*	1.32 (1.02, 1.71)
Ethnicity – White	-0.40	0.19	0.035*	0.67 (0.45, 0.96)
PharmaCare	0.39	0.16	0.014*	1.48 (1.08, 2.03)
Material deprivation (reference: most privileged)				
Moderately privileged	-0.25	0.12	0.040*	0.78 (0.62, 0.99)
Least privileged	-0.13	0.10	0.19	0.88 (0.72, 1.07)
Unknown/missing	0.14	0.28	0.60	1.16 (0.68, 2.03)
Elixhauser comorbidity index (reference: 0)				
1	-0.16	0.12	0.19	0.85 (0.67, 1.08)
≥ 2	-0.082	0.12	0.50	0.92 (0.72, 1.17)
Cirrhosis	0.05	0.12	0.64	1.06 (0.84, 1.33)
Diabetes	-0.12	0.11	0.28	0.89 (0.72, 1.10)
Hepatitis B (HBV)	0.049	0.16	0.76	1.05 (0.77, 1.45)
Hepatocellular carcinoma (HCC)	0.84	0.42	0.044*	2.31 (1.08, 5.61)
Major mental illness	-0.34	0.10	0.0012*	0.72 (0.58, 0.87)
Injection drug use (IDU) diagnosis	0.027	0.20	0.89	1.03 (0.69, 1.54)
Opioid substitution therapy (OST)	-0.25	0.15	0.091	0.78 (0.59, 1.04)
Problematic alcohol use	-0.14	0.11	0.20	0.87 (0.70, 1.08)
Ledipasvir-sofosbuvir (reference: sofosbuvir)	0.16	0.12	0.17	1.18 (0.93, 1.49)
Treatment duration (reference: 56 days)				
84 days	-0.18	0.14	0.20	0.84 (0.64, 1.10)
112 days	-0.90	0.34	0.0088*	0.41 (0.21, 0.80)
168 days	-0.74	0.15	< 0.001*	0.48 (0.35, 0.64)
Quarter 1 fixed effect	-1.46	0.41	0.00040*	0.23 (0.10, 0.51)
Quarter 2 fixed effect	0.21	0.29	0.46	1.24 (0.71, 2.19)
Quarter 3 fixed effect	-0.090	0.27	0.73	0.91 (0.54, 1.54)
Quarter 4 fixed effect	0.15	0.24	0.54	1.16 (0.72, 1.88)
Quarter 5 fixed effect	0.22	0.22	0.31	1.25 (0.81, 1.93)
Quarter 6 fixed effect	0.037	0.14	0.79	1.04 (0.79, 1.36)
Quarter 7 fixed effect	0.0070	0.14	0.96	1.01 (0.78, 1.29)

Note: The Quarter 8 fixed effect variable is not displayed as it had singularities in the model.

* $p < 0.05$