Overcoming Hepatitis C: Changes in quality of life, healthcare use and substance use in HIV-coinfected patients after antiviral therapy

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DEDICATION

I would like to dedicate this work to my parents, Estella Au and Albert Yeung, and to my brother, Man Yuk Yeung.

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ABSTRACT

Background:

In chronic hepatitis C virus (HCV) mono-infection and HIV/ HCV co-infection, the goal of antiviral treatment is a sustained virologic response (SVR). Some clinical benefits of SVR have been identified among HIV co-infected patients. However, endpoints beyond liver-related outcomes have not been well documented in co-infected patients who often have concurrent problems. We examined changes in health-related quality of life (HRQOL), health service use and substance over time among patients treated for HCV, in particular SVR-achievers and non-responders.

Methods:

HIV/ HCV co-infected patients with detectable HCV RNA were selected from the Canadian Co-infection Cohort and followed every six months. HRQOL was self-reported using the EuroQOL-5D visual analogue scale from 0 to 100 (worst to best health). Incidence rate ratios (IRR) for health service utilization and proportion of current users for substance use were determined. Linear and negative binomial regressions were used to model the effects of SVR on HRQOL and healthcare utilization respectively.

Results:

Of 1002 chronic HCV patients, 169 (17%) received treatment— 65 (38%) achieved SVR, 46 (27%) did not, 35 (21%) had ongoing treatment and 23 (14%) had unknown treatment response. EuroQOL scores improved in SVR-achievers after treatment (median (Q1, Q3): from 71 (60, 80) to 80 (70, 95.8)), but not in non-achievers (median (Q1, Q3): from 70 (48, 80) to 68 (50, 80)). Overall, SVR-achievers used fewer health services than non-achievers, particularly emergency visits and hospitalizations (IRR (95% CI): 0.36 (0.1, 1.0) and 0.17 (0.0, 0.5), respectively). One exception was walk-in clinic visits (IRR: 3.26 (95% CI: 1.3, 10.6)). Achieving SVR was associated with markedly decreased in-patient service use (IRR: 0.21 (95% CI: 0.07, 0.64). All Patients reduced tobacco smoking and illicit drug use behaviours, but alcohol consumption increased post-treatment among all patients (percentage reporting consumption: from 49% pre-treatment to 64% post-treatment in SVR-achievers; from 44% to 61% in non-achievers).

Conclusions:

HCV treatment and SVR can have a range of effects on HRQOL, healthcare use and substance use in HIV/ HCV co-infection. Longer follow-up is required to determine the duration of health benefits.

RÉSUMÉ

Contexte:

Pour les patients infectés par le virus de l'hépatite C (VHC), l'objectif du traitement antiviral est d'atteindre une réponse virologique soutenue (RVS) qui procure des avantages en santé mesurables par rapport à la mono-infection en VHC. Cependant, l'existence de tels avantages pour les patients co-infectés par le VIH qui ont des problèmes de santé supplémentaires n'est pas claire. Nous avons examiné les changements de la qualité liée à la santé de la vie (QVLS), l'utilisation des services de santé et l'utilisation de substances au cours du temps chez les patients traités pour le VHC, en particulier les répondeurs et les non-répondeurs au traitement, dans la cohorte de co-infection VIH/VHC canadienne.

Méthodes:

Des patients co-infectés VIH/VHC avec ARN positif du VHC (avec ou sans traitement anti-VHC antérieur) ont été sélectionnés à partir de la Cohorte canadienne de coïnfection VIH-VCH et suivis aux six mois. Les patients se sont auto-évalués de 0 à 100 (du pire au meilleur état de santé) pour la QVLS en utilisant l'échelle visuelle analogique du questionnaire EuroQol-5D. Nous avons examiné les scores médians

QVLS, les ratios des taux d'incidence des services de santé et la fréquence de consommation de drogues avant et après le traitement anti-VHC. Par ailleurs, nous avons utilisé la régression linéaire pour examiner l'effet de la RVS sur le changement en pourcentage de QVLS. Une régression binomiale négative a permis de modéliser la relation entre la RVS et la fréquence des services de santé utilisés.

Résultats:

À partir des 1002 patients VHC chroniques, 169 (17%) ont reçu un traitement - 65 (38%) ont atteint la RVS, 46 (27%) n'ont pas attient la RVS, 35 (21%) ont reçu un traitement continu et 23 (14%) avaient des résultats inconnus. Pour les répondeurs au traitement, les scores EuroQOL se sont améliorés après le traitement (médiane des scores: 71 à 80). Les non-répondeurs n'ont démontré aucune amélioration au cours du temps (scores médians: ≤ 70). Globalement, l’utilisation des services de santé était plus faible pour les répondeurs au traitement que pour les non-répondeurs., particulièrement pour les visites à l'urgence et les hospitalisations (ratios des taux d'incidence à six mois (post-traitement: 0,36 et 0,17, respectivement). À l’exception des visites aux cliniques sans rendez-vous (ratios des taux d'incidence à six mois post-traitement: 3,26).

L’atteinte de la RVS a diminué de manière significative la fréquence des visites des patients hospitalisés. Les patients ont réduit leur consommation de tabac et les comportements de consommation de drogues illicites, mais la consommation d'alcool post-traitement a augmenté chez tous les patients (de 49% à 64% chez les répondeurs et de 44% à 61% chez les non-répondeurs).

Conclusions:

La RVS peut avoir des effets multidimensionnels sur la QVLS, l'utilisation des soins de santé et l'utilisation de substances. Un meilleur état de santé a été noté et moins de services de santé ont été utilisés par les répondeurs au traitement. L'augmentation de la consommation d'alcool après la RVS nécessite une investigation plus approfondie puisqu’elle pourrait contrecarrer les avantages du traitement anti-VHC. Un suivi plus long est nécessaire pour déterminer la durabilité des avantages pour la santé de la RVS dans la co-infection.

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LIST OF ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
APRI	aspartate aminotransferase-to-platelet ratio index
ART	antiretroviral treatment
CI	confidence interval
EQ-5D	European Quality of Life-five dimensions questionnaire
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IDU	injection drug use
IR	incidence rate
IRR	incidence rate ratio
MSM	men who have sex with men
PY	person-year
Q1	first quartile
Q3	third quartile
RR	risk ratio
RNA	ribonucleic acid
SD	standard deviation
SF-36	Medical Outcomes Study 36-item short form
SVR	sustained virologic response
VAS	visual analogue scale

PREFACE

This thesis contains six chapters. Chapter one is the introduction outlining the background, rationale and objectives of the thesis. Chapter two is the literature review examining the epidemiology of HIV, hepatitis C, and co-infection in Canada. Chapter three outlines the methodology. Chapter four summarizes the overall findings. Tables and figures appear at the end of the chapter. Chapter five interprets and discusses the findings. Chapter six contains concluding remarks. A full reference list appears at the end of the thesis. This thesis conforms to the guidelines and requirements of a chapter-based thesis at McGill University.

CHAPTER I: INTRODUCTION

While the media coverage has not been extensive for hepatitis C virus (HCV) in the past, hepatitis C is a serious health concern. The urgency became apparent in August 2012 when the Centers for Disease Control and Prevention urged HCV testing for the generation of baby boomers, born in 1945 to 1965 (1). One in 30 baby boomers are estimated to be infected, but many (21%) are unaware of their infection (1). Universal HCV screening linked with the appropriate care and treatment can prevent the consequences of HCV including chronic liver disease, liver cancer, liver transplantation and death. Further, successful HCV treatment, known as sustained virologic response (SVR), can improve quality of life.

Due to shared routes of transmission, individuals at risk of HCV infection are also at risk of human immunodeficiency virus (HIV) infection. The interplay of HCV and HIV in co-infection makes for a complicated clinical situation. As the advent of antiretroviral therapy (ART) has prolonged the lives of individuals with HIV, their new challenges include living with aging-related illnesses and co-morbidities. Liver disease has overtaken acquired immunodeficiency syndrome (AIDS) as one of the leading causes of hospitalization and death among individuals with HIV/ HCV (2).

Studies in Canada and elsewhere have noted unacceptably low HCV treatment initiation rates (3, 4). A review of fifteen pooled studies found a treatment eligibility rate of 39% and an initiation rate of 19% among patients with HCV alone (5). Treatment uptake is further diminished with HIV co-infection, down to 7% nationally in the United States (6). Among those treated, fewer still proceed to clear their HCV infection. The review noted only 3% of all hepatitis C patients channelled through all stages: meeting treatment eligibility to initiating treatment to successfully responding to treatment (5). More effective direct-acting antivirals and interferon-free therapies in the pipeline are expected to improve SVR rates in the next 5-10 years opening the door for much wider use of HCV treatment (7).

Given the low number of patients treated for HCV and subsequently cleared of HCV, larger, multicentre cohorts are needed to study the impact of antiviral therapy and SVR. HCV treatment and SVR may have far-reaching effects beyond clinical events, such as self-perceived well-being and patient behaviours. These have not been documented in the setting of HIV-HCV co-infection where multiple competing health issues may exist. We hypothesize that achieving SVR will improve quality of life, reduce health services used, and reduce substance use behaviours in HIV/HCV co-infected patients despite the presence of concomitant HIV infection.

In this thesis, we examine changes in self-reported health and healthcare utilization over time, related to the receipt and outcome of HCV treatment in the Canadian HCV-HIV Co-infection Cohort. We extend the analysis to individuals treated for HCV and spontaneously cleared of HCV in this cohort.

The primary objectives are, among HIV/ HCV co-infected:

To examine health-related quality of life, healthcare utilization, substance use trends and mortality in co-infected individuals among untreated patients and those treated for HCV, including differences between SVR achievers and SVR non-achievers

Secondary objectives are:

To characterize: (a) patients who receive HCV therapy; and (b) patients who spontaneously clear HCV with respect to HRQOL and health service utilization to assess the role of active HCV replication in affecting these health outcomes.

CHAPTER 2: LITERATURE REVIEW

EPIDEMIOLOGY

Epidemiology of Hepatitis C Virus

HCV is known as a silent killer. Infected individuals often do not experience symptoms and are unaware of their infection for many years (1). Chronic infection leads to serious sequelae after a long latency including liver failure, cirrhosis and hepatocellular carcinoma (8). Within 20-30 years, 20-30% of chronic hepatitis C patients will develop cirrhosis, and subsequently, 5-10% of cirrhotic patients will develop hepatocellular carcinoma (9).

Prior to the discovery of HCV, a number of hepatitis cases appeared but were identified neither as hepatitis A nor hepatitis B. Accordingly, the unknown disease was called non-A non-B hepatitis. After its identification in 1989, the ribonucleic acid (RNA) virus was given its current name (10). HCV is responsible for the pandemic that infects 170 million worldwide (11). HCV has eleven genotypes (designated by 1 through 11) and many subtypes (designated by a, b, c, etc). Types 1a and 1b account for 60% of the global infections, and are endemic in North America, Europe, and Japan (12). Genotype 1 and 1a in particular is currently the most difficult to treat (12). Type 3 predominates in Southeast Asia.

Type 4 is found in the Middle East and north and central Africa (12). Type 5 is almost solely found in South Africa (12). The remaining types are found throughout Asia.

Hepatitis C has become Canada's leading indication for liver transplantation (13). In Canada, an estimated 250 000 people are infected (0.8% of population), many of whom (21%) are undiagnosed and unaware of their infection (14). In recent years, incident cases reported have declined (15). Nonetheless, there are 3200 - 5000 new infections and 8000 - 13 000 attributable deaths each year (16). HCV incidence is driven primarily by injection drug use (IDU) (70-80%) through sharing drug paraphernalia such as needles, crack pipes and straws (15). Before the common practice of screening blood, transfusion was an important route of transmission (15). Now, there are almost no incident cases of transfusion-related hepatitis in Canada (15).

Minority groups are disproportionately affected by hepatitis C. Historical determinants, social determinants and the physical environment contribute to the health disparities seen. Acute HCV infection rates are 5.5 times higher in Aboriginals than the general Canadian population (15). An estimated 3% of the Aboriginal population in Canada is infected with HCV (14). The prevalence is even greater among street-involved Aboriginals, among whom 22.3% of Métis

and 19.4% of First Nations persons are infected (17). Among the injection drug users of this urban Winnipeg study, the prevalence of HCV was 47.7% (17). The incidence rate (IR) in Eastern Canada injection drug users was 27.1 per 100 person-years (PY) (95% CI: 23.4-30.9 per 100 PY) (18). National surveillance data suggest almost two-thirds (65.7%) of injection drug users are HCV seropositive (19). Young adults may be facing increasing rates of infection contrary to the overall decline (20, 21). In particular, young women have higher rates than young men, possibly reflecting the sociological dynamics and power structures that impede women from negotiating safer drug use or sexual practices (15).

Epidemiology of HIV and Co-infection

In the wake of the silently booming HCV epidemic, HIV also emerged. The blood-borne retrovirus was first described in 1985 and since then, has had an important impact across the globe (22). There are two subtypes (HIV-1 and HIV-2). HIV-1 group M has driven the pandemic, leaving 34 million [31.4 million–35.9 million] people infected (23). As ART continues to be scaled up, rates of AIDS have stabilized. The aims of ART are to suppress HIV viral load to <50 copies/mL, restore CD4+ cell count, prevent HIV transmission, prevent drug resistance, and improve quality of life (24). There are over 20 ART medications available which fall into six classes: nucleoside analogs, non-nucleoside reverse transcriptase

inhibitors, protease inhibitors, fusion inhibitors, integrase inhibitors and C-C motif chemokine receptor antagonists.

In Canada, an estimated 65 000 people are living with HIV—26% of whom remain undiagnosed (25). AIDS-related deaths have been declining since 1995, but the total death toll has reached 22 300 Canadians (25). Each year there are 2300 - 4300 new cases of HIV (25). Men who have sex with men (MSM) account for the largest proportion of new infections (44%) and prevalent cases (51%) (26). The epidemic has been resurging in recent years among MSM likely due to increased unprotected sex and risky behaviours (27, 28). Heterosexual sex accounts for 36% of new infections and 31% of all cases (25). IDU accounts for 17% of new infections and 20% of all cases (25). During 2001 to 2004, the IR of HIV in the IDU population was 2.3–3.3 per 100 PY (19). IDU is the most common route of transmission among women, who account for 26% of new infections and 22% of prevalent cases (25). HIV/AIDS is another health concern affecting minorities disproportionately. Aboriginal people represent 3.8% of the Canadian population but account for 8% of all cases in the country (25). Their infection rate is 3.6 times greater than that of non-Aboriginals (25).

The common transmission routes shared by HCV and HIV make HIV/HCV co-infection fairly common. Worldwide, up to 10 million people are co-infected (29).

In Canada, 20% of HIV-positive individuals have hepatitis C and 5.2% of all HCV-positive individuals have HIV (30). In the IDU population, the prevalence of co-infection is estimated to be 11.7% in Canada (19). A study in British Columbia found young injection drug users to have a co-infection IR of 5.2 (95% CI: 3.8, 6.9) per 100 PY (13). While sexual transmission of HCV is rare in the absence of HIV infection, the acute HCV infection rate is mounting among the MSM population with HIV (31, 32). The main risk factor is multiple unprotected sexual contacts (32).

Concomitant HIV and HCV infection makes for complicated clinical situations. Liver disease, and in particular HCV-related liver disease, has overtaken AIDS-related illness as the leading cause of mortality and morbidity among individuals with co-infection (2, 33, 34). The rate of end-stage liver disease was 3.14 cases per 100 PY in the Canadian Co-infection Cohort (35). Furthermore, clinical outcomes have been consistently worse in HIV/HCV co-infected individuals compared to monoinfected individuals. A study of 3990 people from Denmark showed that co-infected individuals had greater mortality than individuals with HIV alone (mortality rates: 59 deaths/ 1000 PY versus 39 deaths/1000 PY) (36). The discrepancy widened after the year 2000 (mortality rates: 57 deaths/ 1000 PY versus 19 deaths/ 1000 PY). In a multi-centre study from the United States, co-infected individuals had a higher death rate than HIV-monoinfected individuals

and had a 10.9 fold greater risk of cirrhosis after adjusting for age (37). Compared to the HCV-monoinfected, people with co-infection develop hepatocellular carcinoma faster (means: 26 years versus 34 years after infection) (38) and have shorter survival (hazard ratio for death: 1.63) (39).

NATURAL HISTORY OF HIV/ HCV CO-INFECTION

The coexistence of HIV and HCV in one host sets the stage for viral interaction. Observational studies show that HIV affects the natural history of hepatitis C, accelerating the rate of liver fibrosis (40). More rapid fibrotic progression may be associated with immunosuppression from HIV, where CD4 cell levels are reduced, CD8 and CD4 cells are impaired, and CD28 expression is down-regulated (41). T-cell responses are important to immune responses against viral infections such as HCV. Chronic HIV-associated immune activation may also influence liver disease by increasing pro-inflammatory cytokine levels in the circulation.

Furthermore, microbial translocation is hypothesized to accelerate fibrosis in co-infection compared to HCV-monoinfection (42). Early in primary HIV infection, intestinal CD4 cells are targeted causing a “leaky gut” where bacteria and microbial toxins such as lipopolysaccharide escape into the bloodstream in a process known as microbial translocation. Lipopolysaccharides cause liver

inflammation and fibrosis, and may contribute to faster development of cirrhosis in HCV co-infection (43, 44).

The corollary, namely that HCV alters the course of HIV infection, is the subject of active debate. HCV-associated pro-inflammatory cytokines are hypothesized to be deleterious to HIV disease. Some cohort studies have shown that HCV seropositivity is associated with new AIDS-defining clinical events (33). Furthermore, HCV infection is associated with a faster decline in CD4 count before ART, and a seven-fold slower recovery of CD4 count after ART (45).

TREATING HEPATITIS C

Treatment Overview

While no hepatitis C preventive vaccines have progressed past phase I/II clinical trials to date (46), drug treatment is commercially available. The goal of antiviral therapy is to eradicate HCV, so as to achieve SVR. SVR is defined as the absence of HCV RNA by polymerase chain reaction six months after treatment completion. Once a SVR has been achieved, the patient has a 99% probability of remaining HCV RNA negative in the long-term—in the absence of concomitant HIV infection and subsequent HCV re-infection (47).

Hepatitis C can be treated with combination therapy, which is partially modified for different HCV genotypes and the presence of HIV co-infection and cirrhosis. Pegylated interferon alpha and ribavirin are standard of care for HCV genotypes 2, 3 and 4 (8). Two forms of pegylated interferon are available with varying pharmacokinetics: peginterferon alpha-2a (Pegasys, Roche Pharmaceuticals) and peginterferon alpha-2b (Peg-Intron, Schering-Plough Corporation). Both are self-administered subcutaneously once a week. Ribavirin capsules are taken orally in divided daily doses. Treatment of genotypes 2 and 3 does not use weight-based dosing of ribavirin and lasts for 24 weeks. Weight-based dosing and longer treatment durations may be used in some cases of HIV-coinfection. Combination therapy of genotype 4 uses weight-based ribavirin dosing and lasts for 48 weeks. Genotype 1 is most common but unfortunately most difficult to treat. Combination therapy requires an additional NS3/4A protease inhibitor: boceprevir (Victrelis) and telaprevir (Incivek). Guidelines do not recommend one antiviral agent over the other as they have similar efficacies when compared to placebo (48, 49). No head to head randomized controlled trials have been conducted. Triple therapy for genotype 1 consists of pegylated interferon, weight-based ribavirin and a daily orally-administered protease inhibitor. Boceprevir and telaprevir have increased response rates enormously over standard therapy but they still require at least 24-48 weeks of pegylated interferon /ribavirin with its inherent toxicity. Furthermore, the cost of HCV treatment has substantially

increased with combination direct-acting antiviral therapy. Boceprevir alone costs $25 200- $46 200 and the total regimen costs $36 837- $66 148 (50). Telaprevir alone costs $34 968 and the total regimen costs $45 000 - $50 000 (50). The lifetime healthcare cost of an individual infected in 2011 is estimated at $64,490 ($46,780-$73,190) (51). Currently, drug development is progressing at a rapid pace with several direct-acting agents close to licensure (7). This will change the face of HCV treatment as high efficacy interferon-based and interferon-free treatments become a reality and open the door for many to be treated. However, the costs of treating large numbers of HCV patients may be prohibitive as the newer generation of direct-acting agents will be even more expensive (52).

Treatment Response

Different HCV genotypes are associated with different treatment responses. SVR rates from dual therapy in genotypes 2 and 3 mono-infection are 80%, and only 50-70% in genotype 4. Before the introduction of triple therapy for genotype 1 in 2011, SVR rates were 40-50% using dual therapy. Boceprevir and telaprevir have significantly improved response rates, to 67-75% among treatment-naïve patients.

Response rates are less well documented for individuals with HIV co-infection. No clinical trial has explicitly compared SVR rates between co-infected

individuals and HCV-monoinfected individuals. However, it has been suggested that HCV antiviral therapy may be less effective among the co-infected. Studies for dual antiviral therapy (pegylated interferon and ribavirin) in HIV/HCV co-infected individuals showed low rates of SVR (44-73% for genotype 2 and 3, and 17-29% for genotype 1) (53, 54). As in HCV-monoinfection, genotype strongly predicts response rates. However, HIV-related immunosuppression, as measured by pre-treatment CD4+ T cell count, does not seem to predict SVR.

Treatment Initiation

While SVR is desirable regardless of HCV genotype or HIV status, HCV treatment initiation rates remain low. In the United States, initiation rates range from 12 to 28% in chronic HCV-monoinfected individuals (55-57) and 7% in co-infected individuals (6). Higher treatment uptake would be expected in Canada under universal health care. Yet in one Canadian study, antiviral uptake was as low as 1.1% for a community-based cohort of inner city residents (58). In a community-based methadone maintenance program for illicit drug users, the initiation rate was 3.1% (59). It is worthwhile to note that only 5.4% of patients were offered treatment. An academic hepatology outpatient clinic fared best with a treatment initiation rate of 38% (4). Only one study reported national data Canada (17). Reasons for not initiating HCV treatment include medical contraindication, potential treatment non-adherence as perceived by the

healthcare provider, substance abuse, psychiatric co-morbidities, and patient preference (57, 60-62). Other associated factors include increasing age, minority race, unstable housing conditions and having less experienced healthcare providers (4, 55). When healthcare is provided without charge, socio-political barriers to HCV treatment are minor, as found in the Irish healthcare system (63). Individual and provider level barriers play more substantial roles. Among patients attending an integrated HIV/ HCV clinic, the most predictive individual-level barriers were IDU, receipt of opiate substitution, high levels of alanine aminotransferase, and CD4 count <200 cells/uL(63). HCV viral load, HIV viral load, HCV genotype, ongoing ART and gender were not found to be predictive (63). Among patients attending a tertiary care clinic for co-infection in Ottawa, the most common reason for failing to initiate HCV treatment was that HIV management took priority (22% of referrals) (64). Other reasons included loss to follow-up (12%) and patient refusal (12%) (64). While physicians in an international survey cited patient-related factors as the most significant barrier (65), others have noted improvements to HCV treatment initiation through provider-level interventions (52). Practitioners may withhold HCV treatment because of limited knowledge, experience and confidence in HCV management (7). Within the Canadian Co-infection Cohort, the role of the treatment centre was appreciable even after accounting for case mix (unpublished data). Reluctance to treat may be based on patient psychiatric conditions and substance abuse, both

of which are prevalent in the co-infected population (66). A systematic review has, however, demonstrated feasibility and effectiveness of treating these populations (67). Provider-level interventions include establishing multidisciplinary teams, better educating healthcare providers and recognizing substance use as a treatable disorder than an absolute contraindication (52, 62). On the healthcare system and infrastructure level, barriers include geographic accessibility, long wait-times, provincially refused reimbursement of treatment costs, and out-of-pocket costs (7).

Treatment Outcomes

SVR is associated with better outcomes with respect to histology, clinical events and survival. Post-treatment liver biopsies show histologic improvements compared to pre-treatment biopsies not only in HCV-monoinfected individuals, but also in HIV-coinfected individuals (68, 69). Fibrosis usually regresses with successful treatment, and cirrhosis may regress to a limited extent as well. This can be explained by the liver's regenerative properties when the agent of injury is removed. Fibrosis is a pathological process where excess matrix proteins are deposited in the extracellular space. Stellate cells increase scarring and matrix production. In fibrosis regression, there is an increase of collagenase activity and apoptosis of activated myofibroblast-like hepatic stellate cells.

SVR is also associated with reduced morbidity and mortality. In monoinfected SVR-achievers compared to non-responders, there are lower risks of liver-related mortality (relative risk, RR, (95% confidence interval, CI): 0.23 (0.10, 0.52)), hepatocellular carcinoma (RR (95% CI): 0.21 (0.16, 0.27)) and hepatic decompensation (RR (95% CI): 0.16 (0.04–0.59)) (70). Causality is difficult to establish because the 26 studies from the meta-analysis of over 5000 patients were not randomized, and had relatively short follow-up periods compared to the lengthy duration of HCV infection. SVR is not only inversely associated with liver-related mortality. The large Veteran's Affairs Study of 16 864 patients showed SVR is associated with reduced all-cause mortality (hazard ratios for genotypes 1 to 3: 0.70, 0.64 and 0.51 respectively) after controlling for age, body mass index, and co-morbidities (71). A meta-analysis of eight European studies and 286 patients found SVR achievers had 5-year survival rates comparable to the general population (standard mortality ratio (95% CI): 1.4 (0.3, 2.5)) (72). As with HCV-monoinfected individuals, individuals co-infected with HIV experience similar clinical benefits after clearing HCV in treatment (73). The Spanish study found SVR-achievers, compared to non-achievers, had lower rates of liver decompensation (IR (95% CI): 0.23 per 100 PY (0.01, 1.3) vs. 4.33 per 100 PY (3.2, 5.8)), hepatocellular carcinoma (IR (95% CI): 0 per 100 PY (0, 0.8) vs. 0.83 per 100 PY (0.4, 1.6)), and liver transplantation (IR (95% CI): 0 per 100 PY (0, 0.8) vs. 1.02 per 100 PY (0.5, 1.8)) (73). In a follow-up study after five years,

individuals with successful HCV treatment compared to non-achievers had both reduced liver-related mortality (IR (95% CI): 0.10 per 100 PY (0, 0.2) vs. 1.11 per 100 PY (0.8, 1.4)) and lower all-cause mortality (IR (95% CI): 0.26 per 100 PY (0.1, 0.4) vs. 1.82 per 100 PY (1.5, 2.2)) (74).

SVR may also impact patient quality of life and other patient behaviours. However, to my knowledge these have not been documented in the co-infected population.

HEALTH-RELATED QUALITY OF LIFE

Health-related Quality of Life Overview

Health-related quality of life (HRQOL) is broader than physical and clinical characteristics. It encompasses non-medical aspects including the psychological, interpersonal, spiritual, economic and environmental. This includes perceived health, outlook on life, daily living, social support and activity.

A person's HRQOL can be reflected in a single utility score, which is a numerical value representing an individual's preference for a health outcome. The scale ranges from zero, the equivalent to death, to one, the equivalent of perfect health. Health preference scores can be measured directly through standard gamble and time trade-off approaches, or indirectly through HRQOL

questionnaires mapped onto an econometric scoring algorithm. Many generic HRQOL questionnaires have been developed. They apply across different populations with varying demographic and health profiles, allowing for cross-comparisons.

In the hepatitis C and HIV literature, two commonly used tools are the Medical Outcomes Study 36-Item Short Form (SF-36) and European Quality of Life-five dimensions (EQ-5D). The SF-36 contains 36 questions measuring eight health domains (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health). The SF-36 has demonstrated good reliability and validity for HIV-infected and chronic hepatitis C patients (75, 76). The EQ-5D contains one question for each of five health dimensions: mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression (77). Respondents indicate the level of perceived problems for each dimension (level 1, no problem; 2, some problems; and 3, extreme problems). The health domains can be scored into a composite utility score (zero to one). In the EQ-5D, respondents also rate their health using a 20 centimetre vertical visual analogue scale (VAS), from zero (worst imaginable state) to 100 (best imaginable health state possible). There are caveats to reporting HRQOL ratings as VAS scores. VAS measures the strength of preference under conditions of certainty rather than uncertainty. However, utility

theory requires uncertainty and elements of choice (78). Empirically, VAS data may be influenced by end aversion bias, where respondents are reluctant to use the extreme ends of a continuous scale (78). Compared to utility scores, respondents tend to report lower scores (worse HRQOL) on the VAS (79).

In the hepatitis C population, the EQ-5D has been shown to perform as well as other longer questionnaires (SF-36 and Sickness Impact Profile-68) in terms of reliability and construct validity (80). In terms of sensitivity to response differences, the EQ-5D could discriminate between patients with compensated cirrhosis and decompensated cirrhosis (80). In the advanced HIV population, the EQ-5D has been shown to have good construct validity and was moderately well correlated with the Medical Outcomes Study HIV Health Survey (81). However, the EQ-5D was less responsive to monitoring adverse events (81). The EQ-5D has been tested for validity and reliability and has been successfully applied in populations living with AIDS (82).

Health-related Quality of Life in Co-infection

Few studies have examined the HRQOL of HIV/HCV co-infected individuals, as the focus has predominately been on the monoinfected. HRQOL impairment is seen in the HIV monoinfected (83, 84) and the HCV-monoinfected populations

(85, 86). HRQOL improves in the latter group with antiviral therapy and SVR (87, 88). It is not known if HRQOL improves with SVR in co-infected individuals.

Some suggest that HIV/HCV co-infected individuals have worse HRQOL compared to the HIV-monoinfected (34). The disparity in HRQOL may not be directly attributable to the co-morbid HCV infection, but rather to poverty, IDU, depression, physical symptoms, healthcare utilization and poor access to HCV treatment (34, 89). Other studies suggest co-infected individuals have similar HRQOL to the HIV-monoinfected (56, 90) and to the HCV-monoinfected (91). Lack of a statistically significant difference in HRQOL may be related to the studies' small sample sizes.

HEALTH SERVICE UTILIZATION

Health Service Use in Co-infection

The literature is sparse regarding healthcare utilization among people with concurrent HIV and HCV infections. A search identified eight papers which discuss health resource utilization in co-infected people. Such research is frequently done in the context of an HIV patient cohort or an HCV patient cohort, where co-infected individuals are a small subgroup.

Overall, co-infected individuals appear to use more healthcare services than HIV-monoinfected individuals. An American study on quality of life among 135 urban HIV-infected IDUs compared to 57 urban co-infected IDUs also examined health service utilization as a secondary objective (89). Although both groups had regular health service contacts, co-infected individuals had significantly more physician office visits within the last six months of filling the questionnaire (proportion, 97.8% versus 86.4%). Co-infected individuals had significantly more emergency room visits and hospitalizations in the preceding six months (odds ratios, 2.18, 2.71 respectively). In a multi-centre prospective cohort study also conducted in the United States, Linas and colleagues confirmed that co-infected patients had greater incidences of hospitalizations, emergency department visits and disability days compared to HIV-monoinfected patients, whilst adjusting for CD4 levels (92). The greatest disparity in utilization was seen among individuals with CD4 ≤ 350 cells/ microL. HCV serostatus, age, sex, history of AIDS-defining event, current CD4 count, and current HIV RNA were significantly associated with resource utilization. When these factors were adjusted for in the analysis, the rate ratios comparing co-infected and HIV-monoinfected were 1.8 for hospital nights, 1.7 for emergency visits and 1.6 for disability days. Further, co-infection was associated with days spent in bed and days spent with reduced daily activities.

The corollary, that co-infected populations have greater healthcare utilization than HCV-monoinfected populations, also appears to hold true. A Canadian study surveyed IDUs from one injection site about health services used during the preceding six months (93). Co-infected participants reported significantly greater proportions of having seen a doctor or nurse (92% versus 81%), having gone to the emergency room (32% versus 22%, p= 0.004), and having been hospitalized (17% versus 9%) compared to HCV-monoinfected. In addition, co-infected participants spent longer in hospital than monoinfected participants (median, 7 days versus 5 days). However, co-infected individuals were no more likely to use ambulatory services (3% versus 4%). It is interesting to note that monoinfected individuals reported higher rates of HCV-related symptoms, but co-infected participants believed their viral hepatitis was affecting them more. Accordingly, the co-infected group received significantly greater hepatitis-related follow up care such as blood work, liver biopsies and specialist referrals (proportion, 89% versus 69%).

Several studies have specifically addressed hospitalizations. Two studies from an AIDS centre in Madrid reported the proportion of hospitalizations due to HCV (94, 95). Their first study from 1991 – 1996 showed 143 (8.6%) of 1670 admissions were due to decompensated liver disease (94). Ninety-three (89%) of these liver-related admissions were caused by HCV alone or in combination with other

hepatotropic viruses. According to the clinic's 1996 – 2004 data, chronic liver disease admissions increased over the years and became the second highest cause of hospitalization after bacterial pneumonia (95). HCV alone was the cause of 161 of 345 (47%) chronic liver disease hospital admissions, and combinations with other hepatic viruses were the cause of 216 (63%) admissions. Of the 31 chronic liver disease-related in-hospital deaths over the nine year period, 23 (74%) were attributable to HCV alone and 6 (19%) were attributable to HCV in combination with other hepatic viruses.

Grant and colleagues also examined time trends for hospitalizations in the United States using national data (96). From 1994 to 2001, HCV patients had 25-30% annual increases in hospitalizations, charges, hospital days and physician visits. HIV co-infected patients experienced nearly 3 times as many liver-related hospitalizations in 2001 compared to 1994. In this same time period, they experienced a 7.5 fold increase in overall hospitalizations. HIV hospitalizations occurred 3.4 times more frequently and cost 2.9 times more than HCV liver-related hospitalizations.

A Canadian study confirmed the growing burden of HCV infection on hospital systems (97). Administrative hospital data from the Calgary Health Region were examined from 1994 to 2004. Of the 4002 admissions with a primary or

secondary diagnosis of HCV infection, 869 (22%) hospitalizations were liver-related. During the 11 year period, liver-related hospitalizations, lengths of stay and in-hospital mortality quadrupled, increasing an average of 15 to 18% per annum. HIV co-infected patients accounted for 11% of the hospitalizations, 8.1% of which were liver-related. These individuals tended to be younger and more often male, compared to their HIV-negative counterparts. They accounted for an increasingly greater proportion of HCV-related admissions through the years. As incidence of HIV-related complications decreases and survival improves, HIV co-infected patients live long enough to develop HCV-related sequelae (74). HIV co-infected people experienced large average annual increases in frequency and lengths of stay for both liver-related admissions and all-cause HCV admissions (annual increases, 30-40%) (97).

Gebo and colleagues examined the relationship of HCV to hospital admission rates, intensive care utilization and discharge diagnoses in an American urban cohort of 3730 HIV patients (98). Overall, liver-related admissions increased 5 fold from 1995 to 2000 (5.4 to 26.7 per 100 PY). HCV co-infection was a risk factor for hospitalization (incidence rate ratio (IRR), 1.75), as were female gender, Black race, age <37 years and CD4 count <200 cells/ mm^3. There was no difference in mean lengths of stay between HIV-monoinfected and HCV-

coinfected patients (7.1 versus 7.0 days). Likewise, there was no difference in intensive care utilization.

The above studies clearly demonstrate the growing impact of HCV and HIV co-infection on health service utilization. Temporal trends indicate liver-related complications are increasing and now represent leading causes of hospitalizations and mortality as other complications of HIV disease are better controlled by antiretroviral therapy and patients survive long enough to develop advanced liver disease. Comparisons between co-infected individuals and monoinfected individuals indicate the former fare worse and make greater use of healthcare. These findings have implications for costs and projections of future burden on our healthcare systems that need to be addressed.

Costs

In the United States, hepatitis C accounts for approximately 27 000 hospitalizations and $500 million in hospital costs annually (96). The overall burden of total direct healthcare costs exceeds $1 billion USD (99). In Canada, the treatment of HCV-related disease may cost the healthcare system an estimated $103 to $158 million each year until 2040 (100). Other Canadian projections suggest liver-related HCV hospitalizations will cost as much as $240 million in the year 2020 (97).

One study examined healthcare system costs from HCV infections and a subset of HIV/ HCV co-infections. Krajden and colleagues determined predictors of costs and estimated net costs of HCV infection comparing HCV-seropositive individuals with propensity score-matched HCV-seronegative individuals (matched on socioeconomics and co-morbidities including HIV infection) (101). The perspective was that of a Canadian provincial ministry of health, where only publicly insured direct medical costs were included. The authors found that hospitalization was the highest driver of costs compared to same-day surgery costs, drug costs, and medical services plan costs (physician, outpatient services, outpatient diagnostic and laboratory services). Costs increased with disease progression. Net costs for early disease stage after diagnosis and late disease stage 6 months prior to death were $1850 and $6000 (2005 CAD) respectively. Among cases, costs were further driven up by HIV co-infection in all HCV disease states. Other factors were associated with to increased costs including age, co-morbidities, mental illness and illicit drug use, but their effect was not seen in all HCV disease stages.

In summary, HIV/ HCV co-infection is very common in vulnerable populations, namely among Aboriginals, injection drug users and MSM. HIV negatively impacts the course of HCV progression and leads to reduced quality of life and

increased morbidity, mortality and costs from health services. Existing HCV treatments are effective, but are underutilized and very costly. It is important to have longitudinal data on the impact of co-infection on quality of life and health service use. In particular, it is important to understand the impact of effective HCV therapy on these outcomes.

CHAPTER 3: METHODS

SETTING & PARTICIPANTS

The Canadian Co-infection Cohort has been recruiting individuals from 18 HIV referral centers across Canada (one site in Nova Scotia, five in Québec, six in Ontario, one in Alberta, four in British Columbia, one in Saskatchewan) since 2003 and is ongoing. The present study used data collected from 2003 to January of 2013. Appendix I lists the HIV referral centres and their dates of recruitment. Each HIV clinic routinely screened its patients for HCV infection. All eligible patients were approached for cohort enrolment. The cohort eligibility criteria were 1) age over 16 years old; 2) documented HIV infection (HIV positive by enzyme-linked immunosorbent assay with Western blot confirmation); and 3) evidence of HCV infection (HCV seropositive by enzyme-linked immunosorbent assay with recombinant immunoblot assay II or enzyme immunoassay confirmation, or if serologically false negative, then HCV RNA positive). Details of the cohort profile are reported elsewhere (102).

Participants were seen in clinic every six months to complete an extensive questionnaire and to provide a blood sample. Information on sociodemographics, HRQOL, health service use and substance use was self-reported. Clinical

characteristics and HCV treatment information were ascertained by the research coordinator. Polymerase chain reaction with a lower detection limit of 50 international units/ millilitre tested for the presence of HCV RNA in the blood samples (Roche COBAS ® AMPLICOR assay, Roche Molecular Systems, Inc., Branchburg, NJ, USA). Participants received $15 compensation per study visit.

INCLUSION/ EXCLUSION CRITERIA

The total cohort as of January 2013 recruited 1153 participants. For this study, a subcohort of all patients without SVR at cohort entry was included. This comprised both participants with ongoing chronic HCV infection (HCV RNA positive) and participants who had previously spontaneously cleared their HCV infection (HCV seropositive, but HCV RNA negative). Patients receiving HCV treatment at the time of cohort entry were excluded. The EQ-5D and health service use data were only captured in the cohort questionnaire as of 2007. Patients whose last visit was before 2007 did not have these data and were therefore excluded.

PARTICIPANT GROUPS

Overall sample —Figure 1 outlines the study flow. The two major groups in the study sample are: (i) participants with ongoing chronic HCV infection (detectable HCV RNA, either treatment-naïve or treatment-experienced at cohort entry) and

(ii) participants who had already spontaneously cleared their HCV infection (undetectable HCV RNA and treatment-naïve at cohort entry). Participants with no HCV RNA results (but a positive serologic test) were assumed to have chronic HCV infection. Participants with missing HCV treatment history were assumed to be treatment-naïve.

Among the participants with ongoing chronic HCV infection, treatment status was classified as: (i) HCV treatment started after cohort entry, (ii) prior HCV treatment with treatment failure and no retreatment, or (iii) untreated after cohort entry.

Subsample: Participants who started HCV treatment after cohort entry—This subgroup was the focus of our primary analysis, because trends before and after treatment could be observed. Their treatment outcomes were (i) SVR, (ii) no SVR, (iii) still on treatment, or (iv) unknown. Traditionally, SVR status is ascertained six months after HCV treatment completion using a polymerase chain reaction assay with a lower limit of detection of 50 international units/ millilitre or less. Current evidence suggests that failure to achieve SVR can be reliably assessed by 12 weeks of therapy or earlier (103-105). Patients who have not responded by 12 weeks (called null response) have nearly no probability of responding afterwards (8, 106). On the other hand, patients who have responded by 12 weeks may relapse after treatment completion (107). Relapse most often

occurs within 12 weeks of treatment discontinuation regardless of HIV infection status (108). For these reasons, in the present study SVR-achievers were defined as having undetectable HCV RNA at least six months after treatment completion; non-achievers as having detectable HCV RNA at least 12 weeks after treatment initiation; unknown status as having no HCV RNA results available; and still on treatment as having not stopped therapy at the last recorded visit.

Hepatitis C Treatment

We considered both current and historic treatment regimens. Information on past treatment, current treatment, start dates and end dates were collected by trained research coordinators at each visit. Coordinators verified data from medical record reviews at the recruiting HIV centre.

EXPOSURE ASSESSMENT

SVR—In the primary analysis, comparing SVR achievers and non-achievers with respect to HRQOL and other outcomes, the exposure of interest was SVR as defined above.

HCV infection—In the secondary analysis, the exposure of interest was the presence versus absence of ongoing chronic HCV infection at cohort entry.

Hence we compared participants with ongoing HCV infection with those who had already spontaneously cleared their HCV infection by the time of cohort entry. The analysis included both participants who received treatment during follow-up (regardless of treatment outcome) and participants who did not receive treatment during follow-up.

OUTCOME ASSESSMENT

Health-related quality of life— The self-administered EQ-5D measured current HRQOL using (i) VAS scores, and (ii) five dimensions of health (77, 109). On the VAS, participants rated their current overall health state from 0 being “worst imaginable health” to 100 being “best imaginable health”. For the health domains, participants reported three levels of difficulty: no problems, some problems, and extreme problems. For our analysis, we collapsed the latter two levels in order to create dichotomous outcome variables (any problems versus none). We compared the two groups using a two-sample test of proportion. Next, we combined the health domains into a single health preference score using general population value sets from Canada and the United States Valuation methods from the countries have been described elsewhere (64, 110). Algorithms for calculating health preference scores were accessed from the Agency for Healthcare Research and Quality and the University of British Columbia (65, 110). Utility scores incorporate public preferences which are informative to policy-

makers. They allow for comparisons of disease and treatment outcomes having HRQOL measures on a generic scale.

Health services—Participants reported the frequency of visits to six health services: (a) walk-in clinic, (b) emergency room, (c) overnight stay in a hospital, (d) a general practitioner, (e) an HIV clinic, and (f) a specialist (e.g. liver, diabetes). At cohort entry, participants reported use in the preceding six months. During follow-up, participants reported use since the last interview. See Appendix II for the open-ended questions from the questionnaire.

Substance use—The drug history section of the questionnaire was self-administered; data were collected on current substance use (Y/N), frequency of current use, and past use. Participants reported extensively on injection drug use, snorting/ sniffing, marijuana smoking, tobacco smoking, and alcohol consumption. Binge drinking was defined in our study as having six or more drinks on one occasion, as described in the Alcohol Use Disorders Identification Test (18).

Liver fibrosis—In relation to examining alcohol consumption, we indirectly assessed liver fibrosis in participants over time. Specifically, we used the aspartate aminotransferase to platelet ratio index (APRI) score as a surrogate

marker for fibrosis. APRI was calculated as follows for each participant at each visit: 100 × (aspartate aminotransferase [international units per litre] ÷ upper limit of normal [international units per litre]) ÷ platelet count [10^9 per litre] (111). An APRI score less than 0.5 is considered indicative of the absence of fibrosis and APRI ≥ 1.5 indicative of significant fibrosis (i.e. equivalent to greater than or equal to F2 on the METAVIR scale on liver biopsy) (112, 113).

Mortality—Detailed mortality data were collected using specific case report forms (i.e. data sources used, patient risk factors, co-morbidities, medications before death, etc.) and through linkage with provincial vital statistics/death certificates in Quebec, Alberta and British Columbia. Causes of death were classified centrally as one of six categories: end-stage liver disease, AIDS, cancer, overdose, other, or unknown. Details of classification are described elsewhere (35).

STATISTICAL ANALYSIS

We examined HRQOL, health service use and substance use in two analyses. Analysis 1 compared outcomes in SVR-achievers with non-achievers. This examined the impact of clearing HCV pharmacologically. Analysis 2 compared outcomes in participants with ongoing chronic HCV (including the subgroups: treatment starters, treatment failures, and never treated) with those in participants who had spontaneously cleared their HCV infection at the time of

cohort entry. This examined the impact of clearing HCV spontaneously. All statistical analyses were performed using Stata 11 (StataCorp. 2009. College Station, TX: StataCorp LP.).

Analysis 1: SVR-achievers versus non-achievers

Health-related quality of life—Firstly, we summarized the HRQOL data over time. We calculated median VAS scores for the two participants groups from pre-treatment to one year post-treatment. VAS scores were compared using the two-sample Mann-Whitney U test. We calculated absolute change in VAS score for each individual from pre-treatment to (i) six months post-treatment completion and (ii) one year post-treatment completion. We reported the median absolute change overall and the median absolute change stratified by tertiles of baseline VAS scores. We performed a multiple linear regression on the VAS absolute change adjusting for pre-treatment VAS scores. We selected a linear regression because the absolute change in VAS scores did not violate the normality assumption. SVR-achievers and non-achievers may differ in HRQOL to begin with because of differences in gender, income, end-stage liver diseases, stigma experienced, etc. Hence, adjusting for pre-treatment HRQOL would be a proxy for both known and unknown confounders. In addition to describing and modelling the VAS scores, we described the five dimensions of health. We calculated the proportion of participants with any problems in each dimension

over time. Next, we calculated and compared the median utility scores over time among SVR achievers and non-achievers using the two-sample Mann-Whitney U test.

Health service use—Secondly in analysis 1, we examined health service utilization. We calculated IRs and IRRs at two time-points: pre-treatment and six months post-treatment. The IR for each health service was calculated for SVR-achievers and non-achievers respectively using the equation: number of visits/ total PY. The total PY were summed from every individual's time contribution since the last interview. We calculated an IRR using the equation: $IR_{exposed}$/ $IR_{unexposed}$, where exposure was SVR.

Next, we modelled health service use after treatment as predicted by SVR (yes/no). The health services modelled were in-patient visits (overnight hospital stays and emergency room visits), out-patient visits (visits to the general practitioner, HIV clinic, and specialist), and walk-in clinic visits. We adjusted for potential confounding using health service use prior to treatment. Differences in utilization were evident among SVR-achievers and non-achievers before treatment. Such disparity could be explained by age, sex and many other confounders. Hence, adjusting for pre-treatment utilization would be a proxy for both known and unknown confounders. We selected a negative binomial

regression because the count data were over-dispersed, where the conditional variance exceeded the conditional mean. Overall, our model equation was:

log (event frequency) = log (exposure time) + beta0 + beta1 * (event rate prior to treatment) + beta2 * (SVR)

The log exposure time was an offset to account for varying PY contributions from each individual since the last interview.

Substance use—We described substance use over time from cohort entry to one year post-treatment. Specifically, we calculated the proportion of SVR-achievers and non-achievers using injection drugs, non-injection drugs, marijuana, tobacco and alcohol at baseline, six and twelve months. Given that alcohol consumption can accelerate liver fibrosis (114), we analyzed fibrosis. We determined the median APRI scores for SVR-achievers and non-achievers over time and compared the scores using the two-sample Mann-Whitney U test.

Mortality—Finally, we examined causes of death and compared mortality rates between SVR-achievers and non-achievers.

Analysis 2: Chronic HCV and spontaneous clearers—Firstly, we described HRQOL by calculating median VAS scores at cohort entry. Secondly, we described healthcare use by calculating IRs at cohort entry. At recruitment,

participants reported utilization in the preceding six months. We calculated IRRs at cohort entry comparing the chronically-infected and clearers, where the exposure was current HCV infection. Furthermore, we compared the chronic HCV subgroups, treatment starters and never treated, by calculating the IRRs at cohort entry where the exposure was HCV treatment.

TIME-POINTS

The two analyses above considered four time-points overall: cohort entry, pre-treatment, six months post-treatment, and one year post-treatment. Pre-treatment referred to the visit where HCV treatment was initiated. If treatment was initiated between study visits, we considered the visit immediately prior to the initiation date to be the pre-treatment visit. Six months post-treatment referred to the visit that took place six months (± 3 months) after HCV treatment completion. One year post-treatment referred to the visit that took place 12 months (± 3 months) after HCV treatment completion.

SENSITIVITY ANALYSES

Redefining SVR

To increase sample size in the primary analysis, we used a modified definition of SVR as supported by growing evidence (detecting treatment failure at 12 weeks post-treatment initiation and success at six months post-treatment completion) (8,

103, 104, 106). In sensitivity analyses, we re-examined the health outcomes among SVR-achievers and non-achievers using (i) the gold standard definition of SVR (both failure and success ascertained at least six months after treatment discontinuation for all participants), and (ii) a broader definition of SVR (failure as detectable HCV RNA at least 12 weeks post-treatment initiation and onwards; success as undetectable HCV RNA at least three months post-treatment completion).

Additional Time-points

Post hoc, we examined two additional time-points in Analysis 1 comparing the HRQOL of SVR-achievers and non-achievers. Originally, we analyzed HRQOL six (±3) months after treatment completion, meaning participants were omitted from analysis if they were not seen during that period. In sensitivity analyses, we retained participants by analyzing the first visit after treatment completion and the visit when SVR status was determined. The latter visit could have been anytime beyond six months after treatment completion for SVR-achievers and anytime beyond 12 weeks after treatment initiation for non-achievers. This visit where status was determined may not have necessarily occurred during the time window specified in the original analysis.

Firstly, we examined the median EQ-VAS scores at the two time-points. Next, we used linear regression to model individual absolute change in scores from pre-treatment to the additional time-points. We adjusted for the same covariates as in the model used for the primary analysis. In addition, we included a time variable to account for the variable duration from the end of HCV treatment to the new time-points.

ETHICS

The research protocol was approved by the research ethics boards of all participating cohort sites. Participants provided written informed consent to enroll in the cohort and to have personal data used in nested studies including the study presented here.

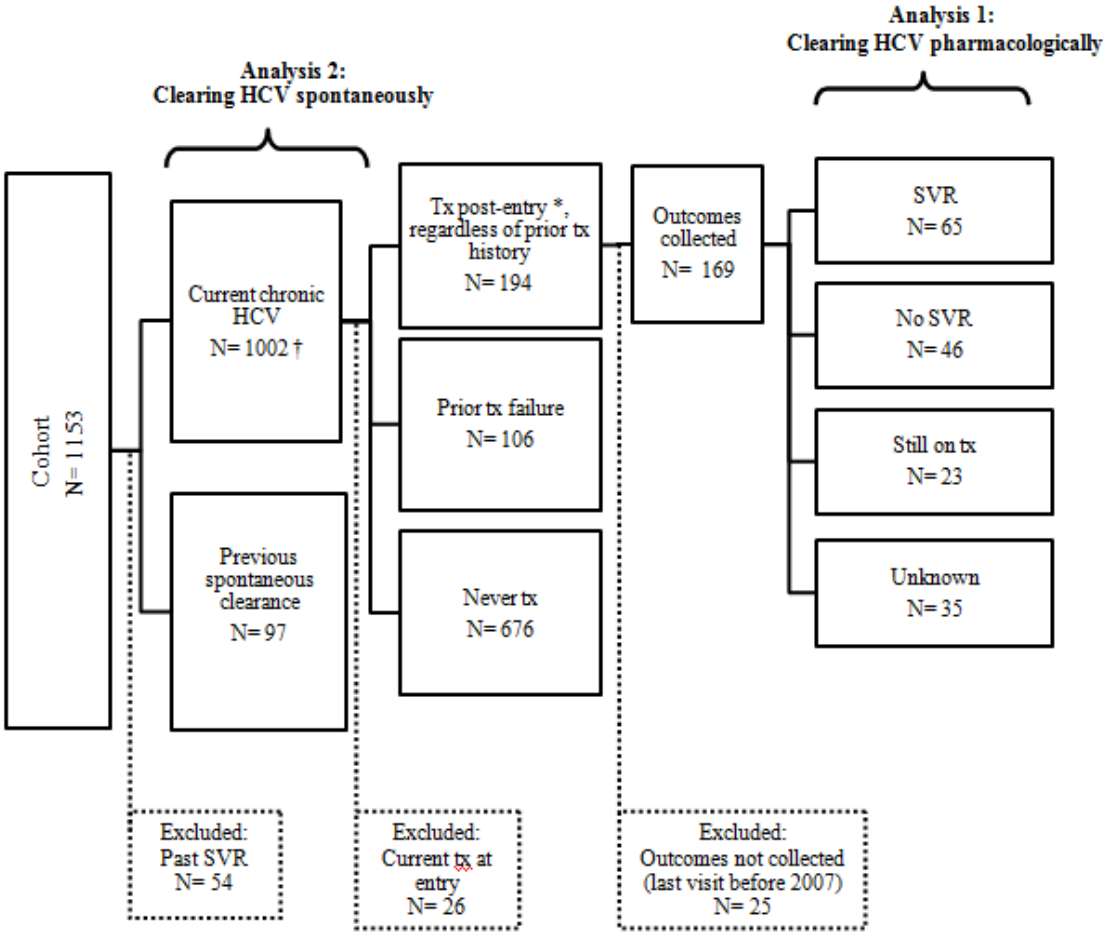
CHAPTER 4: RESULTS

STUDY POPULATION

Figure 1 shows the study flow. The cohort recruited 1153 participants. The study sample included a total of 1099 eligible participants of whom 1002 (91.2%) were chronically infected with HCV and 97 (8.8%) had spontaneously cleared their HCV infection. Among the chronic group, there were 676 participants (67.5%) who were never treated for HCV, 106 (10.6%) who failed prior treatment and 194 (19.4%) who started treatment during follow-up. One hundred sixty-nine who started treatment (87.1%) had treatment outcomes data collected—of whom 65 (38.5%) achieved SVR, 46 (27.2%) did not achieve SVR, 35 (20.7%) had ongoing treatment and 23 (13.6%) had unknown treatment outcomes.

Over time, 44 SVR-achievers (68%) and 19 non-achievers (41%) came to a study visit six (±3) months after treatment completion. Twenty-two SVR-achievers (34%) and 18 non-achievers (39%) came to a study visit twelve (±3) months after treatment completion.

Figure 1: Study flow of participant selection.



† Assumed participants had current chronic HCV if no HCV RNA tests were ever done at visits, (N=120)

* N=178 were treatment naive

‡ Assumed participants missing past HCV medications data did not have prior treatment, (N=9)

Abbreviations: HCV hepatitis C virus, tx treatment, 6m post-tx six months post-treatment completion, 1yr post-tx one year post-treatment completion

Tables 1A and 1B show the sociodemographic and clinical characteristics of the participants according to treatment status and SVR status respectively. Overall, the majority of participants were middle-aged white men with a history of injection drug use. Majority of the sample (77%) had monthly income of less than $1500 and were unemployed (77%), mostly due to health reasons. Few were immigrants (9%). SVR-achievers and non-achievers differed in terms of age, gender, education and income although there was no statistical significance. The most common HCV genotype was genotype 1 (overall: 58%) which accounted for 78% of infections among non-achievers as compared to only 55% of SVR-achievers.

Table 1A: Participant characteristics at cohort entry.

	All: Chronic HCV and Cleared (N= 1099)	Tx post-entry (N=194)	No Tx post-entry: Prior tx failure and Never tx (N=782)
Age, median (Q1, Q3)	44.6 (39, 50)	43.4 (36, 48)	44.5 (39, 50)
Female (%)	288 (26.2)	30 (15.5)	212 (27.1)
Ethnicity (%) [a]			
Aboriginal	174 (15.8)	15 (7.7)	131 (16.8)
Black	42 (3.8)	10 (5.2)	30 (3.8)
White	858 (78.1)	160 (82.5)	609 (77.9)
Born outside Canada (%)	97 (8.8)	41 (21.1)	56 (7.2)
Married/ common law (%)	208 (19.0)	34 (17.5)	152 (19.4)
Living situation (%)			
Fixed address	941 (85.6)	170 (87.6)	664 (8.5)
Live in shelter	89 (8.1)	14 (7.2)	65 (8.3)
Homeless	52 (4.7)	7 (3.6)	39 (5.0)
≥ High school (%)	281 (25.6)	59 (30.4)	191 (24.4)
Unemployed (%)	842 (76.6)	131 (67.5)	624 (79.8)
For health reasons	672 (61.1)	97 (50.0)	507 (64.8)
For lifestyle reasons	83 (7.6)	14 (7.2)	59 (7.5)
But able to work	48 (4.4)	12 (6.2)	30 (3.8)
Monthly income ≤ $1500 (%)	843 (76.7)	843 (76.9)	600 (76.7)
HCV genotype (%)[b]			
1	638 (58.1)	120 (61.9)	487 (62.3)
2	41 (3.7)	10 (5.2)	30 (3.8)

3	154 (14.0)	39 (20.1)	106 (13.6)
4	26 (2.4)	8 (4.1)	16 (2.0)
Ever injected drugs (%)	890 (81.0)	145 (74.7)	645 (82.5)
Current substance use (%)			
Alcohol	565 (51.4)	99 (51.0)	413 (52.8)
Tobacco smoking	843 (76.7)	129 (66.5)	619 (79.2)
Marijuana	573 (52.1)	89 (45.9)	430 (55.0)
Cocaine	733 (66.7)	109 (56.2)	542 (69.3)
Crack	270 (24.6)	44 (22.7)	198 (25.3)
Heroin	420 (38.2)	53 (27.3)	313 (40.0)

[a] More than one ethnicity may be reported.

[b] May not add to 100% due to missing data.

Abbreviations: HCV hepatitis C virus, tx treatment, Q1 first quartile, Q3 third quartile

Table 1B: Participant characteristics at cohort entry and at pre-treatment visit.

	Analysis 1		Analysis 2	
	Pre-treatment		Cohort Entry	
	SVR (n= 65)	No SVR (n= 46)	Chronic HCV (n= 1002)	Cleared (n= 97)
Age, median (Q1, Q3)	45.9 (38, 51)	48.4 (45, 53)	44.5 (39, 50)	45.1 (40, 50)
Female (%)	13 (20.0)	7 (15.2)	246 (24.6)	42 (43.3)
Ethnicity (%) [a]				
Aboriginal	5 (7.7)	3 (6.5)	149 (14.9) †	25 (25.8) †
Black	2 (3.1)	2 (4.4)	41 (4.1)	1 (1.0)
White	54 (83.1)	39 (84.8)	789 (78.7)	69 (71.1)
Born outside Canada (%)	11 (16.9)	6 (13.0)	90 (9.0)	7 (7.2)
Married/ common law (%)	10 (15.6)	9 (19.6)	194 (19.4)	14 (14.4)
Living situation (%)				
Fixed address	58 (89.2)	41 (89.1)	862 (86.0)	81 (83.5)
Live in shelter	7 (10.8)	4 (8.7)	80 (8.0)	10 (10.3)
Homeless	0 (0.0)	1 (2.2)	46 (4.6)	6 (6.2)
≥ High school (%)	20 (30.8)	11 (23.9)	262 (26.2)	19 (19.6)
Unemployed (%)	47 (72.3)	38 (82.6)	772 (77.0)	73 (75.3)
For health reasons	38 (58.5)	33 (71.7)	618 (61.7)	57 (58.8)
For lifestyle reasons	1 (1.5)	1 (2.2)	74 (7.4)	9 (9.3)
But able to work	4 (6.2)	2 (4.4)	42 (4.2)	6 (6.2)
Monthly income ≤ $1500 (%)	45 (69.2)	37 (80.4)	762 (76.1) †	83 (85.6) †
HCV genotype (%) [b]				
1	36 (55.4) *	36 (78.3) *	626 (62.5) †	14 (14.4) †
2	5 (7.7)	0 (0.0)	40 (4.0)	1 (1.0)

3	13 (20.0)	7 (15.2)	149 (14.9) †	5 (5.2) †
4	2 (3.1)	1 (2.2)	26 (2.6)	0 (0.0)
Ever injected drugs (%)	47 (72.3)	35 (76.1)	805 (80.3)	85 (87.6)
Current substance use (%)				
Alcohol	27 (41.5)	20 (43.5)	521 (52.0)	46 (47.4)
Tobacco smoking	44 (67.7)	30 (65.2)	766 (76.5)	79 (81.4)
Marijuana	31 (47.7)	22 (47.8)	530 (52.9)	45 (46.4)
Cocaine	6 (9.2)	8 (17.4)	664 (66.3)	69 (71.1)
Crack	0 (0.0)	1 (2.2)	247 (24.7)	23 (23.7)
Heroin	2 (3.1)	0 (0.0)	375 (37.4)	45 (46.4)

[a] More than one ethnicity may be reported.

[b] May not add to 100% due to missing data.

* $p<0.05$, two tailed, two sample test of proportions between SVR and No SVR

† $p<0.05$, two tailed, two sample test of proportions between Chronic HCV and Cleared

Abbreviations: HCV hepatitis C virus, tx treatment, Q1 first quartile, Q3 third quartile

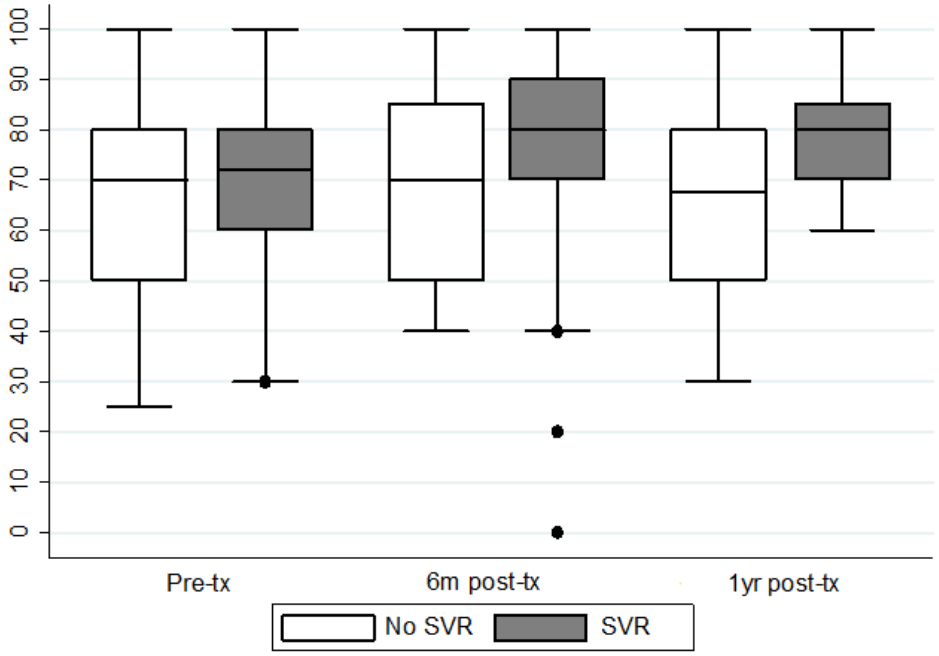
HCV TREATMENT RATES

In the Canadian Co-infection Cohort, the cumulative incidence of HCV treatment initiation after cohort entry was 19.4% overall (194 treated/ 1002 chronic HCV). The cumulative incidence of SVR was 44.5% (65 responders/ 146 with known treatment outcomes); 58.5% (N=38) among HCV genotypes 1, 4 and 27.7% (N=18) among HCV genotypes 2, 3 (N=9 missing genotype).

ANALYSIS 1: SVR-ACHIEVERS AND NON-ACHIEVERS

Health-related quality of life—Figure 2 shows the median VAS scores over time. SVR-achievers and non-achievers scored similarly prior to HCV treatment (median (Q1, Q3): 71 (60, 80) and 70 (47.5, 80) respectively). SVR-achievers had improved six months after treatment completion (median (Q1, Q3): 80 (70, 90))) and plateaued there at one year. Non-achievers remained essentially at baseline levels six months and one year after treatment completion (median (Q1, Q3): 70 (50, 85) and 67.5 (50, 80) respectively). Differences in median VAS scores were statistically significant one year post-treatment ($Z = -2.77$, $p < 0.01$).

Figure 2: Health-related quality of life rating using the EQ-5D visual analogue scale (range: 0 to 100).



	Before tx	6m post-tx	1yr post-tx
SVR	71 (60, 80)	80 (70, 90)	80 (70, 95.8) *
No SVR	70 (47.5, 80)	70 (50, 85)	67.5 (50, 80) *

Medians (Q1, Q3) are reported.

* $p<0.05$, two-tailed, two-sample Mann-Whitney U test

Abbreviations: tx treatment, SVR sustained virologic response

Table 2 summarizes the absolute change in VAS scores over time, calculated for every individual. SVR-achievers experienced a median 13 unit individual improvement from baseline to one year post-treatment completion. Non-achievers experienced a modest individual change of 5 unit improvement from baseline to one year post-treatment. Table 3 summarizes the absolute change over time, stratified by baseline HRQOL scores (low tertile, intermediate tertile and high tertile). People in the low tertile improved VAS scores regardless of SVR status (>18 unit improvement). People in the intermediate tertile drove the overall results seen in Table 2, where SVR-achievers improved VAS scores and non-achievers deteriorated. People in the high tertile decreased in HRQOL regardless of SVR status, although the decrease was much more substantial among non-achievers (16 unit decline). These changes observed at the low and high tertiles may reflect regression to the mean.

Table 4 shows the linear regression results of SVR (yes/no) as the predictor and VAS absolute change as the outcome (pre-treatment to six months post-treatment and to one year post-treatment). After adjustment, SVR-achievers had a greater improvement in VAS scores compared to non-achievers (by 3.4 units and 11.2 units at six months and one year post-treatment, respectively). SVR was significantly associated with HRQOL improvement at one year, despite the imprecision. Pre-treatment HRQOL was a significant confounder.

Table 2: Absolute change in VAS scores within individual: (a) from pre-treatment to six months post-treatment, (b) from pre-treatment to one year post-treatment, and (c) from six months post-treatment to one year post-treatment.

SVR	Before tx	6m post-tx	1yr post-tx
Before tx	x	15 (-5, 20)	12.5 (5, 20)
6m post-tx	x	x	0 (-9.5, 5)
NO SVR	Before tx	6m post-tx	1yr post-tx
Before tx	x	3 (-2, 20)	5 (-7.75, 20)
6m post-tx	x	x	-5 (-12.5, 1)

Medians (quartile 1, quartile 3) are reported.

Table 3: Absolute change in VAS scores, by low, intermediate and high baseline score tertiles.

	Baseline score tertile		
	Low {25-60}	Intermediate {61-80}	High {81-100}
Pre-tx to 6m:			
SVR	18 (9.4, 26.6) [n=15]	2.1 (-6.8, 11.0) [n=26]	-2.5 (-34.3, 29.3) [n=2]
No SVR	19.1 (7.1, 31.1) [n=11]	-12.3 (-42.7, 18.3) [n=4]	-1.0 (-6.4, 4.4) [n=4]
Pre-tx to 1yr:			
SVR	20.6 (10.8, 30.5) [n=8]	9.5 (4.0, 15.0) [n=14]	-- [n=0]
No SVR	18.6 (6.6, 30.5) [n=9]	-3.3 (-17.7, 11.0) [n=6]	-16.3 (-67.6, 35.0) [n=3]

Baseline VAS scores are shown as {tertile}. Means (95% CI) are reported. Sample sizes are shown as [n].

Abbreviations: VAS visual analogue scale, SVR sustained virologic response, tx treatment

Table 4: Linear regression models for absolute change in VAS scores.

	Simple	Multiple
Pre-tx to 6m:		
Presence of SVR (Y/N)	-0.82 (-12.2, 10.6)	3.38 (-7.0, 13.7)
Pre-treatment VAS score (units)	-0.56 (-0.8, -0.3)	-0.58 (-0.9, -0.3)
Intercept		42.90
Pre-tx to 1yr:		
Presence of SVR (Y/N)	8.10 (-2.3, 18.5)	11.15 (2.8, 19.5) *
Pre-treatment VAS score (units)	-0.53 (-0.8, -0.3)	-0.58 (-0.8, -0.3)
Intercept		40.54

Coefficients (95% CI) are reported.

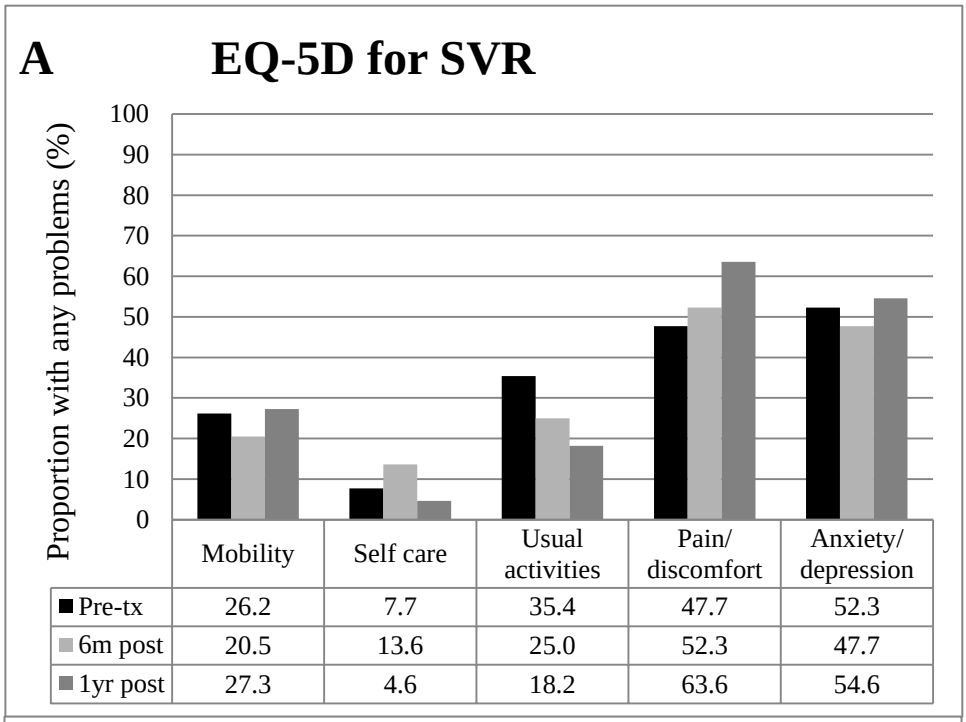
* Statistically significant 95% CI

Abbreviations: VAS visual analogue scale, tx treatment, SVR sustained virologic response

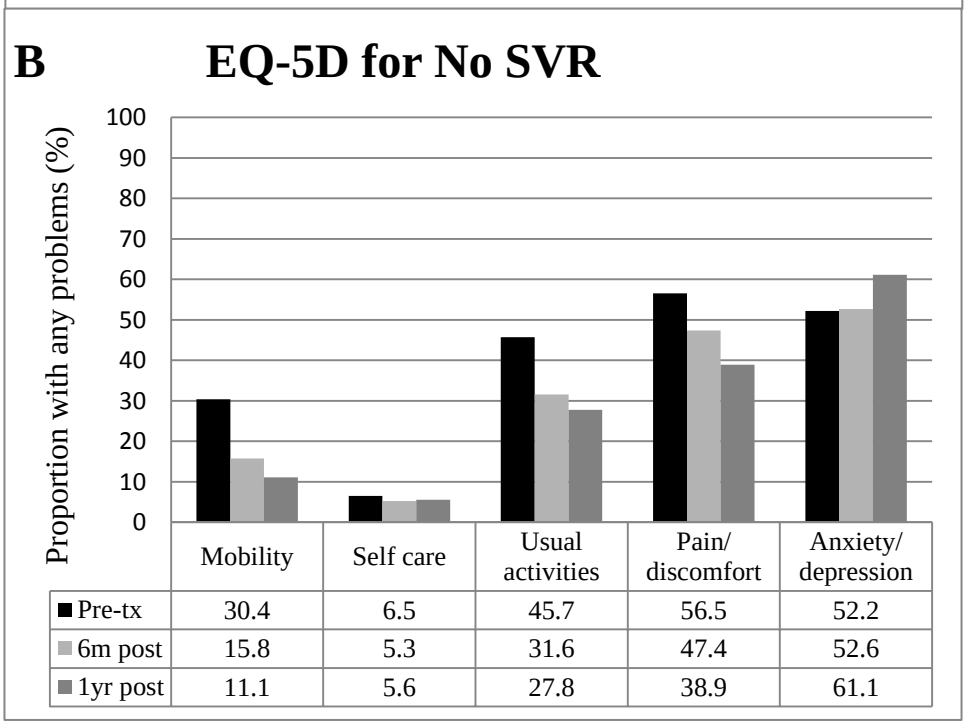
Figure 3 shows the percentage of participants reporting any problems in the five health dimensions of the EQ-5D. Problems with pain/ discomfort and anxiety/ depression were most common (reported by almost half of the participant groups), followed by problems with usual activities. The SVR group reported less difficulty overall compared to the no SVR group. HCV treatment did not systematically decrease the number of problems reported in SVR-achievers. Rather, improvement was only seen in the usual activities dimension. On the other hand for non-achievers, HCV treatment decreased the number of problems in all dimensions except anxiety/ depression.

Table 5 shows utility scores. The scores remained relatively constant over time (fluctuating around 0.83) regardless of SVR status and value set used.

Figure 3: Changes in the five dimensions of health (EQ-5D questionnaire) over time reported by SVR achievers (Panel A) and SVR non-achievers (Panel B).



	Mobility	Self care	Usual activities	Pain/ discomfort	Anxiety/ depression
Pre-tx	26.2	7.7	35.4	47.7	52.3
6m post	20.5	13.6	25.0	52.3	47.7
1yr post	27.3	4.6	18.2	63.6	54.6



	Mobility	Self care	Usual activities	Pain/ discomfort	Anxiety/ depression
Pre-tx	30.4	6.5	45.7	56.5	52.2
6m post	15.8	5.3	31.6	47.4	52.6
1yr post	11.1	5.6	27.8	38.9	61.1

Note: No statistical significance between SVR and No SVR (two-tailed two sample test of proportion)

Table 5: Utility scores based on value sets from Canada and the United States.

	Before tx	6m post-tx	1yr post-tx
Canadian value set:			
SVR	0.83 (0.71, 1)	0.83 (0.74, 1)	0.84 (0.72, 1)
No SVR	0.77 (0.60, 0.92)	0.83 (0.71, 1)	0.82 (0.66, 1)
American value set:			
SVR	0.83 (0.77, 1)	0.83 (0.80, 1)	0.83 (0.74, 1)
No SVR	0.82 (0.60, 0.93)	0.84 (0.75, 1)	0.83 (0.70, 1)

Medians (quartile 1, quartile 3) are reported.

Health service use—Table 6 shows the IRRs comparing SVR-achievers and non-achievers for health services used over time. Incidence rates over time are reported in a supplementary table (Appendix III: Table S1) and show HCV treatment, regardless of outcome, appeared to yield benefits. At baseline, those with achiever SVR used fewer health services than their peers, suggesting substantial confounding from other patient characteristics. SVR-achievers also fared better than non-achievers post-treatment—in particular emergency room visits and overnight hospital stays. The discrepancy in healthcare utilization became especially pronounced for overnight hospital stays after HCV treatment. The most frequented service was the HIV clinic which included seeing doctors, seeing nurses, refilling medications, and having bloodwork done and antiviral therapy work-up. The second most frequented service was the general practitioner. While SVR-achievers sought general practitioners more often than non-achievers prior to treatment, the trend reversed post-treatment. This trend reversal was also seen in specialist visits but without statistical significant. Walk-in clinics were the only visits to be used by SVR-achievers more than non-achievers both before and after HCV treatment.

Table 6: Incidence rate ratios for health services used.

	Analysis 1		Analysis 2	
	SVR vs. No SVR		Chronic vs. Cleared	Start tx vs. Never tx
	Before tx	6m post-tx	Cohort entry	Cohort entry
Walk-in	4.37 (2.5, 8.1)*	3.26 (1.3, 10.6)*	1.10 (1.0, 1.3)	0.60 (0.5, 0.7)*
Emergency	0.18 (0.1, 0.3)*	0.36 (0.1, 1.0)	1.40 (1.1, 1.9)*	0.53 (0.4, 0.7)*
Overnight hospital	0.63 (0.3, 1.2)	0.17 (0.0, 0.5)*	1.65 (1.3, 2.2)*	0.17 (0.1, 0.2)*
GP	1.33 (1.0, 1.7)	0.67 (0.5, 1.0)	1.16 (1.0, 1.3)	0.67 (0.6, 0.7)*
HIV clinic	0.85 (0.7, 1.0)	0.67 (0.5, 1.0)	1.42 (1.2, 1.7)*	1.28 (1.1, 1.4)*
Specialist	1.95 (1.4, 2.6)*	0.80 (0.5, 1.4)	2.03 (1.5, 2.7)*	0.73 (0.6, 0.9)*

Incidence rate ratios (95% CI) are reported.

* Statistically significant 95% CI

Abbreviations: SVR sustained virologic response, tx treatment, GP general practitioner

Table 7 shows the negative binomial model for health service use at six months post-treatment completion. After adjustment, SVR-achievers used in-patient services 79% less frequently than non-achievers. They also used out-patient services 34% less frequently although this result was not statistically significant. For walk-in clinic visits, the simple linear regression showed SVR-achievers had potentially greater utilization, but the trend reversed after adjustments. Pre-treatment walk-in clinic use was a strong confounder.

Table 7: Negative binomial model of health service use.

	Univariate	Multivariate
In-patient visits		
Presence of SVR	0.23 (0.08, 0.70)	0.21 (0.07, 0.64) *
Intercept		2.66
Out-patient visits		
Presence of SVR	0.74 (0.40, 1.39)	0.66 (0.37, 1.18)
Intercept		0.96
Walk-in visits		
Presence of SVR	2.47 (0.02, 30.70)	0.61 (0.09, 4.20)
Intercept		8.28

Incidence rate ratios (95% CI) are reported.

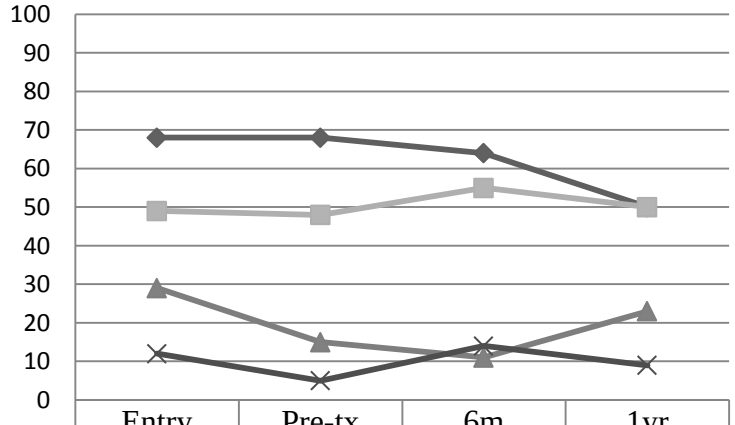
* Statistically significant 95% CI

Abbreviations: SVR sustained virologic response, tx treatment

Substance use—Figure 4 shows the percentage of participants using drugs and alcohol over time. More details are presented in Supplementary Table 2 (Appendix III). Overall, tobacco and alcohol were the most highly used substances, followed by marijuana. The proportion of tobacco smokers declined for SVR-achievers and non-achievers after cohort entry (68% to 50% one year post-treatment and 63% to 39% one year post-treatment, respectively). For marijuana use, the proportion of smokers remained high over time, fluctuating around 50% for both groups. A surge occurred one year post-treatment (61%) specifically for non-achievers. SVR-achievers and non-achievers reduced use after cohort entry (29% at entry to 15% pre-treatment and from 26% at entry to 20% pre-treatment, respectively). Sniffed or snorted drugs were least commonly reported. Among non-achievers, the number of users reduced to zero after HCV treatment. For alcohol consumption, SVR-achievers reduced their drinking before treatment started (from 49% at entry to 42% pre-treatment), but escalated greatly after HCV treatment (55% and 64% six months and one year post-treatment, respectively). Among non-achievers, no dip was seen, but a similar surge occurred after treatment (61% one year post-treatment). Binge drinking followed the same trajectories as current alcohol use but at lower levels.

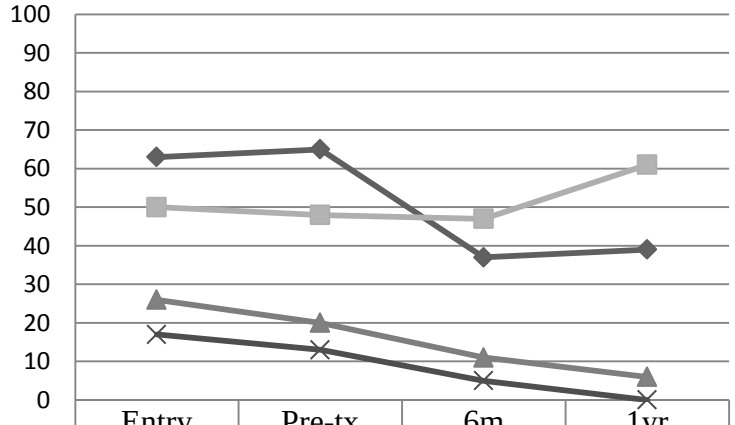
Figure 4: Percentage of current users (%) over time among SVR achievers (Panels A and C) and non-achievers (Panels B and D).

A Substance use in SVR



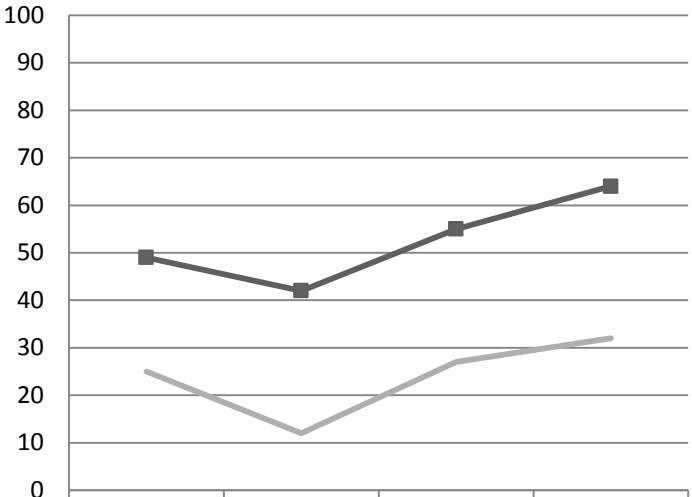
	Entry	Pre-tx	6m	1yr
Current smoking	68	68	64	50
Current pot use	49	48	55	50
Current IDU	29	15	11	23
Current snorting	12	5	14	9

B Substance use in No SVR



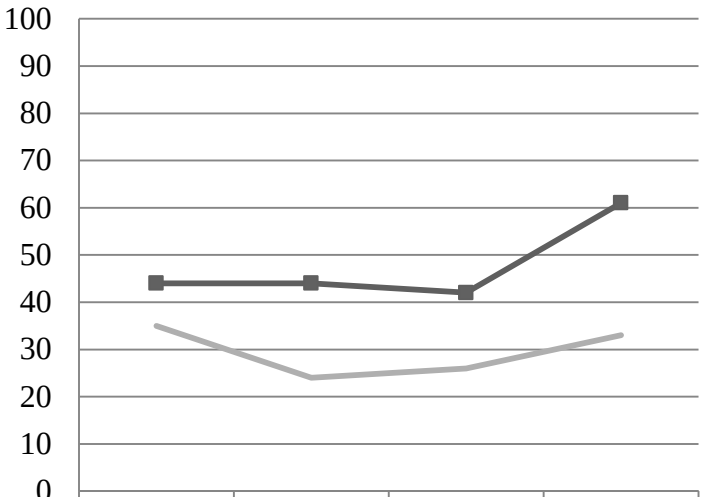
	Entry	Pre-tx	6m	1yr
Current smoking	63	65	37	39
Current pot use	50	48	47	61
Current IDU	26	20	11	6
Current snorting	17	13	5	0

C Alcohol use in SVR



	Entry	Pre-tx	6m	1yr
Current alcohol use	49	42	55	64
Current binging	25	12	27	32

D Alcohol use in No SVR



	Entry	Pre-tx	6m	1yr
Current alcohol use	44	44	42	61
Current binging	35	24	26	33

Table 8 shows median APRI scores over time for both participant groups. Despite elevated alcohol consumption, liver fibrosis improved with successful HCV treatment among SVR-achievers. APRI scores stabilized below baseline levels (median APRI: 0.7 pre-treatment to 0.4 post-treatment). However for non-achievers, liver fibrosis worsened over time (median APRI: 0.8 pre-treatment to 1.0 post-treatment).

Table 8: Liver fibrosis over time, as measured by APRI scores.

	Before tx	6m post-tx	1yr post-tx
SVR	0.70 (0.40, 1.09)	0.41 (0.34, 0.59)	0.43 (0.32, 0.80)
No SVR	0.80 (0.49, 1.68)	1.00 (0.53, 2.75)	1.09 (0.48, 2.03)

Medians (Q1, Q3) are reported.
Abbreviations: APRI aspartate aminotransferase-to-platelet ratio index, SVR sustained virologic response, tx treatment

Mortality—At the end of this study, there was one recorded death (proportion: 1.5%) among SVR-achievers due to atherosclerotic heart disease. There were three deaths (proportion: 6.5%) among non-achievers, one due to lung cancer and two to unknown causes. The mortality rates were 0.35 deaths per 100 PY and 1.33 deaths per 100 PY, respectively. The IRR was 0.26 (95% CI: 0.0, 3.3).

ANALYSIS 2: CHRONIC HCV AND SPONTANEOUSLY CLEARED HCV

Health-related quality of life—The median VAS score at cohort entry was 70 (Q1, Q3: 50, 80) among current chronic HCV participants. Its subgroups, treatment starters, prior treatment failures and never treated, also had median scores of 70 at entry. VAS scores among participants with spontaneous clearance were slightly lower (median (Q1, Q3): 65 (50, 76)).

Health service use—Table 4 shows IRRs comparing the rates of health services use in the six months preceding cohort entry, between the two participant groups. Participants with chronic HCV used more services overall, particularly for specialist visits and overnight hospital stays (IRR (95% CI): 2.0 (1.5, 2.7) and 1.7 (1.3, 2.2), respectively). Further, those who started HCV treatment during follow-up used fewer services compared to those who never received treatment (Table 6). One exception was HIV clinic visits, where treatment starters attended more often (IRR (95% CI): 1.3 (1.1, 1.4)).

SENSITIVITY ANALYSES

Redefining SVR

All analyses were re-run using the gold standard definition of SVR, where HCV RNA status was uniformly ascertained six months post-treatment completion. Three non-achievers from the original analysis were reclassified as participants

with unknown treatment outcomes. Next, analyses were re-run using the broad definition of SVR, where status was ascertained at three months post-treatment completion for SVR-achievers. Seven participants originally with unknown outcomes were reclassified as SVR-achievers. Results from both these sensitivity analyses did not differ from the original analysis and thus are not reported in detail.

Additional Time-points

Supplementary Table 3 (Appendix III) shows the median HRQOL scores at the first visit after treatment completion and at the visit where SVR status was determined. The median HRQOL scores at the first visit after treatment completion and at the visit of SVR status determination were the same as in the primary analysis. In the linear regression sensitivity analysis (Appendix III: Supplementary Table 4), SVR achievers tended toward improved HRQOL although results were not statistically significant.

CHAPTER 5: DISCUSSION

HCV treatment and SVR can have multidimensional effects on HRQOL, healthcare use and substance use among patients with HIV/HCV co-infection. SVR-achievers reported better health and used fewer health services. SVR was associated with a significant improvement in VAS scores over time and a significant reduction in in-patient admissions, as compared to subjects who did not achieve SVR. The effects of HCV treatment and SVR on these outcomes have not been previously reported in the literature.

Treatment Initiation

In the Canadian Co-infection Cohort, the HCV treatment initiation rate (19.4%) was more than double the national uptake in the United States (7%) among co-infected veterans (118). An additional 54 patients were successfully treated before cohort entry. Canada's universal healthcare and mixed insurance plans may explain the greater access to HCV treatment. Smaller Canadian studies have reported similar initiation rates among patients with HCV alone: 18.6% in three East Toronto community-based centres and 37.8% in a large Montreal hospital liver clinic (4, 119). HIV co-infection may add medical and social barriers to meeting treatment eligibility criteria and to accessing treatment. The present

study's HCV uptake rate reflects recruitment settings different from those of the smaller studies. We recruited from both major cities and smaller cities in an effort to reflect the Canadian landscape and its diversity of HIV treatment centre and patient characteristics. To our knowledge, this study is one of the first to describe national initiation rates for HCV treatment.

Sustained virologic response rates

The cohort response rates compare very favourably with SVR obtained in randomized trials for pegylated interferon and ribavirin (~80% in HCV genotype 2 and 3 mono-infections, <40% in genotype 1) (120). In HIV/HCV co-infection trials, SVR rates are on average 20% lower for both genotype 1 and 3 (37, 53). No randomized controlled trial has directly compared HCV treatment in monoinfection versus co-infection. Triple therapy trials (additional NS3/4A protease inhibitor) for the less responsive HCV genotype 1 have also shown marked improvement in SVR (120). In the present study, too few (N=3) participants received direct-acting agents to stratify by HCV treatment regimen.

Health-related quality of life

HRQOL may be influenced by the biological impact of the HCV infection and/or the psychological impact of knowing one's HCV status.

Visual analogue scale scores—Before treatment, any differences in VAS scores between SVR-achievers and non-achievers may correspond to differing distributions of gender, income and genotype in the two groups. Due to limited power and a small sample size, we selected one covariate (pre-treatment VAS score) to try to control for these potential confounders, rather than selecting many covariates to determine predictors of HRQOL. The multiple linear regression at one year post-treatment showed SVR yielded a statistically significant improvement on HRQOL. The effect was seen despite reduced statistical power from the small sample size retained at one year. The improvement in HRQOL among SVR-achievers seemed to be driven by the majority of individuals who had intermediate baseline VAS scores. Participants in the low tertile had substantially improved HRQOL regardless of SVR status. This may be regression to the mean. Too few participants were in the high baseline tertile to draw inferences. Overall, initiating HCV treatment may have a positive effect on individuals initially faring poorly.

We are unaware of good comparisons in the literature to benchmark our findings on VAS score improvements. No studies have reported the EQ-5D VAS specifically in a co-infected population. In HIV monoinfected populations, the EQ-5D VAS has been reported only in resource limited settings of developing countries (82, 121-123). In a Vietnamese convenience sample, respondents

(N=1016) from antiretroviral therapy clinics reported a mean VAS score of 70.3 (95% CI: 69.2, 71.5) overall. By disease stage, the VAS mean scores were 76.7 for asymptomatic participants and 67.8 for AIDS participants. In a South African study, participants from antiretroviral therapy clinics run by Medecins Sans Frontières had a mean VAS score of 60.4, which was significantly lower than that of community controls (mean: 80.1) (122). Mean VAS scores improved after HIV treatment from 61.7 (SD: 22.7) before initiation to 76.1 (SD: 18.5) one year post-initiation (123). In a South African public HIV care program, the median VAS score for individuals awaiting treatment was 60 (Q1, Q3: 50, 70) (82). Individuals receiving treatment reported better scores (median (Q1, Q3): 70 (50, 80)). The average scores found in the HIV literature are similar to our population, although one would expect better HRQOL in a developed country where HIV treatment and care are readily available. The 10-point improvement observed in our study among SVR-achievers from pre-treatment to post-treatment appears clinically important as such a difference is large relative to changes observed in other studies. The Vietnamese study showed patients in very distinct stages of HIV disease (asymptomatic versus AIDS) had differences in VAS scores of less than ten (121). In the oncology literature, changes of 8 to 11 in VAS scores are considered minimally important differences—that is, the smallest change associated with differences perceived by patients (124).

In HCV monoinfection, two studies reported HRQOL in relation to SVR (125, 126). The utility scores are comparable to our population, as the studies are from developed settings. However, they examined HRQOL cross-sectionally rather than longitudinally. A Canadian study recruited from a tertiary referral centre in Toronto (125). A subset of individuals achieved SVR (19%, N=36). Their mean time between interview and end of HCV treatment was 2.9 years (SD: 2.6). SVR-achievers reported a mean utility of 0.74 (95% CI: 0.68, 0.81). The scores were not truly utility scores because they were calculated as: VAS scores (0 to 100) divided by 100. A second study in Sweden recruited from nine outpatient centres (126). A subset of SVR-achievers (11%, N=52) reported a mean utility of 0.79 (SD: 0.21).

Five health dimensions—For SVR-achievers, clearing HCV appeared to be associated with improvements in usual activities only. This may be attributed to reduced HCV-related symptoms. The sustained reporting of other health problems may be rooted in their HIV status, other co-morbidities and underlying socioeconomic issues.

Widespread problems with pain/ discomfort and depression/ anxiety seen in our study were also documented in individuals with HIV (82). Psychiatric conditions are prevalent in HIV and HCV infections, approaching 50% among adults with

HIV and 73% among veterans with HCV (127, 128). Clinical depression and anxiety can be pre-existing conditions, psychological effects of diagnosis, biological effects of the viruses, and aggravated or induced side effects of interferon-based HCV treatment (127, 128). It is unknown how long symptoms induced from HCV treatment carry over after therapy. This can cloud evaluations of HRQOL post-treatment.

Utility—Using utility scores did not seem to detect any changes in HRQOL after initiating HCV treatment or after achieving SVR. Utility scores may not be well-suited for the question at hand. It is likely that changes in HRQOL were not large enough to be detected by the EQ-5D, being a generic, three-level response tool.

Health service use

SVR is associated with reduction in emergency visits, which are most costly to the healthcare system. SVR could result in substantial cost savings. Achieving SVR reversed the directionality of the specialist and general practitioner IRRs so that SVR-achievers used fewer services than non-achievers. While patients normally cannot forego urgent medical attention that requires hospitalizations or acute ambulatory care, non-achievers may be able to forgo visits to specialists or feel such follow-up is not warranted if no further treatment is to be offered. SVR-achievers, on the other hand, may be more concerned about their health and

subsequently seek more non-emergency health care. For emergency care, there was higher engagement among non-achievers which may reflect greater disenfranchisement with primary HIV care or under-managed co-morbidities.

Few Canadian data are available reporting rates of health service use in similar populations. A 1994-2000 study from British Columbia examined individuals with HIV who commenced antiretroviral therapy (N=2730) using linked administrative data (hospital separation data and medical services plan) (129). Druyts reported the following IRs per 100 PYs: 406 in-patient days, 8 ICU days, 1823 general out-patient visits, and 931 specialist visits. Our study is the first to examine national healthcare utilization among individuals with co-infection.

Substance use

Treatment initiation and outcome status are major psychological experiences that can invoke behavioural changes. For instance, marijuana use markedly increased post-treatment in non-achievers, potentially for coping with the psychology of treatment failure or managing physical symptoms of HCV. This is of concern as some studies have associated cannabis use with liver fibrosis progression although others have not (19, 130). Medical professionals likely would advise patients to avoid injecting drugs and drinking alcohol to improve treatment response (131-133). This may explain the reduction of injection drug

use from cohort entry to pre-treatment in both SVR-achievers and non-achievers. Alcohol consumption was also reduced in this time period, but only among SVR-achievers. This may be related to their eventual successful treatment response (133). Regrettably, alcohol consumption after treatment jumped to levels above baseline for both groups. Participants may have perceived successful completion of HCV treatment as a license to consume more.

Alcohol and liver fibrosis—Liver biopsy is the gold standard for measuring liver fibrosis. However, it is invasive, not frequently performed, and subjected to tissue sampling errors and interpretation variation (134). We used APRI as a surrogate marker, easily calculated from two laboratory values measured at each study visit. Aspartate aminotransferase levels in particular react immediately to changes in hepatocellular membranes. Hence APRI scores can change rapidly in response to alcohol consumption. The use of APRI scores has been validated in an HIV/HCV co-infection population (113). Studies in the population have shown APRI accurately predicted cirrhosis (135) and have the following characteristics as compared to liver biopsy: sensitivity of 52%, specificity of 100%, and area under the receiver operating characteristic curve of 0.85 (112).

Surprising in our study, elevated alcohol consumption among SVR-achievers did not coincide with higher APRI scores (worsening liver fibrosis). Rather, there was

a regression of liver fibrosis. The benefits of clearing HCV may have had a stronger influence on the liver than the harm from greater alcohol use in the short term. However, this trend was not seen for non-achievers. Liver fibrosis worsened over time, which may correspond to their increased alcohol use without HCV clearance.

Mortality

There were few deaths overall, none of which were liver-related. The all-cause mortality rates were comparable Berenguer's long term data in Spain (SVR-achievers, 0.26 versus non-achievers, 1.82 per 100 PY) (74).

Strengths and Limitations

The present study uses longitudinal data to follow participants before and after treatment. In the cohort, we tried to recruit from diverse populations (i.e. Aboriginals, women, injection drug users). There are several limitations to this study. Firstly, we had a very small sample size due to the low uptake of HCV treatment. Subsequently, our models were constrained by the number of covariates adjusted for and our model estimates were imprecise. Our sample may not be generalizable to all individuals treated for HCV. It was limited to individuals who volunteered to join the cohort and was limited to the mechanism by which they were recruited. Further, our Canadian sample profile may not reflect populations treated under healthcare systems without universal coverage.

Secondly, we used a more lenient definition of SVR to increase sample size. The sensitivity analysis showed that this led to a misclassification of three participants as non-achievers, but reclassifying them did not results change overall. Another source of information bias could be that HIV centres did not run polymerase

chain reaction tests at every study visit. A number of participants (N=120) were not tested at baseline and were assumed to have chronic HCV. After HCV treatment, participants without any tests were classified as unknown even though they could have been a SVR-achiever or non-responder in actuality. While assays are very sensitive (lower limit of 50 international units/ millilitre or less), a single negative HCV RNA test may not necessarily equate to SVR because viral loads may transiently decline (106).

Thirdly, attrition was substantial in the two groups which can compromise comparisons between pre-treatment and post-treatment values. The differential attrition may introduce selection bias. One would expect the sickest to drop out. Many participants remained in the cohort during follow-up but had missed their six month post-treatment visit and/or one year post-treatment visit; hence, they were excluded from analyses. To address this issue, we performed sensitivity analyses of HRQOL at alternate time-points where participants would not be excluded (i.e. first visit after treatment completion and visit when SVR was determined). The results were similar to the original analysis despite the high drop-out of participants.

Finally, there is inherent bias in analysis 2 comparing participants with HCV and participants with spontaneous clearance. In terms of healthcare utilization, the

analysis examines time before cohort entry, meaning people must survive the preceding six months to make it into the cohort.

In the present study, we should be cautious about several points. Firstly, we assumed the direction of causality (that SVR preceded substance use behaviours). Some argue reverse causality applies to alcohol use, but a systematic review suggested no relationship between alcohol consumption and SVR rates (115). In terms of illicit drug use, there is concern that active substance use is associated with low HCV treatment adherence which in turn is associated with treatment failure (7, 116). While we assumed a causal relationship between HCV treatment, SVR and patient HRQOL and utilization behaviours, it is important to note that a cohort study can only demonstrate associations. Associations may be biased by known and unknown confounders as patients are not randomized to interventions in a cohort study. The second point of caution is in interpreting self reported outcomes. Participants may be subjected to poor recall. Participants reported utilization since the last interview, which may be at least six months ago. Further, HIV/ HCV co-infection is linked to cognitive impairment (117), which may affect the ability of participants to respond. Major health service events like hospitalizations or emergency room visits would be less prone to poor recall. However, reports of general practitioner visits and walk-in visits may be less reliable. Linkage to health services data is

underway for the cohort and can address this limitation in the future. Measuring substance use as a self-report may have introduced social desirability bias. Some participants may hide illicit behaviours and we may be underestimating substance use.

CHAPTER 6: CONCLUSION

HCV treatment and effective response have important benefits to health-related quality of life, health service use, substance use and mortality in the Canadian HIV/ HCV co-infection population. These outcomes are especially pertinent to patients, healthcare practitioners and policymakers given the large proportion of HIV-infected persons who are co-infected in Canada, most of whom are at risk for end-stage liver disease but have yet to be treated for HCV infection. This work provides stronger evidence for the broad range of potential health and patient-centred benefits associated with curing HCV. These range from improved quality of life, liver-related morbidity and reduced health services use. These findings come at a time when the possibility of treating and curing most HCV infected patients is imminent, since new treatments are increasingly effective and well tolerated. The potential impact on the health care system may be substantial, if our findings are borne out and are sustained over a longer follow-up duration.

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Appendix I

HV centres in the Canadian Co-infection Cohort and their recruitment dates:

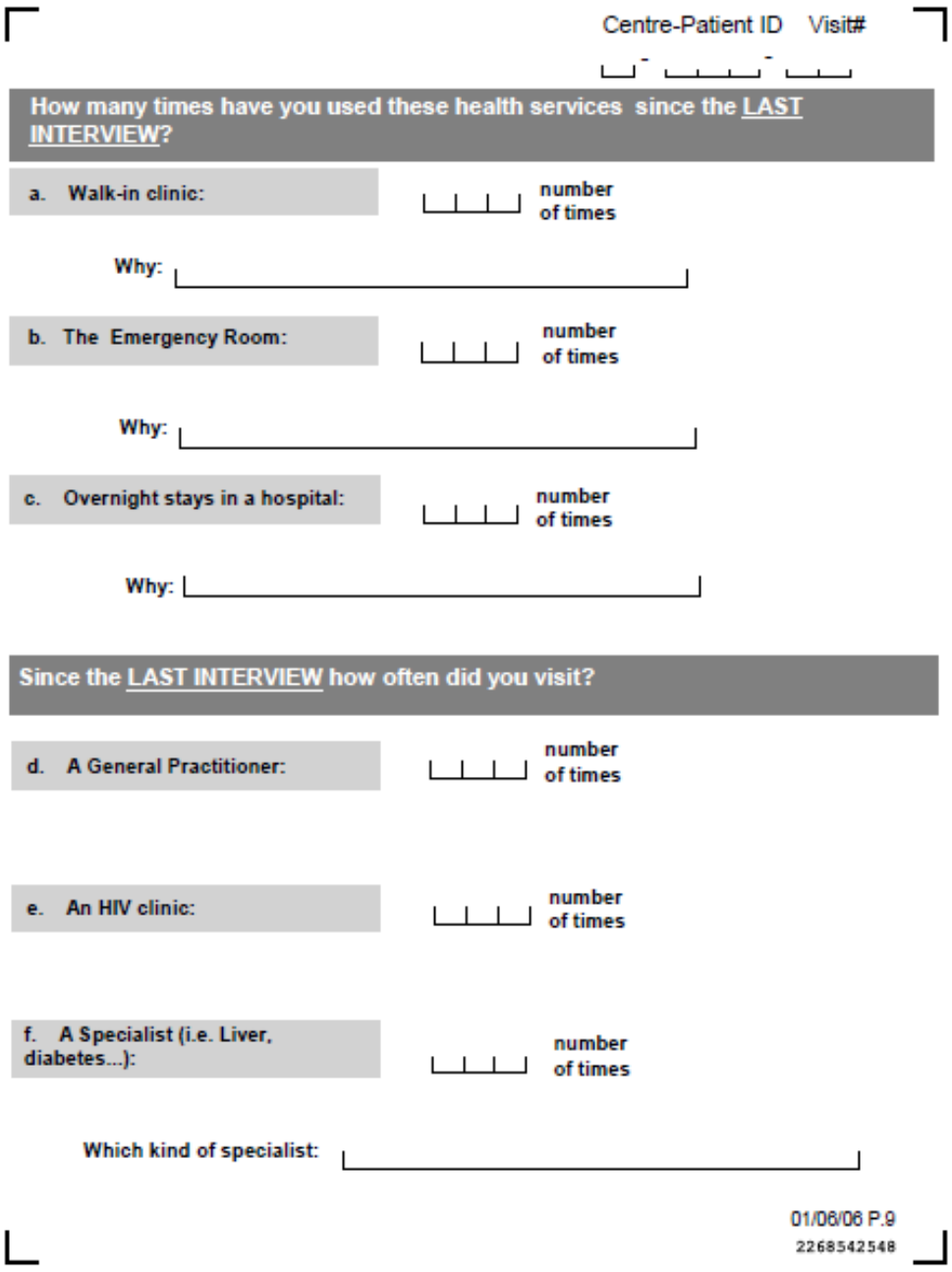
Centre	Province	Recruitment Period
Ottawa General Hospital	Ontario	06/07/2007- present
Toronto General Hospital	Ontario	25/07/2007- present
Sudbury	Ontario	24/06/2008- present
Sunnybrook	Ontario	04/02/2009- present
McMaster	Ontario	06/08/2008- present
Windsor	Ontario	14/11/2007- present
Hopital Notre-Dame	Quebec	05/06/2003- present
Clinique Medicale du Quartier Latin	Quebec	31/07/2007- present
Montreal General Hospital	Quebec	20/04/2004- present
Montreal Chest Institute	Quebec	25/04/2003- present
Quebec City	Quebec	29/02/2012- present
Halifax	Nova Scotia	07/02/2008- present
South Alberta Clinic	Alberta	19/06/2007- present
Saskatoon	Saskatchewan	Began after study period
Native Health Centre	British Columbia	31/03/2009- present
BC Centre for Excellence	British Columbia	02/07/2008- present
Pender Clinic	British Columbia	05/09/2007- present
Oak Tree Clinic	British Columbia	23/09/2008- present

Appendix II

Open-ended questions from health service use section of questionnaire

(participants reported utilization in the preceding six months at cohort entry and

utilization since the last interview at subsequent study visits):



Appendix III

Supplementary Table S1: Health service use since last follow-up.

	SVR vs. No SVR	
	Before tx	6m post-tx
Walk-in clinic	1.86 vs. 0.42	1.63 vs. 0.50
Emergency room	0.42 vs. 2.38	0.32 vs. 0.90
Overnight hospital stay	0.42 vs. 0.67	0.24 vs. 1.40
Visit to general practitioner	3.87 vs. 2.92	3.50 vs. 5.22
Visit to HIV clinic	5.28 vs. 6.21	3.14 vs. 4.71
Visit to specialist	3.42 vs. 1.76	2.01 vs. 2.51

Incidence rates (SVR vs. No SVR) are reported.

Abbreviations: SVR sustained virologic response, tx treatment

Supplementary Table S2: Substance use reported at four visits (cohort entry, before treatment, six months post, one year post) for SVR achievers and SVR non-achievers. Participants reported use in preceding six months at cohort entry and reported use since last visit at follow-up visits.

SVR	Entry (N= 65)	Before (N= 65)	6m (N= 44)	1yr (N= 22)
Current IDU (%):				
Currently inject drugs	19 (29.2)	10 (15.4)	5 (11.4)	5 (22.7)
During last month (%):				
Shot, not every week	7 (10.8)	5 (7.7)	3 (6.8)	1 (4.6)
Shot, ≥1 days/ week	4 (6.2)	0 (0.0)	0 (0.0)	1 (4.6)
Current non-IDU (%):				
Currently snort/ sniff drugs	8 (12.3)	3 (4.6)	6 (13.6)	2 (9.1)
Current marijuana use (%):				
Currently smoke pot	32 (49.2)	31 (47.7)	24 (54.6)	11 (50.0)
Frequency of smoking				
Not every week	12 (18.5)	8 (12.3)	9 (20.5)	6 (27.3)
1-6 days/ week	8 (12.3)	9 (13.8)	9 (20.5)	1 (4.6)
Everyday	12 (18.5)	13 (20.0)	6 (13.6)	4 (18.2)
Current tobacco smoking (%):				
Currently smoke cigarettes	44 (67.7)	44 (67.7)	28 (63.6)	11 (50.0)
No. Cigarettes/ day among smokers, mean (95% CI)	13.1 (10.7, 15.6)	14.7 (12.2, 17.1)	15.7 (12.3, 19.0)	7.1 (4.4, 9.8)
Stopped smoking since last visit	NA	1 (1.5)	5 (11.4)	4 (18.2)
Current alcohol use (%):				

Currently drink	32 (49.2)	27 (41.5)	24 (54.6)	14 (63.6)
No. of drinks with alcohol on a typical day of drinking				
1 to 2	20 (30.8)	19 (29.2)	16 (36.4)	11 (50.0)
3 to 4	9 (13.9)	5 (7.7)	6 (13.6)	1 (4.6)
5+	3 (4.6)	2 (3.1)	2 (9.1)	2 (4.6)
Consume ≥ 6 drinks at one time				
Less than monthly	10 (15.4)	5 (7.7)	7 (15.9)	4 (18.2)
At least monthly	6 (9.2)	3 (4.6)	5 (11.4)	3 (13.6)
Stopped drinking since last visit	NA	8 (12.3)	0 (0.0)	2 (9.1)
No SVR	**Entry (N= 46)**	**Before (N= 46)**	**6m (N= 19)**	**1yr (N= 18)**
Current IDU (%):				
Currently inject drugs	12 (26.1)	9 (19.6)	2 (10.5)	1 (5.6)
During last month (%):				
Shot, not every week	6 (13.0)	3 (6.5)	1 (5.3)	1 (5.6)
Shot, ≥1 days/ week	11 (23.9)	4 (8.7)	1 (5.3)	0 (0.0)
Current non-IDU (%):				
Currently snort/ sniff drugs	8 (17.4)	6 (13.0)	1 (5.3)	0 (0.0)
Current marijuana use (%):				
Currently smoke pot	23 (50.0)	22 (47.8)	9 (47.4)	11 (61.1)
Frequency of smoking				
Not every week	6 (13.0)	6 (13.0)	3 (15.8)	3 (16.7)
1-6 days/ week	9 (19.6)	4 (8.7)	1 (5.3)	4 (22.2)
Everyday	8 (17.4)	12 (26.1)	5 (26.3)	4 (22.2)

Current tobacco smoking (%):				
Currently smoke cigarettes	29 (63.0)	30 (65.2)	7 (36.8)	7 (38.9)
No. Cigarettes/ day among smokers, mean (95% CI)	16.3 (11.7, 21.0)	18.7 (13.5, 23.8)	18.1 (9.6, 26.7)	22.6 (9.8, 35.4)
Stopped smoking since last visit	NA	4 (8.7)	1 (5.3)	1 (5.6)
Current alcohol use (%):				
Currently drink	20 (43.5)	20 (43.5)	8 (42.1)	11 (61.1)
No. of drinks with alcohol on a typical day of drinking				
1 to 2	10 (21.7)	14 (30.4)	4 (21.1)	4 (22.2)
3 to 4	4 (8.7)	2 (4.4)	2 (10.5)	3 (16.7)
5+	7 (15.2)	5 (10.9)	2 (10.5)	4 (22.2)
Consume ≥ 6 drinks at one time				
Less than monthly	3 (6.5)	8 (17.4)	2 (10.5)	2 (11.1)
At least monthly	13 (28.3)	3 (6.5)	3 (15.8)	4 (22.2)
Stopped drinking since last visit	NA	3 (6.5)	2 (10.5)	1 (5.6)

Supplementary Table S3: VAS scores at additional time-points.

	VAS score	Time (months) from end of tx to visit
First visit after tx:		
SVR	80 (60, 85)	4.1 (1.2, 5.6)
No SVR	70 (55, 81.8)	3.5 (1.6, 5.8)
Visit when SVR status was determined:		
SVR	80 (70, 90)	10.3 (7.8, 13.2)
No SVR	70 (55, 80)	3.3 (1.5, 5.8)

Medians (Q1, Q3) are reported.

Abbreviations: VAS visual analogue scale, tx treatment, SVR sustained virologic response

Supplementary Table S4: Linear regression models for absolute change in VAS scores from pre-treatment to the additional time-points.

	Simple	Multiple
Pre-tx to first visit after tx:		
Presence of SVR	1.74 (-4.2, 7.7)	2.35 (-3.3, 8.0)
Pre-treatment VAS score (units)	-0.30 (-0.5, -0.1)	-0.31 (-0.5, -0.1)
Time elapsed (months)	-0.04 (-0.6, 0.5)	0.04 (-0.5, 0.6)
Intercept		23.33 (11.9, 34.8)
Pre-tx to SVR status determination:		
Presence of SVR	4.45 (-1.7, 10.6)	4.53 (-1.4, 10.5)
Pre-treatment VAS score (units)	-0.44 (-0.6, -0.3)	-0.49 (-0.6, -0.3)
Time elapsed (months)	0.30 (-0.1, 0.7)	0.17 (-0.2, 0.6)
Intercept		33.7 (22.9, 44.4)

Coefficients (95% CI) are reported.

Abbreviations: VAS visual analogue scale, tx treatment, SVR sustained virologic response