Chronic Hepatitis C Viral Infection: Natural History and Treatment Outcomes in Substance Abusers

by

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Abstract

Hepatitis C is the most common blood-borne viral illness in the North America. Chronic hepatitis C infection may lead to cirrhosis of the liver, liver failure and liver cancer. In North America, injection drug use is the most important risk factor for infection and substance abusing populations are disproportionately affected by the disease. Antiviral therapy exists and approximately 50% of infected individuals can be cured. The aim of this thesis was to provide information to help clinicians and policy-makers minimize the impact of hepatitis C in substance abusers. The thesis is comprised of three studies. The first assessed the rate of progression to cirrhosis for those acquiring infection through injection drug use, using a meta-analysis of 44 studies from the published literature. We estimated that fibrosis progression occurs at a rate of 8.1 per 1000 person-years (95% Credible Region (CR), 3.9 to 14.7) corresponding to a 20-year cirrhosis prevalence of 14.8% (95% CR, 7.5 to 25.5). The second study measured the association between successful antiviral therapy and quality of life. We demonstrated that sustained responders to therapy had higher scores on the hepatitis-specific Medical Outcomes Survey Short-Form-36 (SF-36), Health Utilities Index Mark 2/3 (HUI2/3), and time-tradeoff (TTO) than treatment failures, an average of 3.7 years following antiviral therapy. The third study assessed rates of adherence to antiviral therapy and rates of sustained response in current or former...
substance abusers on methadone maintenance. We demonstrated that while use of illicit substances prior to therapy negatively affected adherence, rates of sustained response were comparable to non-substance abusing populations. Our work indicates the future burden of disease in current and former substance abusers, demonstrates that antiviral therapy can be successful in this population, and indicates that the benefits of successful therapy may extend beyond decreased disease burden to improved quality of life.
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Published work derived from this thesis


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Chapter 1
Introduction and Overview

1 Introduction

Hepatitis C is a blood-borne viral illness responsible for significant morbidity and mortality in Canada and the rest of the world. The estimated prevalence of Hepatitis C virus (HCV) infection in Canada is 0.8-1.0% (240,000-315,000 persons).[1] The screening of the blood supply has virtually eliminated blood products as a source of infection. However, more than 4,500 new infections occur in Canada each year and 70% occur in substance abusers. [1, 2] HCV is probably under treated in the general population with only 10-15% of patients with chronic hepatitis C receiving current antiviral therapies.[3] Substance abusers chronically infected with HCV are even less likely to be treated. Centres specialized in treating this difficult population providing addiction therapy in addition to antiviral therapy are likely to have the highest success rates associated with HCV treatment.[4, 5]

From a public health perspective, addressing HCV infection in those who are current or former substance abusers is the major challenge for the next few decades. However, addressing HCV in patients with substance abuse issues is complex. The impact of ongoing substance use on adherence to treatment, and treatment success is unclear. The relative impact of HCV infection on the lives of patients with substance abuse issues may be small when compared to the impact of drug addiction. Policy options for reducing the impact of HCV in this population include prevention, harm reduction efforts such as needle exchange, safe injection facilities and drug substitution therapy as well as increased access to antiviral therapy. Preventing new infections and treating those already infected can potentially minimize transmission to uninfected users. The willingness to allocate funds to reduce the impact of HCV for substance abusers, awaits definitive proof of value for money.

The thesis works presented here address key issues surrounding treatment of chronic HCV for patients who are current or former substance abusers. The first study investigates the natural history of disease focusing on individuals who acquired infection through injection drug use. The second study assesses the association between successful antiviral therapy and quality of life in a real-world setting. While the second study is not focused on a substance abusing population, the
implications of the study provide insight into the policy implications for substance abusers. The third study evaluates the impact of ongoing substance abuse on adherence to antiviral therapy and therapeutic success, in a population of substance abusers on methadone maintenance replacement therapy that were treated with antiviral therapy.

2 Overview and organization of the thesis

Chapter 2 provides background on hepatitis C beginning with an introduction to virology, epidemiology, natural history and treatment with antiviral therapy. Substance abuse and quality of life are discussed in terms of the evidence related to the impact of HCV infection. An introduction to cost-effectiveness analysis provides a policy framework that can be used to interpret the thesis findings. Chapter 2 closes with a brief introduction to the research questions and the rationale for each of the 3 studies that comprise the thesis.

Chapter 3 provides an introduction to the methods employed in the thesis. The emphasis of chapter 3 is on Bayesian statistical approaches, given that these methods are not commonly used. Chapter 3 also includes sections on meta-analysis, meta-regression, co-morbidity adjustment and quality of life measurement.

Chapter 4 is the manuscript entitled, “The natural history of hepatitis C infection acquired through injection drug use.” The study involved a comprehensive search of the literature assessing cirrhosis in those who acquired infection through injection drug use. A meta-analysis and meta-regression of the identified studies produced summary estimates of the rate of progression to cirrhosis in this population, adjusting for study characteristics and patient characteristics at the aggregate level.

Chapter 5 is the manuscript entitled, “Sustained responders have better quality of life and productivity compared to treatment failures long after antiviral therapy for hepatitis C.” The study involved analyzing a subset of data from a larger study, in which more than 700 individuals from tertiary care clinics in the Greater Vancouver area completed questionnaires on quality of life, co-morbid illness, costs and productivity. Detailed reviews of patient medical records were also conducted. Analyzing the responses of a subset of more than 200 individuals previously treated with antiviral therapy, we were able to compare quality of life measures between sustained responders and treatment failures more than 3 years after antiviral therapy had
been completed. After adjusting for factors known to impact quality of life, such as age, gender and co-morbid illness, we measured the association between successful treatment and quality of life scores. More than half of the respondents reported a history of substance abuse. Very few respondents reported active substance abuse. Thus the study results apply to the general population of individuals with chronic HCV infections, many of whom acquired HCV infection through injection drug use, but who are no longer active substance users.

Chapter 6 is the manuscript entitled, “Treatment of hepatitis C infection for current or former substance abusers in a community setting.” The study involved a retrospective review of the medical records of clients at the Ontario Addiction Treatment Centres (OATC) who underwent antiviral therapy. The OATC is a network of primary care centres that provide methadone maintenance therapy for individuals with opiate addictions. The centre also provided antiviral therapy for hepatitis C to its clients. Treatment services were coordinated by an infectious disease specialist and administered by specially trained nurses. Clients underwent frequent urinalysis for illicit drugs, before, during and after antiviral therapy. We were able to use this data to assess the impact of illicit substance use on adherence to therapy and response to therapy.

Chapter 7 is a discussion of the implication of the study results. Questions arising from the study results are discussed along with proposed next steps.
3 Hepatitis C Virology

Hepatitis C Virus (HCV)

The hepatitis C virus (HCV) is a member of the Flaviviridae family of viruses and lone member of the genus Hepacivirus. Flaviviridae are characterized by single-stranded, positive sense, RNA genomes. HCV was first identified by Harvey Alter in 1978 and named non-A, non-B hepatitis. [6] There are 6 HCV genotypes and due to the extremely high mutation rate of the viral polymerase enzyme, further mutations occur within a genotype to produce quasi-species.[7, 8] Virulence and pathogenesis does not appear to be determined by genotype, but genotype does predict response to antiviral therapy.[9, 10]

The viral genome

The positive sense ribonucleic acid (RNA) strand of the HCV genome is transcribed to an intermediate negative-sense strand of RNA which is then transcribed to create positive stranded replicates of the genome. The positive stranded genome functions as the template to encode a polyprotein which consists of structural and non-structural proteins. The structural proteins include the nucleocapsid, and the E1 and E2 envelope proteins. The non-structural proteins include the NS2-3 protease, the NS3 serine protease and RNA helicase, and the NS5B RNA polymerase.

Viral entry

The hepatitis C virus envelope proteins E1 and E2 form a heterodimer that mediates binding of the virus to receptors on the membrane of hepatocyte cells. The hepatocyte host proteins CD81, SR-BI, and claudin-1 junction protein mediate binding of E1 and E2. Additional receptors may also be involved in enhancing the binding of the hepatitis C virus to the membrane, including GAGs (linear polypeptides that are frequently present on the cell membrane), low density
lipoprotein (LDL) and very low density lipoprotein (VLDL) receptors. Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and lymph node-specific intercellular adhesion molecule-3-grabbing integrin (L-SIGN) are calcium-dependent lectins expressed on liver sinusoidal endothelial cells that may facilitate the infection process by trapping the virus for subsequent interaction with hepatocytes. The virus is incorporated into the cytoplasm by an endosome coated with clathrin. Acidification of the endosome causes the release of the nucleocapsid into the cytoplasm.[11]

**Viral replication**

Replication of HCV is rapid and $10^{12}$ virus particles can be created per day in an individual. The RNA-dependent RNA polymerase enzyme is extremely error prone, particularly in the hypervariable regions of the E1 and E2 proteins. The rapid rate of virion production and error prone nature of the polymerase enzyme result in a high degree of variability of the HCV genome. [11, 12] When mutations result in viable quasispecies, they allow the HCV virus to evade the host immune system.

**Immune mechanisms related to viral persistence**

The HCV virus maintains a balance between evasion of the host immune response via escape mutations and viral fitness. The immune system exerts selective pressure on the virus. During acute infection, the strength of the immune response and the breadth of viral epitopes targeted by the T cells determines whether or not the infection will persist. Self-limiting HCV infections are associated with fewer escape mutants than persistent infections. Escape mutations have been observed in a variety of virus particles including anchor proteins that allow for antigens to be presented to T cells and envelope proteins (E1 and E2) which contact the T-cell antigen receptor allowing for recognition and activation and molecules involved in antigen processing. Once persistence has been established, the rate of escape mutation slows considerably and the virus often reverts to the consensus sequence for the genotype. [13, 14] The reason for the change in the T cell immune response over time is not completely understood but it is thought that the T cell response is established early on in infection with limited ability to recruit new T cells. The failure of the T cells to respond to new epitopes may result from a phenomenon that has been called “original antigenic sin”. Original antigenic sin refers to the immune system’s preferential
use of memory cells. During HCV infection, the immune system responds to viral antigens encountered early on in the infection and produces memory cells. The immune system does not readily adapt to new antigens that result from mutations in the HCV virus. It relies on memory cells corresponding to the original antigens.

**Tests for HCV infection**

Serological tests for antibodies to hepatitis C virus (HCV) are useful to indicate whether or not an individual has been exposed to hepatitis C. The presence of HCV RNA is the definitive measure of HCV infection, and can be performed with nucleic acid testing (NAT) available in several different forms. Qualitative PCR using reverse transcriptase polymerase chain reaction (RT-PCR) has a lower detection limit of 40 IU/ml (Ultra-Qual) and 50 IU/ml (AMPLICOR V2.0 and Ampliscreen v2.0). Qualitative PCR using transcription-mediated amplification (TMA) has an even lower detection limit of 5 IU/ml (Procleix HIV-1/HCV assay and Versant). Due to the lower detection threshold of qualitative PCR tests, these tests are used to test for rapid virological response to antiviral therapy (measured at 4 weeks) and sustained virological response to antiviral therapy (measured at 24 weeks), as well as to confirm HCV viremia in blood and organ screening.

Quantitative PCR tests use RT-PCR or branched DNA chain amplification techniques to measure the concentration of the virus in the serum. Quantitative PCR tests have a wide variability in the range of detection of HCV RNA, with the lower limit of 600 IU/ml (Monitor v2.0) and upper limit of 100 million IU/ml (TaqMan real-time PCR). Quantitative tests are useful for measuring pre-treatment viral levels, and early virological response to therapy (measured at 12 weeks), defined as a 2 log drop in viral load.

**4 Epidemiology**

**Prevalence**

Based on estimates from the World Health Organization, approximately 3% of the world’s population has been infected with HCV and 170 million are chronically infected worldwide.[15] Seroprevalence data from the United States indicate that approximately 3.2 million persons are chronically infected.[16] The estimated prevalence of Hepatitis C virus (HCV) infection in
Canada is 0.8-1.0% (240,000-315,000 persons).[1] The prevalence of HCV in Africa is 5.3%, the Eastern Mediterranean (4.6%), the Western Pacific (3.9%), South-East Asia (2.15%), and Europe (1.03%). Countries with a particularly high prevalence due to past use of parenteral therapy are Egypt (18.1%) and certain regions within Italy (12.6%). The distribution of genotypes also differs by region. Genotype 1a is commonly found in Northern Europe and North America and Type 1b is commonly found in Southern Europe, Eastern Europe and Japan. Genotype 3 is common in Southeast Asia. Genotype 4 is found mainly in the Middle East, Egypt and central Africa and genotype 5 is found in South Africa. Genotype 2 is associated with the Mediterranean and Far East. Genotype 6 is found in the Middle East.[15, 17-19]

**Incidence**

The screening of donated blood using highly sensitive second and third generation enzyme immunoassay tests has virtually eliminated blood products as a source of infection. However, more than 4,500 new infections are identified in Canada each year and 70% occur in substance abusers.[20] International estimates of the incidence of HCV among IDUs range from 11 to 42 per 100 person years.[21-24] A systematic review and meta-regression of published literature describing HCV infection among IDUs estimated that prevalence is 32.02% (95% CI: 25.31%, 39.58%) after 1 year of injection and 53.01% (95% CI: 40.69%, 65.09%) after 5 years in developed countries. In IDU populations in developing and transitional countries HCV prevalence was 59.13% (95% CI: 30.39%, 82.74%) after 1 year of injecting exposure.[25] Other groups at risk of HCV infection include prisoners [1, 26] and individuals at risk for sexually transmitted diseases due to risky, traumatic sexual practices.[27] Estimates of the rate of vertical transmission are varied, but suggest that vertical transmission occurs in less than 10% of births to infected mothers. Vertical transmission has been defined as detectable anti-HCV in an infant greater than one year old or detectable HCV RNA in an infant less than 1 ½ years old. Vertical transmission rates are significantly higher for those mothers with HCV antibodies who also test positive for HCV RNA compared to anti-HCV positive mothers (4.3% versus 1.7%), HIV co-

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1 A transitional economy is an economy that is changing from a centrally planned economy to a free market economy. (Tanzi 1999)
infected compared to HIV-negative (19.4% versus 3.5%) and IDUs compared to non-IDUs (8.6% versus 3.4%).[28-30]

5 Natural History of HCV Infection

Clinical manifestations of HCV Infection

Acute infection with HCV is usually clinically mild and is infrequently diagnosed. Chronic HCV infection is also for the most part an asymptomatic disease yet some may experience fatigue, malaise, nausea, upper right quadrant pain. Typically levels of the alanine aminotransferase (ALT) enzyme fluctuate over time but HCV RNA levels remain stable. Other clinical complications associated with chronic HCV infection include cryoglobulinemia, glomerulonephritis, porphyria, type II insulin-dependent diabetes and B cell non-Hodgkin’s lymphoma.[31]

The Rate of Chronic Infection

Acute infection with HCV can be self-limiting, but in the majority of cases infection persists in a chronic state. Estimates of the rate of chronic infection for adults acutely infected with hepatitis C are varied. In a study of Irish women infected through contaminated immune globulin, the rate of chronic infection was 55%. [32] In a prospective study of injection drug users the rate of chronic infection was 85%. [33] In a cohort who acquired HCV infection from blood transfusion the rate of chronic infection was 75%, [34] and in a cohort of patients with community acquired HCV infection the rate of chronic infection was 62%. [35] Approximately 2/3 of children acutely infected with HCV develop chronic infection. [36] Ethnicity may also play a role in determining the rate of chronic infection. [37, 38] Recent studies indicate that ethnic variation in clearance rates may result from differential expression of genes responsible for levels of expression of interleukins. [39]

Liver fibrosis and cirrhosis

The model of the development of liver fibrosis is that it is the consequence of an inflammatory response to the virus. Cytokines are released by lymphocytes which in turn stimulate hepatic stellate cells and portal fibroblasts to secrete extracellular matrix proteins such as collagen. [40]
Laboratory experiments in animals demonstrate that fibrosis of the liver can be reversed via apoptosis of hepatic stellate cells, reduced deposition of extracellular matrix proteins and increased activity of collagenase enzymes that degrade collagen deposits.\[41\] Models of progression as a dynamic process between regression of liver fibrosis and progression has been proposed, and demonstrated to occur in man.\[42\]

**Liver biopsy**

Liver biopsy is an important diagnostic tool that allows assessment of the stage and grade of liver disease. Liver biopsy involves taking a sample of liver tissue which is evaluated by a pathologist. Specimen length and reader expertise are important factors in determining the accuracy and reliability of assessing liver disease.\[43\] Optimal biopsies are 25 mm in length or contain at least 11 portal tracts.\[44\] One of the algorithms for classifying the stage of liver disease is the Metavir scoring system.\[45\] The Metavir system assigns a grade to indicate the amount of inflammatory activity and a stage to indicate the amount of fibrosis or scarring. The Metavir grade of inflammatory activity is a number from 0 – no activity to 4 – severe activity. The Metavir stage assesses fibrosis on a five-point scale: F0 - no fibrosis, F1 - portal fibrosis without septa, F2 - portal fibrosis with rare septa, F3 - numerous septa without cirrhosis and F4 – cirrhosis. Other validated scoring systems include the Knodell score \[46\], Ishak score \[47\], Scheuer score \[48\], Batts and Ludwig score \[49\] and Desmet score. \[50\]

**Non-invasive tests for liver fibrosis**

Several non-invasive tests (NITs) are available to assess the extent of liver disease. NITs can be categorized into imaging techniques or serum markers. Furthermore, serum marker tests can be grouped into direct and indirect tests.

**Imaging techniques**

Diagnostic imaging can identify structural changes in the liver resulting from fibrosis. Imaging techniques not specifically designed to evaluate fibrosis include ultrasound, computed tomography scanning and magnetic resonance imaging although parameters such as spleen size, liver surface, portal vein size, hepatic vein spectrum and portal mean velocity have reasonable
accuracy for diagnosing cirrhosis, [51] but the specificity of these tests is generally better than their sensitivity.[52] For example, in identifying fibrosis of the liver the specificity of abdominal ultrasound in combination with platelet counts was greater than 90% but the sensitivity was 51%. Fibroscan is a type of ultrasound technology that correlates hepatic elasticity and liver fibrosis. [53, 54] For identifying cirrhosis of the liver, the sensitivity of Fibroscan has been estimated at 84% and the specificity at 94%. [54] Fibroscan requires minimal training and may require different size “wands” to accurately measure ‘elasticity’ in obese patients. Even then the hepatic steatosis present may interfere with the reading of ‘elasticity’.

**Direct serum markers**

Direct tests assay components of the extracellular matrix in serum, including glycoproteins, collagens, metalloproteinases, tissue inhibitors of metalloproteinases (TIMPs) as well as cytokine levels. Direct tests may target single components or combinations of components. For example, Fibrospect tests for hyaluronic acid, TIMP-1 and alpha2-macroglobulin. Fibrospect has a sensitivity of 83% and specificity of 66% in detecting advanced fibrosis. [55] Direct tests are not routinely available and can be expensive.

**Indirect serum markers**

Indirect tests are generally comprised of routinely available tests with various combinations of AST, ALT/AST ratio, platelet count, AST/platelets ratio, cholesterol, gamma globulin, gamma glutamyl transferase, prothrombin time international normalized ratio (INR) and age. Different types of indirect NITs include the APRI index, Bonacini index, Forns’ test and Fibroindex. The Fibrotest is more expensive and complex, using serum assays of alpha2-macroglobulin, haptoglobin, gamma globulin, apolipoprotein, bilirubin and gammaglutamyl transferase.[56] Stage-specific test thresholds allow Fibrotest scores to be most reliable at the two ends of the spectrum either when there is no fibrosis or when there is cirrhosis. Serum markers are better at ruling out cirrhosis than detecting cirrhosis; the specificity of indirect NITs range from 87% to 100% and exceed the sensitivity of indirect NITs, which range from 17% to 67%. [57]
Non-invasive tests in practice

Currently, use of NITs in practice depends on clinical goals, and liver biopsy remains the ‘gold standard’ in that it gives the most information about the status of the liver – not only in terms of degree of fibrosis but also inflammation, steatosis and status of the intrahepatic bile ducts and portal veins. Even though research demonstrates that combinations of NIT can improve accuracy [57], better validation of NITs using optimal liver biopsy samples is required.[58]

Rates of progression to liver cirrhosis

Cirrhosis of the liver is an important event in the natural history of chronic HCV infection because it is associated with increased risk of advanced liver disease. There is strong evidence indicating that the rate of progression to liver cirrhosis is not constant over time. [59, 60] The rate of progression to cirrhosis likely increases with advanced fibrosis stage. Fibrosis stage classification systems represent ordinal scales and the intervals between stages are not equivalent.

Patient factors influencing the rate of progression to cirrhosis

Several patient factors have been consistently shown to influence the rate of progression to cirrhosis including alcohol consumption, sex, age at infection, ethnicity, co-infection with other viruses including HIV and HBV, levels of alanine aminotransferase (ALT) enzyme (activity of the disease), steatosis and diabetes.

Age

Livers of older persons may be more prone to liver injury or less competent at liver regeneration. Older age at infection is associated with faster rates of progression and increased age is associated with increased rates of progression. Poynard et al demonstrated that patients infected after age 50 had a 67% faster rate of progression to cirrhosis than those infected from age 41 to 50.[61] In liver transplant patients, grafts from older donors progress faster to cirrhosis with recurrent HCV infection than grafts from younger donors.[62] Serial biopsy studies also indicate that the rate of progression increases with increasing age.[63] On the other hand, one modeling study suggests that some of the observed effect of increased progression rates with older age at
infection may be explained by competing mortality risks.[64] The number of co-morbid illnesses increases with age. Death from causes other than liver disease prevents individuals with slowly progressing liver disease from presenting with liver cirrhosis. The population presenting with liver cirrhosis may thus be enriched by those with faster progression to cirrhosis.

Sex

Many studies have demonstrated that males have faster rates of progression to cirrhosis than females, even after controlling for factors such as alcohol consumption.[65] Scientific experiments in primary culture demonstrate that estrogen modulates fibrogenesis by inhibiting stellate cells, providing a potential explanation for the observed phenomenon.[66] Support for this concept comes from a study demonstrating lower fibrosis scores in post menopausal women on hormone replacement therapy.[67]

Alcohol

The effect of alcohol on fibrosis progression is evident at levels of consumption in excess of 40g per day.[61, 63, 68] The impact of low levels of alcohol consumption is less clear. The mechanism by which alcohol increases progression rates may be via steatosis, increased rates of apoptosis, increased viral replication or enhancement of quasi-species development.[69]

Ethnicity

African-Americans experience lower rates of response to antiviral therapy than Caucasian or Asian patients. However they have lower rates of progression to cirrhosis.[70, 71] Less information is available for other ethnic groups but studies indicate that Latino patients in the U.S. may have faster progression rates than Caucasian patients.[72]

Smoking

Some evidence indicates that smoking tobacco [73, 74] and smoking cannabis increase fibrosis progression rates.[75, 76] The mechanism of action is unclear but may be related to hypoxia.
HIV co-infection

In a meta-analysis conducted by Graham et al it was estimated that individuals co-infected with HIV had 3 times faster progression rates ((RR) of 2.92 (95% confidence interval [CI], 1.70–5.01)) than mono-infected patients.[77] A more recent meta-analysis confirmed the effect of HIV co-infection on fibrosis progression and demonstrated that HAART therapy may not attenuate the effect of HIV co-infection on increased progression.[78]

Several different mechanisms have been proposed to explain why HCV and HIV act as co-factors for progression of liver disease. HIV infection is associated with higher levels of HCV viremia. High levels of HCV viremia may impact the liver through direct cytotoxicity or by stimulating an HCV-specific cellular immune response which induces liver injury through the production of cytokines. HIV surface proteins may bind to liver cells and up-regulate cytokine production. HIV mediated reduction in CD4 cell counts, may decrease immune-mediated control of viral quasi-species, allowing for selection of escape mutants. A CD4 cell count, above an approximate threshold of 200 cells per µL is associated with decreased rates of progression to cirrhosis, HCC, end-stage liver disease and death.[79]

HBV

Co-infection with hepatitis B virus (HBV) has been associated with more rapid fibrosis progression rates and an increased risk of developing HCC. The mechanism by which HBV co-infection accelerates fibrosis and leads to HCC may be through direct hepatotoxicity or transformation of liver cells by integration of HBV into the genome.[80]

Histological activity and ALT levels

The degree of inflammatory activity in the liver has been correlated with the rate of fibrosis progression.[81] Several studies demonstrate that individuals with persistently normal levels of ALT in the serum have lower fibrosis progression rates.[63, 82] The association of inflammatory activity with fibrosis progression, and the correlation of ALT levels with fibrosis progression rates, is consistent with the model of chronic liver injury in which secretion of immune mediators promotes stellate cell activity and hence fibrosis.
Genotype

HCV genotype is a strong predictor of response to antiviral therapy. The impact on fibrosis progression rates is less clear. Several studies show that genotype is not associated with fibrosis progression.[63, 83] Recent evidence indicates that due to an increased risk of steatosis in individuals infected with genotype 3, more rapid fibrosis progression is observed.[84, 85] Steatosis or fatty liver disease results in deposits of large vacuoles of triglycerides in the liver.

Metabolic factors

Individuals chronically infected with HCV genotype 3 have higher rates of hepatic steatosis than those with genotype 1 or 2 infections.[86, 87] Steatosis has been associated with increased fibrosis progression rates, higher risk of HCC and lower rates of response to antiviral therapy.[84, 88] However, some studies indicate that the association between steatosis and fibrosis progression disappears after adjustment for BMI.[89]

A link between chronic HCV infection and diabetes mellitus has also been found. Individuals chronically infected with HCV have higher rates of insulin resistance than uninfected controls.[90] Some studies show that diabetes or insulin resistance is associated with a more rapid rate of fibrosis progression.[91, 92] Recent evidence suggests that response to therapy is associated with decreased incidence of diabetes mellitus.[93] A complex interplay of factors is likely behind the association between chronic HCV infection, BMI and insulin resistance and the direction of causality is difficult to ascertain.

Source of infection

There is some evidence that individuals with post-transfusion associated hepatitis experience faster fibrosis progression rates than individuals with past injection drug use.[94] On the other hand, large retrospective analyses of data from tertiary liver clinics demonstrated that after adjusting for age, there is no difference in the fibrosis progression rate by source of infection.[63] The potential interaction between the study setting and the source of infection may be a factor in explaining divergent results. Community-based studies include a large proportion of patients that contracted HCV through injection drug use.[95] A complex interplay of factors may affect estimates of the relationship between source of infection and fibrosis progression rates.
Individuals with different sources of infection may be differentially affected by referral biases and excess mortality and these may impact observed fibrosis progression rates. There may also be a different degree of uncertainty in estimating the duration of infection.

**Advanced liver disease**

**Decompensated cirrhosis**

Clinical events signaling a failing liver (decompensated cirrhosis) include ascites, hepatic encephalopathy or gastrointestinal bleeding of variceal origin. Ascites occurs when high venous pressure in the portal vein causes fluid to accumulate in the peritoneal cavity. Increased pressure in the portal vein also inhibits removal of deoxygenated blood from the esophagus. As a result, esophageal blood bypasses the liver through collateral circulation. Esophageal varices result from increased tension and distention in these veins. Hepatic encephalopathy is a syndrome of altered consciousness caused when the liver is no longer able to remove toxins in the blood resulting in the impairment of brain cells. For those with cirrhosis, the cumulative rate of developing decompensated liver disease is approximately 18% over 5 years, but this depends on the cause of decompensated disease.[96] The survival probability is approximately 50% at 5 years, but individual prognosis depends on factors such as alcohol consumption and response to antiviral therapy.

**Hepatocellular carcinoma**

Similar to the model of fibrosis pathogenesis, HCV-related hepatocellular carcinoma (HCC) is thought to result from the wound-healing response to liver injury. Repeated cell death and regeneration increases the likelihood of a genetic mutation. Also, the HCV virus itself may be mutagenic. Over decades, HCV infection can lead to the uncontrolled development of malignant cells. Angiogenic factors such as vascular endothelial growth factors (VEGFs) and platelet-derived growth factors (PDGFs) play a significant role in carcinogenesis. VEGF mRNA is highly expressed in cancer cell lines, and expression of VEGF increases with cancer stage.[97, 98] Options for treating HCC include resection of the liver, transplantation, radiofrequency ablation, percutaneous ethanol injection, chemoembolization and in those with tumors too large for such procedures sorafenib therapy.[99-102] Sorafenib is an inhibitor of angiogenesis targeting VEGF
and PDGF signaling pathways. Sorafenib therapy has been associated with some improvement in survival.[103] The risk of developing HCC for patients with cirrhosis is 3-5% per year in patients with chronic viral hepatitis C.[96, 104, 105] HCC risk is greatest in those with advanced fibrosis stage.[106] Older males are at increased risk of developing HCC.[107] Alcohol consumption and smoking can increase the risk of developing HCC, as may diabetes and high BMI.[108, 109] Regular consumption of coffee has been reported to decrease risk of HCC.[110]

Liver transplantation

HCV-related liver disease is currently the most common indication for orthotopic liver transplantation (OLT). [111, 112] Due to organ shortages, only a proportion of patients requiring OLT receive a transplant. Living-donor liver transplantation is a potential alternative. Recurrence of HCV infection post transplant is universal, unless the patient goes into surgery with undetectable HCV RNA in serum. Injury of the graft occurs in approximately 80-100% of patients in those who remain infected. Graft injury includes acute recurrence, chronic recurrence and fibrosing cholestatic hepatitis [113], leading to accelerated fibrogenesis and decompensation.[96, 114, 115] Cyclosporin and tacrolimus are the main immunosuppressive regimens employed to prevent rejection.[116] Recurrent HCV infection can be treated with pegylated interferon and ribavirin combination therapy with sustained virologic response rates of approximately 20%, hence the need to aggressively attempt viral clearance prior to transplant. [117, 118] Survival rates following OLT are dependent on re-infection with HCV. Survival is less than what is seen in those infected with chronic hepatitis B because it difficult to control viral replication in CHC. -Survival rates are 67% at 2 years, 62% at 5 years and 62% at 10 years. [119] Recent evidence indicates survival following OLT may be decreasing, potentially due to older age of donors, use of living donors and use of tacrolimus immunosuppressive therapy. [112, 120]

6 Treatment

Antiviral therapy

The best treatment currently available for HCV infection is combination therapy with pegylated interferon (PEG-IFN) and ribavirin.[9, 10] The goal of treatment is the elimination of HCV viral
ribonucleic acid (RNA) from the serum at 24 months post-treatment, known as sustained virological response (SVR). Successful treatment rates range from 45% to 85% depending on the HCV genotype. Patients with genotype 2 or 3 infection are more sensitive to interferon and may only require 24 weeks of treatment. Patients with genotype 2 or 3 infection, achieve SVR rates of approximately 75-80%. Patients with genotypes 1 or 4 require 48 weeks of treatment to achieve SVR rates of 45-56%. Follow-up studies indicate that SVR represents permanent viral eradication for up to 8 years after treatment. Sustained virological response is associated with halting progression of liver fibrosis and regression of hepatic fibrosis. Studies assessing the relationship between SVR and hepatocellular carcinoma have been limited by insufficient follow-up time and small numbers progressing to hepatocellular carcinoma. However, the studies suggest that SVR is associated with decreased incidence of hepatocellular carcinoma. Sustained virological response may also result in increased vitality and improved quality of life. The impact on quality of life is controversial and the results of study 2 address this issue.

**Side effects of antiviral therapy**

Side effects associated with interferon-based therapies include a “flu-like” syndrome of myalgias, fever, lassitude and fatigue, bone marrow suppression, thyroid dysfunction, as well as psychological reactions such as depression, mood lability, irritability, sleep disturbances and decreased concentration. In the patient populations traditionally treated with combination therapies, dropout rates of 10-15% have been observed. Because clinical trials tend to enroll highly selected, highly motivated patients, dropout rates in routine clinical practice are higher.

**Predictors of successful antiviral therapy**

Genotype is the strongest predictor of successful antiviral therapy. Patients with genotype 2 or 3 infection, achieve response rates of approximately 75-80%. Patients with genotypes 1 or 4 achieve response rates of 45-56%. Pre-treatment viral load is also a strong predictor of response to therapy. Early trial data demonstrated that individuals with greater than 2 million virions per ml had a 9% lower rate of SVR than those with a lower serum concentration of virions. Lighter patients and younger patients are more likely to respond to therapy. Female sex has also been
associated with higher response rates, but this may be due to the fact that females are lighter. Weight-based ribavirin dosing improves response rates. The absence of cirrhosis is associated with increased response rates.[9, 10, 128] Efficacy of treatment in HIV-HCV co-infected individuals is lower than in HCV mono-infected individuals. For example, HIV co-infected patients, with genotype 1 infection and high viral load have extremely low response rates (18%), predominantly because they have been treated with inadequate doses of both drugs. HIV co-infected patients with low CD4 cell counts (below 200 cells/microL) have lower response rates. However there is insufficient evidence to establish this as a threshold for therapy. HIV-HCV co-infected patients on the antiviral regimens containing zidovudine are not recommended for therapy since this can interact with ribavirin enhancing ribavirin induced hemolytic anemia.[130]

Race is also a predictor of response to antiviral therapy. African-American patients and Latino patients have lower rates of response to antiviral therapy than Caucasian patients. [129, 131] Recent studies of human genetics demonstrate that variants of the IL28B gene that encode interleukin 28B are predictors of response to antiviral therapy. In a study of approximately 1700 patients of European ancestry, expression of the IL28B C-allele was associated with an approximately two-fold higher rate of sustained virological response to antiviral therapy. [132] The IL28B T-allele associated with treatment failure has been shown to be more common among patients of African descent.[132, 133] The T-allele was associated with lower levels of expression of interleukins. These genetic findings partially explain the differential response rates to antiviral therapy among the races. The variations in the IL28B gene have also been linked to spontaneous clearance of acute HCV infection. Latino patients have lower response rates than non-Latino whites.[131] The impact of IL28B gene expression has not been investigated in explaining these differential response rates.

The rate of chronic infection after re-infection

Given that one of the key concerns about treating active injecting drug users is the possibility of re-infection following successful therapy, two key studies provide evidence to mitigate these concerns by demonstrating that rates of chronic infection are lower following re-infection. [134, 135] In a large study of more than 1000 injection drug users, the incidence of HCV infection for previously uninfected persons was 18.6% and for previously infected persons 9.2%. After adjusting for potentially confounding factors, including age, sex, ethnicity, HIV infection,
housing status, frequency of illicit and injection drug use, previously uninfected persons were 4 times more likely to become infected.[134] In a smaller study of approximately 98 previously uninfected and 164 previously infected injection drug users, previously infected injection drug users were half as likely to develop persistent infection (hazard ratio, 0.45; 95% CI 0.23-0.88).

**Occult infection**

Occult HCV infection is characterized by the detection of HCV RNA employing highly sensitive nucleic acid amplification techniques, in individuals in whom HCV-RNA testing is negative but evidence of prior exposure is present (anti HCV+ve). The sites of HCV-RNA occult infection that have been identified include the liver, serum, and lymphatic cells such as peripheral blood mononuclear cells (PBMCs) and dendritic cells (DCs).[136-138] Studies of occult HCV infection have reported detectable HCV RNA over prolonged periods of time. However these observations are disputed by many and occult infection remains a controversial issue.[139-141]

### 7 Substance abuse

**Substance Abuse and Injection Drug Use in Canada**

Substance abuse is defined according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria as a disorder characterized by the use of a mood or behavior-altering substance in a maladaptive pattern resulting in significant impairment or distress. Individuals often abuse a variety of substances - heroin, hydromorphone and oxycodone, and non-opioids such as cocaine and methamphetamines - either concurrently or over their lifetimes using different routes of administration. Injection drug use (IDU) is the biggest risk factor for HCV infection. However use of crack cocaine is also associated with a high risk of infection.[142] The Canadian Addiction Survey (CAD), conducted in 2004 indicates 3% of Canadians used illicit drugs in the past year, and 16.5% had used them at some point. A study of illicit opioid users in Canadian cities, (OPICAN) indicates that poly-drug abuse is frequent with more than 70% combining opioid and non-opioid drugs.[143] Also, differences can be seen among different regions in Canada. Heroin is the opiate of choice in Vancouver and the distribution among users of heroin, hydromorphone and codeine is more even in Toronto. In Calgary, cocaine/crack and opiates such as morphine, hydromorphone and codeine predominate; heroin use is relatively less.
Substance abuse and Hepatitis C Natural History

HCV is spread in substance abusing populations through risky behaviours such as sharing of needles and other injection equipment, use of crack cocaine and having multiple sex partners where they engage in traumatic sexual behaviours.[23, 144, 145] The effect of substance abuse on the natural history of Hepatitis C is unclear. Some evidence indicates that intravenous drug use decreases the immune response and may leave IDUs more susceptible to HCV-related liver damage.[146] Cross-sectional analysis of liver biopsy among active IDUs in an American inner-city did not show a prevalence of advanced liver disease different from that of non-IDU populations.[147] A prospective cohort study estimated incidence of end-stage liver disease in this population of 3.1 per 1000 person years.[148] However many IDUs have concomitant problems with abuse of alcohol and HIV co-infection which increase the rate of progression to end-stage liver disease.[61, 149] The relative risk of progression to end stage disease was estimated to be 3.6 times higher in IDUs that consume more than 260g of alcohol weekly.[148]

Antiviral therapy for active or recent substance abusers

The best treatment currently available for HCV infection is combination therapy with pegylated interferon (PEG-IFN) and ribavirin. Until recently, guidelines discouraged antiviral treatment of HCV in active substance abusers. The high prevalence of psychiatric co-morbidity, concerns about the way in which substance abusers would react to treatment side effects, and the high risk of re-infection were reasons for this recommendation.[150] Several studies have shown that 70% or more of active or recent substance abusers with HCV infection are willing to be treated.[151] A growing number of reports demonstrate that response rates observed in the general population are achievable in substance abusers regardless of their drug use status.[4, 152] There are better methods for handling side-effect profiles [153], and weak evidence indicates that successful treatment with antiviral therapies can result in cross-genotypic immunity.[122] Arguments against treatment have also been rejected on an ethical basis, but have been argued for on a scientific basis.[151, 154, 155]
Opponents of treatment for active or recent substance abuser cite the following arguments

- Substance abuse is a chronic condition. Therefore, treating HCV infection in active or recent substance abusers means these individuals will likely remain at risk of re-infection.
- Lifestyle issues associated with substance abuse contribute to low quality of life and the impact of HCV infection on quality of life may be small.
- Competing mortality, such as death from other causes associated with substance abuse lifestyles may mean that the disease burden of HCV is a small proportion of overall disease burden for substance abusers. Injection drug users have mortality rates at least twice as large as non-drug users of the same age and sex.[156] One longitudinal study conducted in the UK demonstrated that drug addicts under the age of 45 were more likely to die from drug-related causes than addicts over age 45.[157]
- Lifestyle issues may result in lower rates of adherence to treatment, lower rates of treatment success and a potential waste of resources.
- Substance abusers may be younger at the age of infection and therefore may have a more benign course of liver disease.

The aforementioned arguments seem to advocate for a watchful waiting approach in which clinicians counsel patients regarding transmission risks, address co-morbidities such as depression and wait until substance abuse has ceased permanently before addressing chronic HCV infection. Indeed a significant proportion of patients in clinical trials of interferon-based therapies and those treated in specialist settings are former substance abusers with a remote history of drug abuse.

Proponents of treatment argue as follows

- Progression to end-stage liver disease is accelerated by factors commonly associated with the abuse of illicit drugs such as HIV co-infection, HBV co-infection and abuse of alcohol. Therefore the natural history of infection in this population may not be benign.
- Liver disease may be more advanced once substance abuse issues have been resolved. Success rates of antiviral therapy are lower in patients who are older and those with end-stage liver disease.
• Preliminary evidence suggests that re-infection rates for substance abusers that are successfully treated with antiviral therapies are lower than incidence in the same population – suggesting a protective effect of treatment.

• Removal of infected individuals from the pool of substance abusers may reduce overall transmission and lower the future disease burden in the population.

Multidisciplinary care and treatment uptake

Studies demonstrating treatment success in current or former substance abusers employ a multidisciplinary approach to care including a combination of primary care, addiction therapy, psychiatry and/or counselors.[4, 152] A multidisciplinary approach appears to be necessary to successfully address chronic HCV in this patient population but it may not be sufficient. In a Vancouver primary care clinic involving psychiatrists, counselors and opiate replacement therapy, only 16% of patients received antiviral therapy.[158] A CIHR funded trial to assess the optimal level of support required for treatment of active substance abusers in Vancouver and Victoria is experiencing difficulties in recruitment. As of April 2009, 280 patients had been screened, 45% had been offered treatment and less than 8% (20) had initiated therapy. (Personal communication, CIHR study investigators) Similarly, in an urban population treated at the Boston Medical Centre, only 36% of eligible patients were treated.[159] Of 441 patients with chronic HCV infection attending a community-based specialist addiction services treatment program East London, 83 patients considered therapy and 69 underwent therapy.[160] In a multi-centre study of young injection drug users in the USA, 86% of a total of 216 expressed interested in therapy but only 1/3 of those offered therapy initiated treatment. Poor treatment uptake underscores the complex issues involved in treatment even in the context of comprehensive care.

Factors affecting utilization of antiviral therapy for current or former substance abusers infected with HCV

A useful framework articulated by Mehta et al categorizes factors affecting utilization of antiviral therapy for injection drug users into eligibility - based on clinical and stability criteria, advisability - based on genotype, viral load and co-morbid conditions and acceptability to the patient – based on motivation, lifestyle and social supports.[161] Domains such as eligibility and
acceptability are potentially modifiable. A detailed list of factors identified in the literature is summarized below.[158, 162, 163]

Factors associated with Interest/Willingness to receive antiviral Therapy

- mono-infected (no HIV co-infection)
- reporting health problems
- poor liver status/perceived threat of liver disease/informed by doctor that HCV can cause liver damage
- relationship with doctor/having a usual source of care/supportive medical services
- no evidence of alcohol dependence
- no injection drug use recently
- more ready to quit injection drug use
- previous drug abuse treatment
- treatment effectiveness
- supportive partner

Factors associated with lack of interest/willingness to receive antiviral therapy

- lack of info/knowledge re availability of treatment/lack of info/knowledge about HCV
- don’t understand current disease monitoring
- absence of symptoms/liver status is good
- side effects of treatment
- success rates not good enough/legacy of older, less effective treatments
- homeless less likely to be interested
- impact on work
- impact on family/friends
Cost as a barrier to antiviral therapy

Insights from the cost of addiction therapy illustrate that costs may present a barrier to accessing drug treatment for patients with substance abuse issues. Like antiviral therapy, methadone maintenance typically requires frequent contact with patients and involves considerable cost in terms of patient travel, time and lost productivity.[164-166] In one study, patients enrolled in an outpatient treatment program incurred on average a $50 cost per visit due to travel and lost productivity.[166]

8 Quality of life

Quality of life has been increasingly measured as an outcome of health care and a consequence of illness that is important to both clinicians and patients. The concept of health status has been defined as the aspects of quality of life that relate specifically to a person’s health, and has often been used interchangeably with the concept of health-related quality of life.[167, 168] The domains which comprise health status as defined by Patrick et al are symptoms, functional status (physical, psychological and social functioning), health perception and opportunity.[167] Several questionnaires measuring quality of life have been developed using a psychometric approach, each based on slightly different conceptual bases. Examples of generic quality of life measures include the Quality of Well Being Scale (QWB), the Sickness Impact Profile and the Medical Outcomes Study Short Form 36 (SF 36).[169, 170] The psychometric instrument most commonly used in the measurement of quality of life for Hepatitis C positive patients is the SF-36.

Medical Outcomes Study Short Form 36 (SF 36)

The psychometric instrument most commonly used in the measurement of quality of life for Hepatitis C infected patients is the Medical Outcomes Study Short Form 36 (SF-36). The SF-36 measures quality of life in 8 health dimensions (physical functioning, role physical, bodily pain, general health perception, energy/vitality, social functioning, role emotional and mental health). Scoring of the SF36 results in scores for each of the 8 domains as well as a physical summary score (PCS) and mental summary score (MCS). The Hepatitis Quality of Life questionnaire (HQLQ) was developed to better capture aspects of quality of life that are affected by Hepatitis infection.[171, 172] Scoring of the HQLQ produces all of the SF-36 domain scores in addition to
domains that measure sleep somnolence, work productivity and health distress related specifically to hepatitis infection. (Appendix)

Utility measures of quality of life

The preference-based framework for measuring quality of life is based on assessing the value of a health state which is revealed by individual preference. A utility is a measure of preference for a health state elicited from an individual under conditions of risk. The utility is typically anchored from 0 (equivalent to death) to 1 (equivalent to perfect health). Utility as a measure of quality of life is optimal to inform health care decision-making, because unlike psychometric measures it explicitly accounts for the value an individual places on a health state rather than just a description of that state.[173] Utilities are applied to life years to obtain quality adjusted life years (QALYs), a measure that is commonly used in health care policy models.

Time Trade-Off

The time trade-off (TTO) is a method for eliciting utilities in which an individual reveals her “preference” for the present health state by giving up future life expectancy and trading for perfect health.[174] If a person is indifferent between trading ½ of her remaining life expectancy or remaining in the present health state, the utility for the current health state is 0.5. The TTO has been validated in the HCV population, demonstrating impaired quality of life.[175]

Standard Gamble

The standard gamble is a method for eliciting utilities in which an individual reveals her “preference” for the present health state by indicating the level of risk she is willing to accept to achieve a complete cure. If a person is indifferent between current health and a hypothetical treatment that has 95% chance of cure and 5% chance of immediate death, then the utility for the current health state is 1-0.05, or 0.95.[174] Standard gamble utilities are considered to be the gold standard in utility measurement because the utility is obtained under conditions of uncertainty and the preference is revealed by the willingness to trade off current health against risk of cure.
Health Utilities Index

The Health Utilities Index Mark III (HUI3) is a 15-item questionnaire that classifies individuals into levels of functioning on 8 attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain, with 5-6 levels each.[176, 177] HUI3 scoring involves the use of a preference-based algorithm to calculate utilities with preference weights obtained from members of the general public.[178, 179] Weights from the general public are preferable when utilities are used in cost-effectiveness analyses to inform health care policy.[180] The HUI has been used in the Canadian National Population Health Survey (NPHS). Therefore Canadian norms for health status scores and utilities are available.[176, 181-183]

SF-6D

Utility algorithms obtained by eliciting preferences from the general public are also available for the SF6D, a subset of questions from the SF-36.[184] The SF-6D is a preference-based utility instrument that classifies respondents into 6 dimensions of health (physical functioning, role limitation, social functioning, bodily pain, mental health and vitality), using 11 items from the SF-36 questionnaire. Using preference weights obtained from members of the general public in the United Kingdom, a utility weight ranging from 0.3 to 1 is calculated.[185-187]

Quality of life in patients with chronic HCV infection

Several studies have demonstrated that patients with chronic HCV infection have lower quality of life than the general population.[172, 188-196] Markers of disease severity such as the presence of cirrhosis, or elevated ALT levels are not associated with lower quality of life.[172, 190, 192-194, 197] However the presence of psychiatric comorbidities, medical comorbidities[194], as well as the number of clinical findings of chronic HCV[172], are associated with lower scores.

Cognition

Evidence suggests that chronic infection with HCV is associated with cognitive deficits. In one study investigators measured cognitive function with tests for auditory verbal learning, short and long-term memory, attention, information processing, naming and identification, motor skills,
visual-perceptual organization and word association. The investigators compared 120 patients with chronic hepatitis C to 40 healthy controls and found that patients with chronic HCV infection had no measurable deficit.[190] However, patients with decompensated cirrhosis had worse cognitive function compared to those with compensated cirrhosis and compared to healthy controls. In another study, investigators electro-physiologically measured evoked potentials in the brain to assess cognitive function and demonstrated small, but significant decrements in cognition when 100 HCV infected patients were compared to matched controls.[198] Another study demonstrated cognitive deficits in HCV infected patients attending a tertiary clinic in Australia.[199] In this study, cognitive performance was assessed using tasks to measure detection, identification, matching, attention, memory and learning. Uninfected controls performed better than those with HIV/HCV co-infection, HIV or HCV mono-infection. There was no difference in cognitive performance among the different groups however, indicating there may not have been a measurable isolated effect due to HCV viremia.

Fatigue

Fatigue is a common finding in patients with chronic HCV infection. Studies of fatigue symptoms in CHC patients demonstrate frequent incidence of disabling fatigue. Qualitative interviews conducted with chronically infected patients reveal that patients characterize the fatigue of chronic HCV infection as having both acute and chronic components.[200] Studies have measured fatigue using the Fatigue Impact Scale and the Fatigue Severity Scale.[201, 202] The fatigue impact scale assesses functional limitations due to chronic fatigue in the physical, cognitive and psychosocial domain. The association between chronic HCV infection and fatigue is supported by the fact that individuals with a successful response to antiviral therapy demonstrate improved scores in the vitality subscale of the SF-36.[203]

Depression and Anxiety

Depression and anxiety has been diagnosed in patients with chronic HCV infection using structured psychiatric interviews.[204, 205] After adjustment for age and sex, depression was associated with poorer work and social adjustment, lower acceptance of illness, higher illness stigma, poorer reported thinking and concentration, and higher levels of subjective physical symptoms (all P<.05).[204, 205] Anxiety disorders were also diagnosed but were not correlated
with any risk factor. Depression has also been identified in patients with chronic HCV infection using psychometric scales like the Zung self-report rating scale [206], and the Beck Depression inventory.[190, 204]

**Productivity**

Patients with chronic HCV infection report lower productivity and decreased functioning in aspects of daily life such as work, household functioning, sexual functioning and leisure.[207, 208] Treated and untreated patients completed the Nottingham Health Profile providing information on everyday activities such as occupation, household work, social life, home life, sex life, hobbies and holidays.[207] Treated patients expressed less concern about activities of daily living than untreated patients. The authors did not comment on the virological response of the treated patients. Individuals with a sustained response to antiviral therapy demonstrate significant improvements in work productivity when asked questions about hours worked, days missed from work and self-reported productivity before and after antiviral therapy.[209]

**Awareness of HCV infection and stigmatization**

Awareness of HCV infection has been associated with lower quality of life. In a study conducted among injection drug users in Oslo, Norway questionnaire respondents who had been aware of chronic HCV infection had lower quality of life scores than respondents who had not been aware of infection.[210] In a tertiary care setting, when quality of life measures were compared between patients who were unaware and patients who were aware of infection, those who were aware of infection had lower quality of life scores than those who were unaware.[211] Another study conducted in a tertiary care setting demonstrated that for patients in whom quality of life was measured prior to diagnosis of hepatitis C infection quality of life scores were higher than for patients in whom measurements were obtained after diagnosis.[191] The studies demonstrate that diagnosis with chronic hepatitis C viral infection is associated with a decrease in quality of life, which may result from the anxiety and depression that can accompany being labeled with hepatitis C infection. Structured interviews with patients chronically infected with HCV were used to measure stigmatization defined as being negatively judged by others and as a result of patient’s HCV infection.[212] Qualitative researchers coded participants’ responses and indicated whether or not the patient reported stigmatization. More than one-half of the 247 study
respondents reported stigmatization. Stigmatization was significantly associated with higher depression scores, higher anxiety scores and lower quality of life as measured using the Sickness Impact Profile.

**Sustained virological response to antiviral therapy**

While treatment with interferon therapies worsens quality of life during treatment, studies have demonstrated a significant quality of life improvement for patients that achieve a sustained virological response. Data collected alongside randomized controlled clinical trials, demonstrate a significant improvement in quality of life immediately following sustained response to therapy. [126, 127] The results have been cautiously interpreted because quality of life was measured 24 weeks following therapy and patients may have been influenced by recently learning about viral clearance. Also, patients enrolled in clinical trials represent highly selected populations and it is not clear whether or not these results are generalizable. Responders to therapy report decreased fatigue and improved productivity.[203, 209]

In cross-sectional studies in which patients with a sustained response to therapy are compared to treatment failures, responders have higher quality of life scores. Thein et al performed a systematic review of quality of life data and estimated that patients with a sustained response to antiviral therapy had scores ranging from an average of 0.04 to 0.09 better than those with chronic HCV and compensated cirrhosis.[196] In this analysis, SF-36 data was translated into utility measures on a scale of 0 to 1. A large cross-sectional mail survey of 883 patients in Switzerland identified through hospital clinics, assessed predictors of quality of life using regression analysis. A small, significant difference of less than 3 on the PCS of the SF-36 was demonstrated between responders and non-responders.[213]

**History of substance abuse**

A history of intravenous drug use appears to have no measurable effect on quality of life for HCV positive patients. In a study of HCV positive patients enrolled in a treatment trial, there was no effect of injection drug use as a source of infection on SF-36 quality of life scores.[194] Previous drug use or dependency was not associated with lower SF-36 or HUI3 scores in a study of HCV positive patients that had failed interferon therapy.[192]
Quality of life in patients with substance abuse issues

Individuals with substance abuse problems report worse quality of life than members of the general population, and the profile resembles the profile of patients with psychiatric illness. In a cohort of HCV positive patients, active IDUs had lower quality of life than non-IDUs.[193] A study in which the quality of life of active substance abusers in Oslo, Norway was measured using the SF-36 suggested that chronic infection with HCV was not associated with further quality of life decrements beyond that associated with substance abuse.[210] Among IDUs, those with chronic HCV infection, co-infection with HCV and HIV and those uninfected with either virus had similar quality of life scores. In another study of 299 patients comparing SF-36 scores among HCV/HIV co-infected IDUs to HCV infected IDUs and to HIV infected IDUs, there was no difference among them in quality of life measures.[214] More recent evidence contradicts this finding. In a study of 619 active injection drug users in North Carolina, HCV infection was associated with lower quality of life.[215] Using regression analysis to adjust for demographic and drug use variables HCV infection was associated with lower physical functioning, general health and vitality after adjustment. However, male sex, methamphetamine use and harmful drinking had the largest contribution to quality of life decrements. Divergent findings may be explained by differences in the study populations. In the study conducted in Oslo, respondents were needle exchange clients. In the study conducted in North Carolina, respondents were out of treatment IDUs recruited from the street. It is possible that the quality of life decrement associated with HCV infection is more acutely felt in those IDUs not receiving treatment for addiction. Even though QOL decrements are measurable in active IDUs, decrements associated with substance abuse may have the most impact, and this has implications for the relative importance of HCV antiviral therapy in this population.

Studies assessing quality of life impact in other relevant populations also signify that HCV decreases quality of life. A significant proportion of war veterans report substance abuse problems. Studies conducted on populations of veterans in the United States, also indicate that HCV infection is associated with a decrement in quality of life, even after adjusting for other factors.[216, 217] Lim et al measured QOL in more than 850 war veterans demonstrating significant decrements in the Mental Component Summary (MCS) Score after adjusting for age, demographic factors and psychiatric co-morbidity. In a study of Australian prisoners, HCV and HIV/HCV co-infected prisoners had lower scores on the MCS than uninfected prisoners. The
results were not statistically significant, but the analysis may have been limited by small sample size.[218] In a community-based study of 226 HIV infected homeless and marginally housed individuals that were recruited from homeless shelters, SF-36 data demonstrated that respondents co-infected with HIV and HCV had lower scores on all domains of the SF-36 than HIV mono-infected respondents.[219] After adjustment for sex, ethnicity, insurance status, antiretroviral therapy for HIV, HIV viral load, other co-morbidities, significant differences in QOL remained between HIV mono-infected and HCV/HIV co-infected respondents.

The question of whether quality of life improves for HCV infected IDUs upon completion of successful treatment has not been specifically addressed in HCV antiviral trials.

Quality of life tradeoffs and antiviral therapy

Quality of life tradeoffs may play an important role in treatment decisions. A recent study assessed the relationship between quality of life and treatment decisions among urban patients with chronic HCV infection of whom approximately 55% reported past injection drug use. [220] In this study, HCV infected patients provided preference weights for their own health states and for the side effects of treatment. Patients rated their current health state relatively high compared to the side effects of therapy. A more recent study measured the impact of quality of life on preferences for treatment and found that patients with a higher perceived risk of liver disease and worse HCV-related quality of life had a stronger preference for antiviral therapy.[221] Study participants with a greater perceived risk of disease placed more weight on the expected benefit of treatment than on the risks of antiviral therapy.

9 Cost-effectiveness analysis

While this thesis does not include a cost-effectiveness analysis, the results of the thesis are relevant to cost-effectiveness analysis and can be used to assess different options for preventing and treating hepatitis C.

Cost-effectiveness analysis

Cost-effectiveness analysis is a type of economic evaluation defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences.[222] A cost-
effectiveness analysis assesses the value for money associated with a health outcome. The main output of a cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER). The ICER quantifies the incremental benefit of one therapy compared to another in terms of health outcomes. When health benefits are expressed as utilities, the analysis is known as a cost-utility analysis, although cost-effectiveness analysis is often used as a generic term. The use of decision models in cost-effectiveness analysis is common as it is a powerful method for synthesizing evidence on both the clinical and economic consequences to inform policy decisions.[223]

Markov cohort models

Markov cohort models consist of distinct health states, allowable transitions between health states, and probabilities per unit time for each allowable health state transition. The Markov cohort framework has been used to model the cost-effectiveness of antiviral therapy as treatment for chronic HCV infection.[224-226] The health and economic effects associated with a single cohort of patients with chronic HCV are simulated over the lifetime of that cohort, providing an estimate of the cost-effectiveness of treating a single cohort of patients.[227, 228]

Infectious disease models

Infectious disease modeling can assist in understanding the spread and control of infectious diseases.[229] Treatment of HCV positive IDUs may interrupt the chain of transmission by reducing the number of infected individuals. Interventions that interrupt the transmission of an infectious disease have effects not only on a single cohort but indirect effects on the populations at risk.[230, 231] Infectious disease models allow for changes in transmission probabilities as a feedback on the number of susceptible and infected IDUs in the population. This type of approach is suitable for making future projections on the HCV epidemic in the context where individuals will be prevented from entering the infected population through needle exchange or other preventive efforts as well as removed from the population by successful treatment.

Existing CEA evidence

Several models have been used to forecast health and cost effects of HCV infection in substance abusers. Cumulative direct medical costs associated with untreated IDUs were estimated to
exceed $10M NZ [232], and $6M AUS per 1000 HCV infected IDUs over the lifetime [233, 234], with an additional $13M of indirect costs due to lost productivity.[234] An infectious disease model has been used to estimate the potential impact of preventing HCV infection through needle exchange. The cost-effectiveness of needle exchange in reducing the transmission of HCV among IDUs was estimated as the cost per HCV infection prevented at $250,000.[235]

One study estimated the cost-effectiveness of testing for HCV infection among former injection drug users at £17K per QALY. [236] The ICERs were similar for test and treat strategies in general practice, prisons and drug therapy clinics, ranging from £16K to £20K per QALY.

10 Research questions and rationale

In this thesis we undertake three empirical investigations addressing the following research questions:

Study question 1

What is the rate of progression to cirrhosis for individuals with chronic HCV infected through injection drug use?

Rationale

Cirrhosis of the liver is associated with significant morbidity and mortality due to the increased risk of decompensation and hepatocellular carcinoma. Estimating the rate of progression to cirrhosis is important to understand the prognosis of individuals with chronic HCV infection, and to inform health services policy related to HCV-infected patients with CHC. A recent increase in the number of published studies assessing liver disease in populations that acquired HCV infection through injection drug use make it possible to perform a synthesis of the literature specific to this population. Several factors unique to this population underscore the importance of better understanding fibrosis progression. Substance abusers have a high prevalence of co-morbidities that may increase the rate of progression to cirrhosis, such as excessive alcohol intake, HIV co-infection and HBV co-infection. The effect of co-morbid illness may be unique in this population. Quantifying the rate of progression cirrhosis in this population will inform estimates of disease burden and allow for effective public health decision making.
Study Question 2

Do individuals that have cleared chronic HCV infection following antiviral therapy have better quality of life and work productivity than individuals who failed therapy?

Rationale

The negative impact of chronic HCV infection on quality of life has been well-documented. Fatigue, impaired cognitive ability, depression and anxiety decrease quality of life and reduce productivity at work and leisure. Randomized clinical trials have demonstrated improvements in quality of life immediately following antiviral therapy. No data are available to assess whether or not the impact on quality of life for responders to therapy endures. Information on the long-term quality of life impact associated with successful antiviral therapy will assist patients, clinicians and decision makers in making decisions about therapy and assessing the benefits of policy to improve access to therapy and increase uptake of therapy.

Study Question 3

Can substance abusers on methadone maintenance therapy, who are treated with antiviral therapy for HCV infection adhere and respond to therapy, despite on-going substance use?

Rationale

The prevalence of chronic HCV infection among substance abusers is extremely high. Potentially effective antiviral therapy exists, but substance abusers are least likely to be treated. Concerns about the ability of substance abusers to adhere to therapy amidst on-going substance abuse contribute to the low rate of therapy. Assessing the rates of adherence to antiviral therapy and the rate of response to therapy with close monitoring of the consumption of illicit substances can provide clinicians and policy makers with information to better understand treatment of this population. This can inform clinicians and policy makers developing programs targeted at increasing treatment uptake and treatment success in this population to potentially reduce the high burden of disease.
11 Methods - Study 1

In this section, background information is provided on the methods for Study 1. In study 1 a synthesis of the literature was performed to estimate the rate of progression to cirrhosis, using meta-analysis and meta-regression and Bayesian statistics. The code and data used in the Study 1 analysis is also provided.

11.1 Methods for estimating the rate of progression to cirrhosis

The silent nature of acute infection with HCV and subsequent chronic infection means that it is challenging to assess rates of progression to cirrhosis. Methods for estimating the rate of progression to cirrhosis can be grouped into direct and indirect methods. The direct method of estimation requires serial biopsies. The change in fibrosis is divided by the interval between the biopsies, to estimate the progression rate.[61] Due to the difficulty involved in obtaining serial biopsies from patients, use of this method is not popular. Indirect methods use a single liver biopsy and the estimated date of infection to estimate the fibrosis progression rate.[59, 61, 95] The fibrosis stage is divided by the estimated duration of infection to provide the estimated rate. Because fibrosis progression rates cannot be observed directly, studies of the natural history of chronic HCV infection may be biased by several factors including the study design, the method for determining the date of infection, the timing of patient recruitment into the study (retrospective, prospective), study setting and patient characteristics sex, age at infection, other co-morbidities e.g. alcohol, obesity, co-infection HIV or HBV.

Prospective cohort studies

The ideal study design to estimate the rate of progression to cirrhosis is a prospective cohort study in which individuals are recruited at the time of infection. This is not possible unless there is a single source. One study of Irish women infected through contaminated immune globulin G provides longitudinal data on a cohort with a well-defined date of infection. The women were identified retrospectively in a 1994 screening program.[32] Only 2% of these women developed cirrhosis after 17-20 years of infection. A similar study from Germany also demonstrated slow
rates of progression to cirrhosis. Low estimates for these studies may reflect better prognosis for young females, and lower rates of alcohol consumption. Many studies have assessed incidence of HCV in high risk groups such as injection drug users, and followed them prospectively, however the duration of follow-up was not long enough to assess disease progression rates.[237-240] Follow-up of injection drug users presenting to an Australian hospital with acute HCV infection revealed that 8% had progressed to cirrhosis after 25 years.[241] Although the date of infection is well characterized in these studies, biases may remain due to non-random sampling of the original cohort.

**Retrospective studies and the date of infection**

Most of the estimates of the rate of progression to cirrhosis come from retrospective, non-cohort studies. In these studies, the extent of liver fibrosis is assessed in a sample of patients with chronic HCV infection, and the date of infection is estimated in order to calculate the duration of infection. Some algorithms have been commonly used to impute the date of infection based on risk factors. For individuals in North America with blood transfusions prior to 1990 (before the introduction of sensitive screening assays), the date of first blood transfusion is used to impute the date of infection. For individuals who report injection drug use, the date of first injection is used as the date of infection. A systematic review and meta-regression of HCV infection among IDUs estimated that prevalence was 32.02% (95% confidence interval: 25.31, 39.58) at 1 year of injection and 53.01% (95% confidence interval: 40.69, 65.09) at 5 years in developed countries.[25] This indicates that imputing the first year of injection may result in an overestimate of the duration of infection. Biases associated with patients’ recall of the date of first injection drug use may also impact the validity of retrospective studies. Population-based data on sero-prevalence was analyzed to estimate the time of first injection drug use and the estimates were compared with patient reported date estimates. The study demonstrated that some individuals report a year of first injection that was earlier than the data suggested. Others reported a year of first injection that was later than the data suggested.[242] The majority of studies in the literature providing information on fibrosis progression rates use imputation to estimate the date of infection.
Study setting and referral bias

Studies set in tertiary liver clinics are associated with faster rates of progression than community-based studies. This suggests that there is a selection bias in that sicker patients (with more advanced stage of disease) will tend to be referred to tertiary clinics. For example, a meta-analysis by Freeman et al demonstrated that retrospective liver clinic studies estimated a 20-year prevalence of cirrhosis of 21.9% compared to a prevalence of 6.5% for community-based studies and 3.7% for retrospective studies in blood donors who tested positive for Hepatitis C.[95] A simulation study demonstrated that referral bias can lead to overestimates of fibrosis progression rates as well as misspecification of the relationship between covariates and increased progression to cirrhosis.[243]

Study population and selection bias

Characteristics of the study population, including co-morbidities and competing mortality risks may affect estimated rates of fibrosis progression. A simulation study demonstrated that in populations with competing risks of mortality from other causes estimated rates of progression to cirrhosis can be too high. The reason behind this is somewhat counterintuitive. Slow progressors die from other causes and fast progressors present with cirrhosis, biasing the fibrosis progression rate upward.[64] This is a form of selection bias. This observation has implications for studies of patients who acquired HCV through blood transfusion, because of a high co-morbid burden and hence their need for a blood transfusion. Substance abusers have higher rates of mortality than the general population also due to their co-morbidities. It is possible that this selection bias influences rate estimates for substance abusers.

11.2 Bayesian statistics

Bayesian inference uses evidence to update or newly infer the probability that a hypothesis is true.[244] The relationship between the new inference, previous hypothesis and new data is articulated by Bayes’ theorem, so named because the theorem was derived from the work of Reverend Thomas Bayes. Bayes theorem states that the probability a hypothesis is true is a function of a) the prior belief about the veracity of the hypothesis, b) the probability that the data from the current experiment would be observed if the hypothesis were true and c) the probability of observing the evidence. One advantage of the theorem is that it is consistent with the scientific
method in which new data from experiments impact on the scientist’s knowledge about the true underlying phenomenon.

**Bayes Theorem**

Using formulae, Bayes Theorem can be specified as:

\[ P(H|E) = \frac{P(E|H) \times P(H)}{P(E)} \]

P denotes a probability

H denotes an hypothesis

E denotes the experiment or newly observed data

P(H|E) represents the posterior probability that the hypothesis is true given the new data. It is the updated inference that results from new data.

P(E|H) represents the probability of “seeing” the data if the hypothesis is indeed true. This probability is referred to as the likelihood. It is important to note that the likelihood forms the basis of the frequentist approach to statistics.

P(H) represents the prior probability that the hypothesis is true. The prior may come from a meta-analysis of previous experiments or previously collected data or from expert opinion. A prior belief can also reflect a situation in which little or no information about the veracity of the hypothesis exists. This type of prior is known as an uninformative prior or a diffuse prior. For example, a uniform distribution is one example of an uninformative prior distribution. If a prior probability distribution is uniform for a specific range that indicates that each value in the range has equal probability of being true.

P(E) represents the probability of “seeing” the data regardless of whether or not the hypothesis is true. The probability is the sum of two probabilities: 1) the probability of “seeing” the observed
data if the hypothesis is true and 2) the probability of “seeing” the observed data if the hypothesis is false.

**Diagnostic test example**

The most common use of Bayes’ theorem and perhaps most intuitive is in the context of diagnostic testing. Consider the scenario in which a person is tested for the presence of a particular disease, for example HIV. Prior to testing, a clinician may have an estimated probability that the person is infected with HIV. After performing the test, the clinician would update the probability that the person is HIV infected based on the test results. In this context, the components of Bayes’ theorem would be specified in the following way:

- \(P(H)\) represents the prior probability that the person is HIV+. This prior probability is estimated based on what is known about the patient characteristics including risk factors as well as what is know about the prevalence of HIV in the population the person represents.
- \(P(E|H)\) represents the probability of obtaining a positive test if the person tested is in fact HIV+.
- \(P(H|E)\) represents the new probability a person is HIV + based on the newly obtained test results.
- \(P(E)\) represents the probability of a positive test. The probability of a positive test in this context is the probability of a true positive - the probability that an HIV+ person will correctly test positive (also known as the sensitivity of the test) plus the probability of a false positive – the probability a person who is HIV- would incorrectly test positive (also known as – the specificity of the test).

If we assign the following parameters to the HIV test example:

- HIV prevalence – 0.1%
- Sensitivity of the test – 95%
- Specificity of the test – 98%
The calculation of the posterior probability can be illustrated by considering a population of 100,000 test takers, in which the prevalence of HIV is 0.1%.

**Table: Diagnostic test characteristics**

<table>
<thead>
<tr>
<th></th>
<th>HIV -</th>
<th>HIV +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test -</td>
<td>97,902</td>
<td>5</td>
</tr>
<tr>
<td>Test +</td>
<td>1,998</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>99,900</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100,000</td>
</tr>
</tbody>
</table>

Of the 100,000 only 100 are truly HIV positive and 99,900 are HIV negative. Of those that are HIV positive, 95% (95) will correctly test positive and 5% (5) will falsely test negative. Of those that are HIV negative 98% (97,902) will correctly test negative and 2% (1,998) will falsely test positive. If a person tests positive, then the probability the person is HIV positive is 95 / 2093 = 0.045. The importance of prior information can be illustrated by the difference in the posterior probability of disease (4.5%) and the test characteristics of 95% sensitivity and 98% specificity.

We can use the diagnostic test paradigm to underscore the key distinctions between frequentist and Bayesian inference. We can say that a frequentist approach to diagnostic testing would restrict us to the test characteristics of sensitivity and specificity. We could only estimate the probability of a positive test if the person tested is in fact HIV +ve. This is analogous to the likelihood, or the probability of “seeing” data if our hypothesis is true. (Alternatively, we could estimate the probability of a negative test if the person tested is in fact HIV –ve which is analogous to the probability of “seeing” the data if our hypothesis is not true.) Frequentist statistics provides no functionality to estimate the probability that the tested person is HIV +ve based on the test result. Bayesian inference directly informs this key probability.

---

2 Bayes theorem can also be used to calculate the probability that is illustrated in the above table. (Calculations not shown)
**Bayesian Statistical Modeling**

In any statistical framework, a model specifies the relationships between variables using mathematical equations. A well known example of a statistical model used in both frequentist and Bayesian statistics is the linear regression model.

\[ Y = ax + b \]

which relates a dependent variable \( Y \) to an independent variable \( x \) using a line of slope \( a \). The error term is represented by \( b \).

**Probability distributions**

In Bayesian statistics each variable can be represented as a point estimate or as a distribution. A distribution assigns a probability to a set of values or a range of values and can either be discrete or continuous. In contrast, each probability in the HIV diagnostic test example above was represented by a single point estimate.

**Discrete probability distribution**

In a discrete probability distribution, the values come from a defined set and take on distinct values. The sum of the probabilities over the distinct values within each defined set equals one. Common examples of discrete probability distributions are the Bernoulli and Poisson distributions.

**Continuous probability distribution**

In a continuous probability distribution, the probability of any one value is zero because the probability is not defined for discrete values. Instead, the area under the curve of a continuous probability distribution is 1. Using integration it is possible to estimate the probability for a range of values within a continuous probability distribution. It is also possible to estimate the probability of a single value by considering infinitely small ranges. A probability distribution can be assigned to the values for a parameter such as an odds ratio, a rate or a probability. Common examples of continuous distributions are the Normal, Beta and Gamma distributions.
**Analysis of Bayesian models**

Bayesian statistical models can be analyzed in two ways: analytically and through simulation.

**Analytical analysis of statistical models**

An analytical model can be solved directly using equations and is said to have a closed form solution. In a Bayesian analysis, one special group of models known as conjugate models can be solved analytically. Conjugate models occur when the prior and posterior distributions are of the same type. The following are examples of conjugate models, specifying the conjugate prior, the distribution for the likelihood, and the conjugate posterior distribution.

**Table**: Conjugate distributions

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Prior/Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernoulli</td>
<td>Beta</td>
</tr>
<tr>
<td>Binomial</td>
<td>Beta</td>
</tr>
<tr>
<td>Poisson</td>
<td>Gamma</td>
</tr>
</tbody>
</table>

The Poisson-Gamma conjugate model is highlighted here due to its use in Study 1. The Poisson-Gamma conjugate model provides one solution to overcoming the problems associated with calculating a 95% confidence interval for the Poisson rate with zero count data.

**Poisson rate/ Poisson distribution**

The Poisson distribution is commonly used for modeling rare events. A Poisson distribution expresses the probability of a number of events occurring in a fixed period of time and is thus a rate. A Poisson rate is expressed as the number of events divided by the total follow-up time. (A Poisson distribution can also be used to represent the number of points in an interval such as a volume or distance.)
\[ \lambda = \frac{X}{N} \]

\( \lambda \) – poisson rate

\( X \) – the number of events

\( N \) – the follow-up time

The Poisson distribution is a special case of the binomial distribution. Expressing a rate as Poisson is useful for analysis of rare events that occur with long follow-up times.

**Gamma rate/ Gamma distribution**

The gamma distribution is commonly used to model continuous variables that are constrained to be positive. The gamma distribution is defined by two parameters, the shape parameter and scale parameter. The gamma distribution is also very flexible in that it can have a variety of shapes based on the different values for the parameters.

\[ \gamma = \frac{\alpha}{\beta} \]

\( \gamma \) – gamma rate

\( \alpha \) – shape parameter

\( \beta \) – scale parameter

The term conjugate refers to the situation in which the prior and posterior distributions are the same. In the Poisson-Gamma conjugate model the prior is a Gamma distribution, and the posterior is a Gamma distribution. The likelihood or the data are represented as a Poisson distribution. The posterior gamma distribution is obtained by multiplying the Poisson rate (the likelihood from the data) and the uninformative prior distribution. The formula for the posterior probability from a Poisson-Gamma conjugate model is:
Posterior rate ($\gamma$) = $\alpha + X / \beta + N$

**Diminishing importance of conjugate models**

The use of conjugate models to provide analytic solutions to Bayesian statistical problems was particularly important because the models could be expressed and analyzed without the need for simulation. Due to increased computing speed, conjugate models are decreasing in importance. The increase in computational speed is also contributing to increased use of Bayesian statistics, because simulation allows for analysis of complex statistical models.

**Simulation analysis of statistical models**

Simulation is used to solve complex statistical problems when the problems are intractable. An intractable problem is one that cannot easily be solved analytically using mathematics. The solution may not have a closed form or may have a closed form solution that requires infeasible amounts of computing power. In Bayesian analyses, simulation is used to sample from the posterior probability distribution in order to make new inferences about a hypothesis.

**Simplified simulation example**

A simplified example can be used to illustrate simulation and sampling from the posterior distribution. The following formula specifies a model in which the parameter $C$ is a function of $A$ and $B$.

$$C = A + B$$

The formula is mathematically tractable and given $A$ and $B$ it is trivial to calculate the value $C$. For example, if $A = 1$ and $B = 2$ then $C = 3$. However if $A$ and $B$ were expressed as probability distributions rather than as point estimates, simulation could be used to generate a probability distribution for $C$. Consider $A$ as defined by a normal distribution with a mean of 1 and a standard deviation of 0.5. Consider $B$ as defined by a normal distribution with a mean of 2 and a standard deviation of 0.25. This information can be expressed in the following way:
A \sim \text{norm}(1,0.52)

B \sim \text{norm}(2,0.252)

The simple model above can be re-written in the following way,

\[ C_s = A_s + B_s \]

where the subscript \( s \) connotes that the value is sampled. To solve the problem using simulation, we would sample a value from the distribution for \( A \), sample a value from the distribution for \( B \), add the sample values together and then repeat the process. If a large number of samples are taken, these can be considered a discrete probability distribution for \( C \). From the resulting probability distribution for \( C \), one can indicate the most likely value of \( C \). (As the number of samples approaches infinity, the most likely value will approach 3.) Using the probability distribution for \( C \) provides flexibility to make many other useful statements about the value \( C \). One can indicate the probability that \( C \) is larger than a given value, such as 4, or the probability that \( C \) lies between two values, such as 1 and 3. We have sampled from the distribution of \( C \) by defining the relationship between \( C \) and other variables (the model) and specifying distributions for the other variables. In this manner samples are taken from the posterior distribution of \( C \).

In Bayesian statistics models are used to express relationships among variables expressed as probability distributions and then solved using simulation. Bayesian software can use simulation to generate a posterior distribution for parameters of interest and sample from the posterior distribution.

**Markov Chain Monte Carlo Simulation (MCMC) Techniques**

Markov Chain Monte Carlo Simulation is an algorithm that can be used to analyze Bayesian statistical models. Markov chain Monte Carlo techniques incorporate two key aspects: Markov processes (as denoted by the term Markov chain) and random walks (as denoted by the term...
Monte Carlo). A Markov process is a random process in which the future state of the process depends only on the current state of the process, and not on states of the process prior to the current state. In other words, to predict the future state of a Markov process, only information about the current state is needed. Information about previous states have no impact on the prediction of the future state. In MCMC techniques, random walks occur when a sample is taken from the posterior probability distribution based only on the previously sampled values. The probability associated with the next sampled parameter value depends only on the previously sampled value. During simulation, random walks converge on the posterior distribution for parameters in the model. Convergence indicates that the correct posterior distribution has been found.

Some difficulties in Markov Chain Monte Carlo methods have been specifying algorithms for random walks, computing power to make random walks feasible and ensuring that the simulation has converged on the correct posterior distribution. It may be difficult to ascertain whether or not a simulation has converged and convergence can only be demonstrated indirectly by showing that there is no evidence that the simulation has not converged.

11.3 Non-Bayesian approach to modeling natural history

*Maximum Likelihood Estimates*

Using the maximum likelihood method proposed by Yi et al, given data on stage distribution and time elapsed since infection, a system of equations can be solved to estimate stage specific state transition rates. This method has been used to estimate stage specific transition rates for progression to cirrhosis in chronic HCV infection.[59, 60] Although the approach to estimating state transition rates was innovative, the method has potential limitations related to its basis in frequentist statistics. Maximum likelihood estimation forms the basis of the frequentist approach to statistics. As noted above, the likelihood is an estimate of how likely one is to observe given data if a hypothesis is true. Maximum likelihood identifies the parameters for the underlying population that would have the highest probability of producing the observed data. P-values associated with maximum likelihood estimation indicate that if the null hypothesis were true (i.e. a fibrosis progression rate of 0) what is the probability that I would observe the data? Unlike the Bayesian framework, it does not indicate the probability that the estimated progression rate is
true. (P-values are often misinterpreted as indicating the probability that a null hypothesis is true.) Maximum likelihood estimates can lead to artificially narrow confidence intervals.[245]

11.4 Meta-analysis

A meta-analysis uses statistical methods to combine estimates from several different studies to produce a single summary estimate.[246] Meta-analysis is most commonly used to combine treatment effect estimates obtained from randomized clinical trials of an intervention. Meta-analysis can also be used to estimate a summary treatment effect for observational studies [247] and to produce summary estimates of natural history parameters.[59, 248]

Homogeneity

Estimates from different studies are considered homogenous if the differences in the estimates are thought to arise only due to sampling error. Homogeneity occurs if participants in each study represent a sample from the same population. As a result, the estimate obtained from each study can be expected to differ due to sampling error. When studies are homogenous, the underlying assumption is that each study provides an estimate of the same underlying parameter.

Fixed effects meta-analysis

Fixed effect meta-analytic methods are used to combine estimates from homogenous studies. Fixed effects analyses combine studies weighting each study according to the inverse of the variance in the study estimate. The method gives a more sizeable weight to studies with a smaller variance, and less weight to studies with greater variance. The variance in the estimate is a function of the study sample size and the degree of scatter around the study’s mean estimate. Fixed effect meta-analytic methods are inadequate statistical methods if studies are not homogenous. Used in this context, fixed effects meta-analysis results in artificially narrow confidence intervals around the summary mean estimate.

Heterogeneity

Differences in effect estimates can arise due to more than just sampling error. Heterogeneity can result when study come from different populations. In other words, the participants in each study
cannot be considered a sample from the same population. When heterogeneity exists across studies, the interpretation is that the studies do not provide an estimate of the same underlying parameter, but estimate a slightly different parameter for each population represented. Random effects meta-analytic methods are used to combine estimates from heterogeneous studies. A statistical test for heterogeneity can be used to test the degree of variation in the study estimates under the null hypothesis that each study represents the same underlying population.[246]

**Random effects meta-analysis**

Random effects meta-analysis allows for the existence of heterogeneity. Pooling estimates using a random effects model allows for variation in the underlying effect for each study. In random effects meta-analysis, the variance of the summary estimate has two components: the random effects variance and the estimation variance. If the random effects variance is zero, then the estimate of variance is reduced to the variance that would be obtained with a fixed effects meta-analysis. As a result, performing random effects meta-analysis on studies that are homogenous will result in the same estimate as a fixed effect meta-analysis.

One approach to incorporating random effects analysis is to first perform a statistical test for heterogeneity, then if significant, perform a random effects meta-analysis. Others advocate for the use of random effects models, regardless of the results of tests for heterogeneity, as a form of caution. However, the possibility of type I error for tests of heterogeneity may be as high as 50%.[249] Assumptions of homogeneity may be unrealistic due to differences in study design and patient population, regardless of whether or not statistical tests for heterogeneity are significant.

**Meta-regression**

Meta-regression is a method of estimating the amount of excess variation in a summary estimate resulting from differences among studies.[250] Differences among studies can result from differences in study design or differences in patient characteristics. Meta-regression allows for explanation of how parameters of interest impact the summary estimate in a meta-analysis. Fixed effects meta-regression assumes that the variation among studies is known and explained by the parameters included in the regression model. In random effects meta-regression a random effects
term is included to account for the remaining unexplained variance in the summary estimate once parameters of interest have been accounted for using the regression model. In a manner that is analogous to fixed and random effects meta-analysis, random effects meta-regression is considered a more conservative approach.

**Ecological bias**

One limitation of meta-regression is the potential for ecological bias.[251] Ecological bias occurs when the relationship between the mean estimate of a parameter and the summary estimate does not reflect the relationship between the parameter at the individual level and the summary estimate. In other words, when an analysis is conducted using a mean estimate, it may not reflect the effect of the parameter at the individual level. Simulation studies suggest that the power associated with meta-regression using mean parameter estimates is lower than meta-analyses of individual level data. If meta-regression of mean study parameters indicates a significant relationship between a mean parameter and the outcome, then it is likely that the relationship is very strong. If meta-regression of mean study parameters does not indicate a significant relationship, this is insufficient evidence that no relationship exists.[252]

**11.5 Winbugs code**

**Poisson-Gamma conjugate analysis**

The following code was implemented in the Winbugs software in order to estimate the rate of progression to cirrhosis for each study. As noted above, the use of the Poisson-Gamma conjugate model takes advantage of the conjugate properties to estimate a Poisson rate and 95% CI for all studies, including studies in which no patients had cirrhosis.

```r
# N – study sample size
# TIME – mean duration of HCV infection
# FU – person-years of follow-up time
# X – number of patients with cirrhosis

GammaPoisson <- function(X,N, alpha, beta) {
```
\[
\begin{align*}
\text{alpha.prime} & \leftarrow \text{alpha} + X \\
\text{beta.prime} & \leftarrow \text{beta} + N \\
\text{c(posterior.mean}=(\text{alpha.prime/beta.prime}), \text{q0.025}=\text{qgamma}(0.025,\text{alpha.prime, beta.prime}), \\
\text{q0.975}=\text{qgamma}(0.975,\text{alpha.prime, beta.prime})) \\
\end{align*}
\]

\[
\}
\]

\[
\text{alpha}=0.1
\]

\[
\text{beta}=0.1
\]

---

\# the prior gamma rate is 1 (prior mean rate = alpha/beta = 0.1/0.1)

\# the likelihood expressed by the Poisson gamma rate is X/N

\# the posterior gamma rate is alpha + X / beta + N

---

\textit{Winbugs random effects meta-analytic model}

model

{ }

for( i in 1 : Num ) { 

\text{x[i] \sim dpois(lambda[i])} \# indicates that the rate from each study (x[i]) is modeled as a Poisson distribution; Poisson distributions are parameterized by lambda (also known as the Poisson rate)

---

\text{4 The prior gamma rate will be overwhelmed by the likelihood (the Poisson gamma rate) and the use of the Poisson gamma model results in essentially adding 0.1 to the numerator and denominator of the Poisson rate from each of the studies}
log(lambda[i]) <- alpha[i] + b[1]*(age[i]-mean(age[1:Num])) + b[2]*(male[i]-mean(male[1:Num])) + b[3]*(hiv[i]-mean(hiv[1:Num])) + b[4]*(alc[i]-mean(alc[1:Num])) + b[5]*(alt[i]-mean(alt[1:Num])) + b[6]*bias[i] + log(n[i])

# Formula for the meta-regression relating the log rate to the log rate estimate from each study (alpha[i]), the study variables (e.g. mean age, mean proportion male, etc.), and the log of the follow-up time (log(n[i])

v[i]<-log(lambda[i]) # formula for the variance within each of the studies which is equivalent to the log rate estimate (NB: it is a property of the Poisson distribution that the variance equals the log rate estimate)

p[i]<-1/v[i] # Formula for the precision – the inverse of the study variance. The inverse variance determines the contribution of the study estimate to the overall rate estimate. Studies with a larger variance have smaller weights

alpha[i]~dnorm(logr,taulogr) # Random effects specification indicating that each study estimate comes from a distribution of study estimates centered at logr (the overall rate estimate) and with a precision equal to taulogr (the precision is the inverse of the between study variance)

shrink[i]<- taulogr / (taulogr + p[i]) # the formula for shrinking each study estimate based on the inverse of the between study variance (taulogr) and the inverse of the within study variance (p[i])

}

logr~dnorm(0.0,0.0001) # prior distribution for logr

sigma~dunif(0,10) # prior distribution of the between study standard deviation

taulogr<-1/(sigma*sigma) # formula for the between study standard deviation

rate<-exp(logr) # formula for calculating the rate of progression to cirrhosis

newlogr~dnorm(logr,taulogr) # formula for sampling a new log rate from the overall distribution

newrate<-exp(newlogr) # formula for calculating a new rate sampled from the overall distribution
cirrprev<-1-exp(-rate*20)  # formula for the cirrhosis prevalence at 20 years

for (k in 1:6) {
    b[k]~dnorm(0.0,0.0001)  # prior distribution for each regression coefficient on the log scale
    rr[k] <- exp(b[k]*unit[k])  # formula for the relative risk for each regression coefficient
    prob[k] <- step(b[k])  # formula calculating the probability the regression coefficient exceeds 0 on the log scale (i.e. exceeds 1 on the relative risk scale)
}

12 Methods - Study 2

Study 2 employed regression analysis to assess the relationship between response to antiviral therapy and quality of life, controlling for age, sex and co-morbid illness. Quality of life was measured using the Hepatitis Quality of Life questionnaire (HQLQ), Health Utilities Index Mark II/III (HUI2/HUI3), the time trade-off utility and the SF-36 derived utility measure known as the SF-6D. The productivity of respondents was assessed using a series of questions about time missed from work, volunteering or leisure activities. The impact of co-morbid illness was assessed using the Charlson co-morbidity score and the Index of Co-existent Disease (ICED). The quality of life questionnaires, productivity questions and co-morbid illness questionnaires are contained in a booklet provided in the Appendix. It is important to note that co-morbid illness questionnaires also served as a data abstraction guide for reviewers who recorded information found in the medical records of patients. The methods employed in study 2 are discussed in more detail in the corresponding manuscript found in Chapter 5.

13 Methods - Study 3

Study 3 employed regression analysis to assess the relationship between substance use and adherence to antiviral therapy, and to assess the relationship between substance use and response
to antiviral therapy. The methods employed in study 2 are discussed in more detail in the corresponding manuscript (Chapter 6).
Chapter 4 Study 1 - Natural History

Natural history of hepatitis C infection acquired through injection drug use

14 Abstract

Background/Aims: Our aim was to estimate the rate of progression to cirrhosis for those infected with hepatitis C virus (HCV) through injection drug use.

Methods: We searched the published literature for articles assessing cirrhosis in this population and abstracted data on cirrhosis prevalence, mean duration of infection, mean age, mean alanine aminotransferase (ALT) enzyme levels, proportion male, proportion HIV co-infected, proportion consuming excessive alcohol and study setting. Summary progression rates were estimated using weighted averages and random effects Poisson meta-regression. The impact of co-variates was assessed by estimating the posterior probability that the relative risk (RR) of progression exceeded 1.0.

Results: A total of 47 published articles were identified. After adjusting for covariates, the estimated rate of progression to cirrhosis, in a subset of 44 studies representing 6457 patients, was 8.1 per 1000 person-years. (95% Credible Region (CR), 3.9 to 14.7) This corresponds to a 20-year cirrhosis prevalence of 14.8% (95% CR, 7.5 to 25.5). A 5% increase in the proportion of male participants and a 5% increase in the proportion consuming excessive alcohol were associated with faster progression. (Probability RR>1 = 0.97 and 0.92, respectively) A 5% increase in the proportion HIV co-infected, an increase in ALT of 5 IU/L and studies in settings with a high risk of referral bias were not associated with faster progression. (Probability RR>1 = 0.42, 0.65 and 0.43, respectively)

Conclusion: Analysis of aggregate level data suggests that for patients who contracted HCV through injection drug use prognosis is poor in populations with many male patients and high levels of alcohol consumption. Estimates are consistent across settings with different referral thresholds.
15 Introduction

Hepatitis C is a blood-borne viral illness responsible for significant morbidity and mortality throughout the world. Seroprevalence data indicate that approximately 3.2 million persons are chronically infected in the United States.[16] The screening of the blood supply has virtually eliminated blood products as a source of infection. International estimates of the incidence of HCV among IDUs range from 11 to 42 per 100 person years.[21-23, 240] The prevalence of HCV infection among injection drug users (IDUs) has been shown to be as high as 88%.[253]

Chronic infection with HCV can result in end-stage liver disease such as cirrhosis, liver failure and/or hepatocellular carcinoma (HCC).[254, 255] Many studies demonstrate that treatment of active or recent drug users with antiviral therapies can be successful, especially in the context of addiction therapy.[256, 257] However, very few active or recent drug users receive treatment with antiviral therapies.[258, 259] Due to the large clinical and economic burden associated with end-stage liver disease, and the disproportionate burden of disease in injection drug users, information on the natural history of chronic HCV infection acquired through injection drug use is important for individual counseling and health care policy.

The rate of progression to cirrhosis is perhaps the most important factor in HCV natural history. Cirrhosis is associated with a significant risk of liver failure and hepatocellular carcinoma. Individuals with a history of injection drug use may have a high prevalence of co-infection with HIV and a high prevalence of alcohol abuse. It is important to understand the impact of these characteristics on the natural history of HCV infection and understand the interactions among risk factors that may be unique to this population. We estimated the rate of progression to cirrhosis and the impact of risk factors for patients who acquired HCV infection through injection drug use, using a systematic review of the literature and meta-analysis of relevant studies. The association between risk factors and fibrosis progression rates was assessed at the aggregate level, as we did not have access to individual patient level data. The resulting estimates are most useful for understanding the morbidity and mortality resulting from HCV infection for populations of patients. This information will be useful to clinicians and policy-makers considering ways to expand access to antiviral therapy and improve uptake of antiviral therapy for patients who acquired infection through injection drug use. Patient-level associations
between risk factors and fibrosis progression rates suggested by the analysis should be interpreted with caution.

16 Methods

Literature Search

Medline and Embase literature databases were searched from January 1990 to March 2009, using the following search terms: natural history, hepatitis C, substance abuse and/or human immunodeficiency virus (HIV). (Table 4.5) Our search strategy was developed to identify articles addressing hepatitis C and HIV co-infected patients in addition to HCV mono-infected patients because a significant proportion of co-infected patients acquire infection through injection drug use. Abstracts were reviewed to determine whether or not the article provided information on liver disease for patients likely infected through injection drug use. The files of another researcher involved in the systematic review of hepatitis C natural history were cross-referenced.

Inclusion/Exclusion criteria

The following inclusion criteria were applied to retrieved articles: i) ≥ 90% of study patients (or a sub-group within the study) reported injection drug use as a risk factor for acquiring HCV infection; ii) the article reported on the duration of HCV infection; iii) the number or proportion of patients with cirrhosis was reported; and iv) the study included at least 20 patients with chronic HCV infection. Studies were excluded if it was not clear that study participants had confirmed HCV viremia. Qualitative or quantitative HCV RNA tests were taken as evidence of HCV viremia. In the absence of HCV RNA tests, an author statement that study patients were chronically infected with HCV was accepted as evidence that HCV viremia had been confirmed.

Outcome Assessment

We defined our primary outcome measure as cirrhosis of the liver determined by liver biopsy, imaging techniques or serum markers. Clinical decompensation (ascites, variceal bleeding or hepatic encephalopathy) was also taken as evidence of cirrhosis. When authors reported only the proportion with cirrhosis the number was calculated by multiplying the proportion by the sample
size. When available, multiple publications providing data on the same population were accessed to supplement data in the original article.

Observation Time and HCV infection

The total observation time was calculated from each study by multiplying the mean estimated duration of infection by the meta-analysis sample size to obtain the total person-years of follow-up time. In some studies, the mean duration of HCV infection was reported only by sub-group. To calculate the duration of infection for the entire group, a weighted average was employed based on the size of the reported sub-group and the duration of HCV infection for the sub-group.

Study Design

Study design was characterized based on the timing of study participation compared to the timing of HCV infection. Ideally, the rate of progression to cirrhosis would be assessed using prospective cohort studies in which infected patients are identified at the time of infection and followed up over a time period sufficient to observe liver cirrhosis. However, given the silent nature of HCV infection, true cohort studies are uncommon. One study identified a cohort of individuals with acute HCV infection using a retrospective review of hospital records, and was thus classified as a retrospective cohort study. [24] Studies in which the date of infection was ascertained through patient reported risk factors or review of medical records were considered retrospective non-cohort studies.

Study setting and referral bias

Previous studies have shown that bias can be introduced into progression rate estimates if patients are more likely to be referred at later stages of liver disease.[243] Referral bias explains why studies conducted in tertiary care settings estimate higher rates of progression to cirrhosis than studies in community-based settings.[95] We categorized potential referral bias for each study setting. Studies set in specialist clinics including hepatology, gastroenterology and infectious disease clinics were considered to be high risk for referral bias. Community-based studies, studies set in prison, inpatient or outpatient addiction therapy were considered to be low risk for referral bias. We also assessed whether or not studies conducted in a clinical setting had
different estimates compared to non-clinical settings (community-based studies, studies set in prison).

Analysis

**Progression Rate to Cirrhosis**

The rate of progression to cirrhosis was estimated as a Poisson rate and the number with cirrhosis divided by the total person-years of follow-up. The 95% confidence interval for the rate estimate was calculated using the Poisson-Gamma conjugate model with uninformative priors.[260] Use of this model is equivalent to adding a small quantity of 0.1 to both the numerator and denominator of the Poisson rate to appropriately handle studies reporting that no patients had cirrhosis.

**Meta-Analysis**

A meta-analysis was performed to calculate a single overall estimate of the rate of progression to cirrhosis. A weighted average of the Poisson rates was obtained by first taking the natural logarithm of the rate in each study and then weighting each log-transformed rate by the inverse variance. The weighted average was then transformed back to the original scale through exponentiation. The overall estimate was calculated using both a random and fixed effects model.[261] Meta-analyses were also performed on sub-groups defined by country, year of publication grouped into eras, referral bias, clinical versus non-clinical setting, study design, country, and cirrhosis criteria. The 20-year prevalence of cirrhosis was calculated assuming a cumulative distribution of the exponential survival model.[262]

**Meta-regression**

Meta-regression was performed using a random effects model which conservatively assumed that each study provided a progression rate estimate for a slightly different population. Adjustments were made for mean age, mean proportion male, mean proportion with excessive alcohol consumption, mean ALT levels, mean proportion co-infected with HIV and referral bias. Missing data for means and proportions were imputed using multiple imputation. We originally intended to include studies using non-biopsy methods to diagnose cirrhosis in the meta-
regression. Only a small number of studies diagnosed cirrhosis without biopsy data (n=3). The small numbers and emerging evidence about the poor predictive validity for diagnosing cirrhosis in the absence of biopsy data [263], prompted us to exclude these studies from the meta-regression. Study design was not adjusted for in the meta-regression due to almost complete homogeneity among the included studies. Study setting was not adjusted for because of the small number of non-clinical studies (n=3).

Poisson meta-regression was analyzed using a Bayesian framework. Bayesian statistics uses probabilities to make inferences and makes use of new evidence to update prior information.[244] In this analysis, no prior information about the rate of progression to cirrhosis was assumed, and thus uninformative prior distributions were incorporated. As a result, the data from the 44 studies provided the posterior (or updated) probabilities. The use of Bayesian inference results in a probability distribution for each parameter of interest. In this analysis, posterior probability distributions were generated for the rate of progression to cirrhosis, the 20-year prevalence of cirrhosis and the relative risk of progression for each of the study co-variates.

**Software**

Analyses were implemented using the R statistical package.[264] Meta-regression was performed using the BRugs package within R and Winbugs software release 2.2.0 (1996-2004).[265, 266] Markov Chain Monte Carlo techniques with Gibbs sampling were employed.[267] Markov Chains were initiated with three different sets of values and employed 20,000 iterations each. The convergence of the model was assessed using Brooks-Gelman-Rubin plots.[268]

**17 Results**

The literature search identified 6,679 English and French abstracts. Abstract review identified 764 potentially relevant articles and 47 articles met the inclusion criteria. The mean age of individuals in the 47 studies was 36, with the majority being male. The mean proportion co-infected with HIV across all studies was 50%; 10 studies had no HIV co-infected patients, 15 studies focused on HIV co-infected patients and 9 studies did not report on the number with HIV co-infection. The mean proportion consuming excessive alcohol was 31% and several different definitions of excessive consumption were employed. The most common definitions were
consumption of more than 30g per day (3 studies), 40g per day (6 studies), 50 g per day (10 studies), 80g per day (2 studies) and self-reported abuse/dependence (4 studies). A total of 14 studies did not assess alcohol consumption. France, Spain, Australia and the United States accounted for almost 75% of the studies and only 25% of the studies were conducted in a setting with a low risk of referral bias. (Table 4.1) Most studies estimated the date of HCV infection retrospectively using patient reported year of first injection drug use. In the only cohort study, the date of infection was established through testing of stored sera from patients admitted to an infectious disease hospital with acute hepatitis.[241]

A plot of the unadjusted rate of progression to cirrhosis for each of the 47 studies is presented in Figure 4.1. Study characteristics and the unadjusted progression rate for each study are reported in Table 4.2. Most studies (68%) estimate a rate of progression to cirrhosis below 11.2 per 1000 person years, which corresponds with a cirrhosis prevalence of less than 20% after 20 years of infection. Random effects meta-analysis produced a rate estimate of 9.5 per 1000 person-years for all 47 studies corresponding to a 20-year cirrhosis prevalence of 17.3%.(Table 4.3) The rate estimate from the retrospective cohort study was lower than the 95% confidence interval for the rate estimate obtained from the other 46 studies. Studies in which none of the participants were biopsied (n=3), were associated with higher estimates for the rate of progression to cirrhosis than studies in which a proportion underwent a biopsy. Studies in a non-clinical setting had lower estimated rates than studies in clinical settings. Mean age was highly correlated with mean age of infection and thus was not included in the meta-regression.

Using random effects Poisson meta-regression to adjust for all co-variates the rate of progression to cirrhosis was estimated at 8.1 per 1000 person-years (95% credible interval, 3.9 – 14.7). (Table 4.4) The meta-regression was performed on 44 studies, representing 6,457 patients. The rate estimate pertains to a population with mean age of 36, 75% male, 31% alcoholic, mean ALT level of 109 IU/L, 50% co-infected with HIV (corresponding to the mean overall characteristics of the included studies) in a study setting with low risk of referral bias. Based on this rate estimate, the 20-year prevalence of cirrhosis is 14.8% (95% credible interval, 7.5% - 25.5%). Initiating the Markov chain with different values did not change the baseline result. Brooks-Gelman-Rubin plots demonstrated convergence of the model. (Data not shown) Faster progression was associated with an increase in the proportion of male individuals and an increase in the proportion with excessive alcohol consumption but not with a greater proportion co-
infected with HIV. The probabilities that the relative risk exceeded 1 were 0.97, 0.92 and 0.42 respectively.

18 Discussion

Our study demonstrates that the rate of progression to cirrhosis for individuals who acquired HCV infection through injection drug use is approximately 8.1 per 1000 person years, corresponding to a 20-year cirrhosis prevalence of 14.8%. The key factors associated with an increased rate of progression were the proportion male and proportion with excessive alcohol consumption. Our study found no evidence that studies with a higher proportion of HIV co-infected patients were associated with higher rates of progression. Studies in settings thought to have a high referral threshold were associated with similar rate estimates as studies with a low referral threshold.

A previous, very comprehensive meta-analysis conducted on patients with a variety of etiologies for HCV infection estimated the 20-year cirrhosis prevalence to range from 7% to 18%.[59] The fact that our baseline estimate (14.8%) falls within this interval is consistent with the hypothesis that prognosis does not depend on source of infection.[61] Our unadjusted analysis confirms previous findings that non-clinical settings are associated with significantly lower estimates of cirrhosis prevalence at 20 years than non-clinical settings.[59, 95] Due to the small number of non-clinical studies, we were unable to assess whether this association remains after adjusting for other covariates.

Our results are broadly consonant with previous studies, but there are some important differences. A number of studies have reported higher progression rates in tertiary care settings likely as a result of referral bias.[59, 95] We were not able to confirm this association between setting and prognosis in HCV infected injection drug users. The reason for this is unclear. Many injection drug users are co-infected with HIV and may seek care at tertiary care infectious disease centers. Thus the referral bias, which leads only more severely affected mono-infected patients to seek care, may be attenuated among the co-infected. Contrary to other studies which included patients with HCV infection of all etiologies, we found no association between HIV and cirrhosis progression.[78] Analysis of summary data such as means and proportions can lead to ecological bias, in which the relationship between summary level values and the rate of progression to cirrhosis do not reflect the relationship between individual level values and the
rate of progression to cirrhosis.[251, 252] Using our results to inform policy at aggregate levels is the most conservative approach and any relationship between individual level covariates and rates of progression to fibrosis should be interpreted with caution.[269]

Our study has several limitations. We did not have enough data to estimate stage specific progression rates. Previous studies indicate that fibrosis progression rates increase with advanced fibrosis stage.[59, 60] However, a more recent study of co-infected patients found no evidence of increasing progression rates, suggesting that assuming constant progression rates may not result in biased estimates.[78] In the vast majority of studies included in this meta-analysis, the date of infection was imputed based on patient reported year of first injection drug use, which can overestimate or underestimate the duration of infection.[242] We were unable to adjust for several factors that may influence fibrosis progression rates including genotype, HCV viral load, HBV co-infection, steatosis, CD4 counts and age at infection.

This is the first meta-analysis we are aware of to specifically address natural history in patients acquiring HCV through injection drug use. The analysis provides an estimate of the cirrhosis burden in current and former substance abusers based on population characteristics. While aggregate data pose limitations for covariate analyses, estimates obtained from aggregate data are appropriate for policy-making tools such as cost-effectiveness analysis and population health planning. Our analysis demonstrates that a significant proportion of injection drug users will develop cirrhosis in 20 years, lending urgency to considerations about increasing the availability and uptake of antiviral therapy in this patient group.
# 19 Tables – Study 1

### Table 4.1: Study and patient characteristics (Study 1 – Natural History)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Mean</th>
<th>No. of Studies Missing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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</tr>
<tr>
<td>Proportion male</td>
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<td>0</td>
</tr>
<tr>
<td>Proportion HIV infected</td>
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<td>9</td>
</tr>
<tr>
<td>Proportion with excessive alcohol consumption*</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>ALT levels (IU/L)</td>
<td>109</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
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<td></td>
</tr>
<tr>
<td>Australia</td>
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<td>11</td>
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<tr>
<td>Austria</td>
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<td>2</td>
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<tr>
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<td>2</td>
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<td>Germany</td>
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<td>Italy</td>
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<td>2</td>
</tr>
<tr>
<td>Spain</td>
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<td>17</td>
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<tr>
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<td>2</td>
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<tr>
<td>United States</td>
<td>6</td>
<td>13</td>
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<tr>
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<td>2</td>
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<td>15</td>
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<tr>
<td><em>High risk of referral bias</em></td>
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<td></td>
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<td>Hepatology/Gastroenterology</td>
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<td>30</td>
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<td>HIV/AIDS</td>
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<td>Multiple specialist clinics</td>
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<td>Percent</td>
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<td>--------</td>
<td>---------</td>
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<td>2007-2009</td>
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<td>23</td>
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<td><strong>Cirrhosis criteria</strong></td>
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<td>44</td>
<td>94</td>
</tr>
<tr>
<td>Cirrhosis criteria - None biopsied</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

ALT - alanine aminotransferase enzyme
HIV - human immunodeficiency virus
AIDS - acquired immunodeficiency syndrome

*Studies defined excessive alcohol consumption differently; > 30 g per day (3 studies), > 40 g per day (6 studies), > 50 g per day (10 studies), > 60 g per day (1 study), > 80 g per day (2 studies), self-reported abuse/dependence (4 studies) and other definitions (7 studies). Alcohol consumption was not assessed in 14 studies.
Table 4.2: Unadjusted rate of progression to cirrhosis (Study 1 – Natural History)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample size</th>
<th>Mean age</th>
<th>Mean duration of HCV infection (years)</th>
<th>Follow-up time (person-years)</th>
<th>No. with cirrhosis</th>
<th>Rate of progression to cirrhosis per 1000 person-years**</th>
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</thead>
<tbody>
<tr>
<td>1 Ballesteros, 2004 [270]</td>
<td>21</td>
<td>37</td>
<td>17.5</td>
<td>368</td>
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<td>0.3</td>
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<tr>
<td>2 Benhamou, 1999 [68]</td>
<td>122</td>
<td>35.6</td>
<td>13.5</td>
<td>1647</td>
<td>13</td>
<td>8</td>
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<tr>
<td>3 Benhamou, 2001 [271]</td>
<td>63</td>
<td>37.7</td>
<td>16.6</td>
<td>1047</td>
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<td>3.9</td>
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<td>21.3</td>
<td>4281</td>
<td>23.5*</td>
<td>5.5</td>
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<tr>
<td>5 Boldorini, 1997 [273]</td>
<td>24</td>
<td>27</td>
<td>6.5</td>
<td>156</td>
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<td>7 Cournot, 2004 [275]</td>
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<td>31.9</td>
<td>11.4</td>
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<td>8 Di Martino, 2001 [276]</td>
<td>160</td>
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<td>10.4</td>
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<tr>
<td>15 Grabczewska, 2006 [282]</td>
<td>35</td>
<td>NA</td>
<td>9</td>
<td>315</td>
<td>0</td>
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<td>16 Guadagnino, 2007 [283]</td>
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<td>17 Hallinan, 2007 [284]</td>
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<td>follow-up time (person-years)</td>
<td>no. with cirrhosis</td>
<td>rate of progression to cirrhosis per 1000 person-years**</td>
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<td>11.9</td>
<td>2499</td>
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<td>14</td>
<td>1050</td>
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<td>25</td>
<td>1275</td>
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<td>7.9</td>
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<td>Roudot-Thoraval, 1997 [302]</td>
<td>889</td>
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<td>7112</td>
<td>51.6*</td>
<td>7.3</td>
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<td>Mean duration of HCV infection (years)</td>
<td>Follow-up time (person-years)</td>
<td>No. with cirrhosis</td>
<td>Rate of progression to cirrhosis per 1000 person-years**</td>
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<td>39 Serfaty, 2001 [304]</td>
<td>76</td>
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<td>14</td>
<td>1064</td>
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<td>40 Soto, 1997 [305]</td>
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<td>882</td>
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<tr>
<td>41 Sylvestre, 2005 [306]</td>
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<td>43 Tong, 1996 [307]</td>
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<td>46</td>
<td>18.1</td>
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<tr>
<td>44 Trimoulet, 2002 [308]</td>
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<td>13.9</td>
<td>403</td>
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<td>2.7</td>
</tr>
<tr>
<td>45 Tural, 2003 [309]</td>
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<td>16.2</td>
<td>2041</td>
<td>7</td>
<td>3.5</td>
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<tr>
<td>46 Vergara, 2007 [310]</td>
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<td>1856</td>
<td>19</td>
<td>10.3</td>
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<td>47 Wilkinson, 2009 [160]</td>
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<td>43.8</td>
<td>16.3</td>
<td>978</td>
<td>16</td>
<td>16.5</td>
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</table>

* No. with cirrhosis calculated by multiplying the proportion with cirrhosis by the sample size

** Calculated using the Poisson-Gamma conjugate model. [260]
Table 4.3: Random effects meta-analyses of the rate of progression to cirrhosis (Study 1 – Natural History)

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>Rate of Progression to Cirrhosis per 1000 person-years (95% Confidence Interval)a</th>
<th>20-year cirrhosis prevalenceb</th>
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<tbody>
<tr>
<td>All Studies</td>
<td>47</td>
<td>9.5 (7.6,11.9)</td>
<td>17.3% (14.2%,21.2%)</td>
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<tr>
<td>Referral bias</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lower referral bias</td>
<td>12</td>
<td>10.9 (5.9,20)</td>
<td>19.6% (11.2%,33%)</td>
</tr>
<tr>
<td>Higher referral bias</td>
<td>35</td>
<td>9.1 (7.3,11.4)</td>
<td>16.7% (13.6%,20.4%)</td>
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<tr>
<td>Setting</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-clinical</td>
<td>3</td>
<td>5.7 (2.3, 14.2)</td>
<td>10.8% (4.5%,24.7%)</td>
</tr>
<tr>
<td>Clinical</td>
<td>47</td>
<td>10.0 (8.1, 12.3)</td>
<td>18.1% (15.0%,21.9%)</td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective Cohortc</td>
<td>1</td>
<td>5.6 (2.3,10.3)</td>
<td>10.5% (4.4%,18.7%)</td>
</tr>
<tr>
<td>Retrospective Non-Cohort</td>
<td>46</td>
<td>9.6 (7.7,12.1)</td>
<td>17.5% (14.3%,21.4%)</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of studies</td>
<td>Rate of Progression to Cirrhosis per 1000 person-years (95% Confidence Interval)(^a)</td>
<td>20-year cirrhosis prevalence(^b)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>France</td>
<td>15</td>
<td>10 (7.1,13.9)</td>
<td>18.1% (13.3%,24.3%)</td>
</tr>
<tr>
<td>United States</td>
<td>6</td>
<td>9.6 (4.4,20.8)</td>
<td>17.5% (8.5%,34%)</td>
</tr>
<tr>
<td>Spain</td>
<td>8</td>
<td>8.8 (6.1,12.6)</td>
<td>16.1% (11.5%,22.2%)</td>
</tr>
<tr>
<td>Australia</td>
<td>5</td>
<td>7.4 (3.1,17.7)</td>
<td>13.7% (6%,29.8%)</td>
</tr>
<tr>
<td>Germany</td>
<td>4</td>
<td>14.1 (7,28.5)</td>
<td>24.6% (13.1%,43.5%)</td>
</tr>
<tr>
<td>Italy</td>
<td>3</td>
<td>7.3 (3.7,14.4)</td>
<td>13.6% (7.1%,25.1%)</td>
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<tr>
<td>Era</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996-1999</td>
<td>10</td>
<td>13.8 (9.5,19.8)</td>
<td>24% (17.4%,32.8%)</td>
</tr>
<tr>
<td>2000-2002</td>
<td>13</td>
<td>7 (3.8,12.8)</td>
<td>13% (7.3%,22.6%)</td>
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<tr>
<td>2003-2006</td>
<td>13</td>
<td>8.4 (6.4,11)</td>
<td>15.5% (12%,19.7%)</td>
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<tr>
<td>2007-2009</td>
<td>11</td>
<td>12 (8.2,17.6)</td>
<td>21.3% (15.1%,29.6%)</td>
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<tr>
<td>Criteria for cirrhosis</td>
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<tr>
<td>A proportion biopsied</td>
<td>44</td>
<td>9.1 (7.2,11.3)</td>
<td>16.6% (13.5%,20.3%)</td>
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<tr>
<td>None biopsied</td>
<td>3</td>
<td>19.8 (10.2,38.6)</td>
<td>32.7% (18.4%,53.7%)</td>
</tr>
</tbody>
</table>
a Rates were transformed to the log scale, meta-analysis performed [261], and then converted back to the original scale using exponentiation.

b 20-year cirrhosis prevalence is calculated using the cumulative distribution of the exponential survival model [262]

c 95% Confidence intervals were calculated using the Poisson-Gamma conjugate model [260]
**Table 4.4**: Results of the Poisson Meta-Regression adjusted for all co-variates (Study 1 – Natural History)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% Credible Region</th>
<th>Probability Relative Risk &gt;1</th>
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</thead>
<tbody>
<tr>
<td>Rate per 1000 person-years†</td>
<td>8.1</td>
<td>3.9, 14.7</td>
<td>NA</td>
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<tr>
<td>20 yr % cirrhosis</td>
<td>14.8%</td>
<td>7.5%, 25.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Relative risk of a 5-year increase in mean age</td>
<td>1.06</td>
<td>0.83, 1.33</td>
<td>0.66</td>
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<tr>
<td>Relative risk of a 5% increase in proportion male</td>
<td>1.2</td>
<td>1.00, 1.43</td>
<td>0.97</td>
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<tr>
<td>Relative risk of a 5% increase in proportion co-infected with HIV</td>
<td>1.00</td>
<td>0.96, 1.03</td>
<td>0.42</td>
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<tr>
<td>Relative risk of a 5% increase in proportion alcoholic</td>
<td>1.05</td>
<td>0.98, 1.13</td>
<td>0.92</td>
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<tr>
<td>Relative risk of a 5 IU/L increase in mean ALT</td>
<td>1.01</td>
<td>0.96, 1.06</td>
<td>0.65</td>
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<tr>
<td>Relative risk for settings with high referral bias compared to low referral bias</td>
<td>1.01</td>
<td>0.43, 1.98</td>
<td>0.43</td>
</tr>
</tbody>
</table>
†Rate for mean age (36 years), 75% male, 31% alcoholic, mean ALT level (109 IU/L), 50% co-infected with HIV in a setting with low referral bias

ALT - alanine aminotransferase enzyme levels

NA - not applicable
Table 4.5: Literature search terms used for electronic databases (Study 1 – Natural History)

<table>
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<th>Search Categories</th>
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<td><strong>Medline</strong></td>
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<tr>
<td><strong>Hepatitis C</strong></td>
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<td>Index Terms</td>
<td>hepatitis c</td>
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<tr>
<td>Text Words</td>
<td>hepatitis c; HCV</td>
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<tr>
<td><strong>Natural History</strong></td>
<td>cohort studies; case-control studies; prognosis; disease progression; morbidity; mortality; survival analysis; drug therapy; liver cirrhosis; fibrosis</td>
</tr>
<tr>
<td><strong>Substance Abuse</strong></td>
<td>disease-free survival; medical: futile; treatment outcome; treatment failure; disease adj1 progress; fatal outcome; hospital mortality; natural history; natural adj2 (history or progression); disease duration; etiology; biopsy; interferon; ribavirin; drug therapy; cirrhosis; fibrosis</td>
</tr>
<tr>
<td>Index Terms</td>
<td>substance abuse; needle sharing; methadone</td>
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<tr>
<td>Text Words</td>
<td>drug use; intravenous; injection drug; IVDU; IDU; substance abuse; injection adj2 drug</td>
</tr>
<tr>
<td>HIV</td>
<td>Index Terms</td>
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</table>
20 Figure – Study 1

Figure 4.1: Unadjusted rates of progression to cirrhosis and summary estimates (Study 1 – Natural History)

Error bars represent the 95% confidence interval for the unadjusted progression rate calculated using the Poisson-Gamma conjugate model [260]

For summary estimates, rates were transformed to the log scale, meta-analysis performed [261], and then converted back to the original scale using exponentiation.
Random Effects Summary

Fixed Effect Summary

Progression rate per 1000 person–years

Individual Estimates and Summary

Tong, 1996
McGuinness, 1996
Novick, 1997
Roudot-Thoraval, 1997
Soto, 1997
Boldorini, 1997
Goeser, 1997
Khan, 1998
Pol, 1998
Gordon, 1998
Benhamou, 1999
Thomas, 2000
Ballesteros, 2004
Rey, 2004
Tural, 2003
Buft−Janvresse, 2003
Schaefer, 2003
Trimoulet, 2002
Goisset, 2002
Kramer, 2002
Puoli, 2001
Landau, 2001
Benhamou, 2001
Serfaty, 2001
Octapowicz, 2001
Di Martino, 2001
Romeo, 2000
Rodger, 2000
Thomas, 2000
Benhamou, 1998
Gordon, 1998
Pol, 1998
Khan, 1998
Goeser, 1997
Blondin, 1997
Soto, 1997
Roudot-Thoraval, 1997
Novick, 1997
McGuinness, 1996
Tong, 1996

89
Chapter 5 Study 2 - Quality of Life Following Antiviral Therapy

Sustained responders have better quality of life and productivity compared to treatment failures long after antiviral therapy for hepatitis C

21 Abstract

Introduction: We sought to compare the health status of patients with a sustained response to anti-viral therapy for HCV infection to that of treatment failures, using health related quality of life and preference (utility) measures.

Methods: Sustained responders had undetectable HCV viral levels six months following antiviral therapy. After antiviral therapy participants completed by mail or interview, the Hepatitis-specific Medical Outcomes Survey Short-Form-36 (SF-36), Health Utilities Index Mark 2/3 (HUI2/3), and time-tradeoff (TTO) for current health. Respondents provided information on demographics, substance abuse history, co-morbidities and health history. Detailed clinical information was obtained by chart review. Respondents also indicated whether or not they missed work, volunteer, or household activities during the last 3 months due to hepatitis C or its treatment.

Results: A total of 235 patients (133 responders and 102 treatment failures) completed questionnaires an average of 3.7 years after the end of treatment. Treatment failures had significantly lower scores on the eight SF-36 domains (p<0.01), lower scores on the hepatitis specific domains (p<0.0001) and lower physical (42.5 versus 49.2) and mental (40.5 versus 46.1) component summary scores (p<0.01). HUI3 (0.57 versus 0.70), HUI2 (0.74 versus 0.80), SF-6D (0.65 versus 0.71) and TTO (0.84 versus 0.89) were lower for treatment failures (p<0.05). The regression-adjusted difference in HUI3, SF-6D, PCS and MCS scores was 0.08 (p=0.04), 0.05 (p=0.004), 5.22 (p=0.001) and 5.73 (p<0.0001), respectively. Differences in the HUI2 and TTO scores were not significant after adjustment for demographic and clinical variables. Treatment failures were more likely to have missed work, volunteering or household activities during the last 3 months due to hepatitis C or its treatment (44% versus 9%, p<0.001).

Conclusions: Patients with a sustained response to antiviral therapy for chronic HCV infection have better quality of life than treatment failures. Our study validates the benefits associated with
sustained response to antiviral therapy in a real-world clinic population and demonstrates that these benefits are maintained over the long-term.

Keywords: hepatitis C, quality of life, utility, productivity, antiviral therapy

22 Introduction

Chronic infection with hepatitis C virus (HCV) can result in cirrhosis, liver failure and hepatocellular carcinoma. Individuals with chronic HCV infection also have impairments in quality of life, even in the absence of liver disease. HCV viremia is associated with fatigue [202], impaired cognition [198, 199], stigmatization [210-212], emotional distress [311] and depression.[205, 206] However, the extent that HCV viremia itself contributes to lower health related quality of life is unclear given the high burden of psychiatric and medical co-morbidities in patients with chronic HCV infection.[194, 210] Data collected alongside randomized controlled clinical trials, demonstrates a significant improvement in quality of life immediately following sustained response to therapy.[126, 127] However patients enrolled in clinical trials represent highly selected populations and it is not clear whether or not these results are generalizable. Our study focused on a clinic population and assessed whether or not differences in quality of life between sustained responders and treatment failures persist over the long-term. Using regression analysis to adjust for other factors related to quality of life we addressed whether or not differences were attributable to clearance of HCV viremia. Differences in levels of fatigue and productivity between sustained responders and treatment failures were also assessed.

The majority of studies measure quality of life using psychometric instruments such as the Medical Outcomes Study Short Form 36 (SF-36). While psychometric measures describe the health status of individuals with chronic HCV infection, they do not provide information on what value either the individual or society places on the health status. Nor do they provide a single, summary measure of global health status. Utility measures place quality of life on a scale from 0 to 1 that indicates the strength of preference for a health state and provides a single measure of global health status. Utility measures are also essential inputs into cost-effectiveness analyses, as they are used to weight life expectancy in estimating quality-adjusted life expectancy gains associated with new treatments. Such analyses can inform health care policy on treatment of chronic HCV infection, weighing potential health gains against the costs of treatment.
23 Methods

This analysis is part of a larger study examining the quality of life and economic burden of HCV in a community-dwelling population.[312] The study design included cross-sectional administration of questionnaires along with retrospective review of medical records. A convenience sample of patients with chronic HCV infection was recruited between January 1, 2006 and March 1, 2008 through five health care settings in the metropolitan area of Vancouver, British Columbia, including the BC Hepatitis Program at Vancouver General Hospital, the Solid Organ Transplant Clinic at Vancouver General Hospital, the BC Transplant Society Pre-Liver Transplant Assessment Clinic, the Liver and Intestinal Research Centre and the Gilwest Clinic at Richmond General Hospital. Recruitment occurred via advertisements posted in the clinics, personal referrals and letters from clinicians. Participants had the choice to complete questionnaires by mail (self-administered), by phone (interviewer administered) or in person at the clinic (self-administered or interviewer administered).

Individuals were included in the current analysis if they had a prior diagnosis of chronic HCV infection based on a history of positive HCV RNA and had received previous HCV antiviral therapy. Patients were treated with contemporary conventional therapies, including interferon alpha 2b, alone or in combination with ribavirin, pegylated interferon alpha 2b in combination with ribavirin, (Intron A, Rebetron and Pegentron, Schering Plough, Kenilworth, NJ), interferon alpha 2a and peginterferon alpha 2a, alone or in combination with ribavirin (Roferon A, Pegasys and Copegus, Hoffman La Roche, Switzerland). Response status was classified in the following manner. Sustained responders were defined as those with undetectable HCV viral levels 24 weeks following antiviral therapy. HCV RNA assays were performed at the virology laboratory of the BC Centre for Disease Control, Vancouver, British Columbia (Cobas Amplicor HCV Test V2.0, limit of detection 50 IU/ml , Roche Diagnostic Systems, Mississauga, Ontario, Canada). Treatment failures were defined as those with detectable HCV viremia following antiviral therapy or those with an end of treatment response who relapsed. Individuals were excluded from the study if they were enrolled in a clinical drug trial, had limited English proficiency or limited cognitive status as measured by a score of less than 21 on the Telephone Interview for Cognitive Status [313, 314] or had advanced liver disease at the time of questionnaire completion (decompensated cirrhosis, hepatocellular carcinoma, liver transplant). Patients with advanced disease were excluded from this analysis based on research demonstrating that health
status and quality of life are substantially lower in these patients when compared to other patients with chronic HCV infection.[189]

Data collection

Participants provided information on ethnicity, marital status, education level and monthly income from all sources including employment, retirement and social assistance (disability, employment insurance, family bonus, child tax or native health benefits). Participants answered questions about their medical history including co-morbidities, physical impairments, risk factors for HCV infection, current and past substance use. History of problematic substance abuse was determined by asking participants if they had ever injected or snorted drugs regularly for 4 weeks. A history of dependency on alcohol was determined by asking participants if they had ever become dependent on alcohol. A history of mental health problems was determined by self-report of ever having sought clinical help, been hospitalized or treated with prescription medicine for depression, anxiety or mood disorders. Participants were also asked if they currently injected or snorted drugs.

Medical records of participants who consented to chart review were accessed at the clinics in which patients received care for HCV. Pathology records (liver biopsy results), blood tests (HCV Ab, HCV RNA, ALT), imaging reports and clinic notes were abstracted and used to classify disease stage at the time of questionnaire completion. Medical records were reviewed by a trained research assistant knowledgeable in the field of HCV infection.

Co-morbidity scores

The Charlson co-morbidity score is a weighted index of the number of co-morbid diseases, commonly used to adjust for co-morbidity in studies of hospitalization, mortality and resource use.[315] The Index of Coexistent Disease (ICED), another co-morbidity index, has two subscales measuring severity of disease and physical impairment level, which are condensed into a single composite index with four levels ranging from 0 (no co-morbidities and no physical impairment) to 3 (severe co-morbidities and severe physical impairment).[316] The Charlson score and the ICED were calculated using information from both the medical record and the patient questionnaires. For example, congestive heart failure was considered a co-morbid
condition if the patient reported a history of a single episode of congestive heart failure or physician notes indicated a history of congestive heart failure. Some index items were removed from the scores based on the rationale that they were the primary condition being considered rather than a co-morbid condition (liver disease), or because they may be affected by HCV viremia (items related to mental health status).

Quality of life measures

The Medical Outcomes Study Short Form 36 Version 2 (SF-36 V2) measures health related quality of life in 8 domains (physical functioning, role physical, bodily pain, general health perception, energy/vitality, social functioning, role emotional and mental health) along with a physical summary score (PCS) and mental summary score (MCS). Each of the 8 domains and the summary scores are scored out of 100, with higher scores indicating better quality of life.[317] The Hepatitis Quality of Life questionnaire (HQLQ) is a version of the SF-36 developed to better capture aspects of quality of life affected by hepatitis infection. The HQLQ has four additional domains (also scored from 0 to 100) represented by 15 additional questionnaire items, measuring generic health distress, positive well-being, and hepatitis specific limitations and hepatitis-specific health distress.[171, 172]

The Health Utilities Index Mark II/III (HUI2/HUI3) is a preference-based utility instrument that measures health status (symptoms and functional status) using a 15-item questionnaire.[177] The HUI3 classifies individuals into levels of functioning on 8 attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. The HUI2 classifies individuals using 7 attributes: sensation, mobility, cognition, self-care, emotion, pain and fertility. Using preference weights obtained from members of the general public, an overall utility score is calculated. HUI2 scores range from -0.03 to 1 and HUI3 scores from -0.36 to 1.00. Higher scores indicate better quality of life and negative scores represent states considered worse than death.

The SF-6D is a preference-based utility instrument that classifies respondents into 6 dimensions of health (physical functioning, role limitation, social functioning, bodily pain, mental health and vitality), using 11 items from the SF-36 questionnaire. Using preference weights obtained from members of the general public in the United Kingdom, a utility weight ranging from 0.3 to 1 is calculated, with higher scores indicating better quality of life.[185, 187]
The time trade-off (TTO) is a preference-based direct utility measure in which an individual’s own preference for a health state is revealed by the individual’s willingness to live a shorter but healthier life.[174] The questionnaire prompted respondents to imagine that they have a 20 year life expectancy, and to indicate on a scale of 0 to 20, the number of years of perfect health that are equivalent to 20 years of life in their current health state. A utility score from 0 to 1 was calculated by dividing the number of years of perfect health by 20. Higher scores indicate better quality of life.

Productivity measures

Participants were asked whether or not they missed work, were unable to do volunteer work, household chores or participate in leisure activities during the past 3 months because of hepatitis C or its treatment. Participants also indicated the amount of time for each category in hours or days. Participants were asked whether or not they had difficulty working and provided an estimate of the percent reduction in working capacity. Estimates of lost productivity given in days were translated to lost hours by multiplying by 7. Participants were also asked whether or not they experienced symptoms of fatigue during the past 4 weeks.

Statistical Analyses

Descriptive statistics were used to characterize the patients, including means and standard deviations for continuous variables and proportions for categorical variables. We compared continuous variables between responders and treatment failures using the independent samples student t-test. We compared categorical variables using Pearson’s chi-squared test and Fisher’s exact test where expected cell counts were less than 5. Quality of life measures were compared to normative population data, adjusting for age and sex. The HUI3 norms were taken from the 3,505 Canadian respondents of the Joint Canada/United States Survey of Health.[318] The SF-36 norms were taken from a survey of 9423 randomly selected Canadians.[319] Normative data for the SF-6D were taken from the National Health Measurement Survey, a survey of 3844 non-institutionalized adults living in the United States.[320]

A multivariable linear regression analysis was performed to adjust for factors identified a priori as potential confounders of the relationship between response status and quality of life. Factors
included age, sex, ethnicity, marital status, education level, Charlson co-morbidity and ICED score. Employment status and income were not included in the regression analysis based on the rationale that they may partially mediate the effect of HCV viremia on quality of life. Variables thought to be in the causal pathway between the independent and dependent variable should not be adjusted for in regression analyses due to the potential for over fitting.

The primary quality of life outcome for the linear regression analysis was the HUI3. Regressions using the HUI2, SF6-D, MCS, PCS and TTO as outcomes were performed in secondary analyses. Regression analyses were also repeated with a log transformation and logit transformation of the dependent variable to assess the robustness of results. All analyses were performed using R, version 2.3.0. [264]

Ethics

The research protocol was approved by the University of British Columbia and the University Health Network research ethics boards. Participants provided written informed consent.

24 Results

Of a total of 657 participants in the overall study of HCV in a community-dwelling population, 321 had undergone antiviral therapy at the time of completing the questionnaires. Of these 87 were excluded because they had advanced liver disease at the time of questionnaire completion - 63 had decompensated cirrhosis, 7 had hepatocellular carcinoma and 16 had received a liver transplant. A total of 235 respondents met the inclusion criteria for the analysis; 102 treatment failures and 133 responders. At the time of questionnaire completion, the average time that had elapsed since the end of antiviral therapy for sustained responders and treatment failures was 3.9 years and 3.5 years, respectively. Treatment failures were more likely to be male, infected (or previously infected) with genotype 1, 4 or 6 and had significantly higher levels of alanine amino transferase (ALT) enzyme recorded in the most recent laboratory test report. The number of patients with a biopsy was 155 (66%). 5 of the treatment failures and 6 of the sustained responders had compensated cirrhosis at the time of questionnaire completion. Only 3 patients were infected with HIV (2 treatment failures and one sustained responder). The distribution of Charlson co-morbidity score and ICED scores did not differ between treatment failures and responders. Sustained responders and treatment failures also had similar proportions with a
history of injection drug use, history of dependence on alcohol and history of mental health problems. (Table 5.1) Four respondents indicated active substance abuse (3 responders and 1 treatment failure).

Treatment failures and sustained responders had similar levels of total monthly income, with some variation in source of income. (Table 5.2) Treatment failures were significantly less likely to be employed (51% versus 67%), and a greater proportion of treatment failures received income from social assistance (36% versus 26%) but this difference did not reach statistical significance (p=0.1). Treatment failures had lower productivity at work, volunteering and household activities. (Table 5.2) Treatment failures were significantly more likely to have missed work, volunteering or chores due to hepatitis C or its treatment in the 3 months prior to completing the questionnaires (44 % versus 9%) and significantly more likely to have experienced difficulty working (22% versus 11%). Among those who missed either work, volunteering or chores due to hepatitis C or its treatment the mean number of hours missed was 154 for sustained responders and 177 for treatment failures. Treatment failures who had difficulty with work and leisure, reported a significantly greater percent reduction in work and leisure capacity than sustained responders that reported difficulty with work and leisure. (Table 5.2) The proportion of sustained responders who reported experiencing any fatigue during the 4 weeks prior to completing the questionnaire was 69% compared to 81% of treatment failures (p=0.05).

Treatment failures had lower scores on each domain of the SF-36 (including generic and disease specific domains) and lower scores on all utility measures when compared to sustained responders. (Table 5.3) All of the differences between sustained responders and treatment failures were statistically significant with the exception of the positive well-being scale (p=0.06). Treatment failures had significantly lower quality of life and utility scores than population norms. Sustained responders had similar bodily pain and physical component summary scores when compared to population norms but scored significantly lower on all other measures.

After adjustment for age, sex, ethnicity, marital status, education, Charlson and ICED scores using multivariable linear regression, sustained responders had significantly higher HUI3, SF-6D, PCS and MCS scores than treatment failures. When income and employment were added to the linear regression model, the differences between sustained responders and treatment failures
were no longer significant for the HUI3, but remained significant for the SF-6D, PCS and MCS scores. Performing log and logit transformations of the dependent variables produced results that were qualitatively similar. (Data not shown)

25 Discussion

Our study demonstrates that sustained responders to antiviral therapy for chronic HCV infection have significantly better quality of life than treatment failures, as measured both by psychometric and utility measures. The observed differences remain significant after adjustment for factors known to be associated with quality of life - age, sex, ethnicity, marital status, co-morbidity and the severity of physical impairments - for the HUI3 (our primary outcome), SF-6D, PCS and MCS, but not the HUI2 and TTO, suggesting that viral factors contribute to quality of life independent of host factors. Our results demonstrate that sustained response to antiviral therapy is also associated with improved productivity and increased employment rates. The key implication of this work is that the quality of life improvement shown in randomized clinical trials translates to a real-world clinic population, and quality of life improvements are maintained long after the 24 week follow-up of the clinical trials.[126, 127, 321]

In a study of Swiss clinic patients, significant differences were observed between sustained responders to therapy and treatment failures in the physical component summary score of the SF-36.[213] Multivariable regression analysis indicated that total household income rather than viral factors were significantly associated with quality of life. Adjustment for co-morbid illnesses in this study was not as extensive as our study – diabetes was the only co-morbid illness adjusted for - and this may explain the divergent results. Also, adjusting for income may have attenuated the association between HCV viremia and quality of life if sustained responders had higher income. A systematic review of the literature in which SF-36 data were translated into utilities estimated that the benefit associated with sustained response to antiviral therapy for chronic HCV infection was 0.03 – 0.04 units.[196] A randomized controlled trial involving 69 patients undergoing antiviral therapy obtained longitudinal measures of utility using the European Quality of Life 5 dimension (EQ-5D) instrument.[322] Following therapy sustained responders (n=24) had larger change scores than treatment failures (n=45) (0.02 versus 0), but likely due to small sample size the difference was not statistically significant.
The results of our study related to work and productivity are corroborated by other studies. Research demonstrates that individuals with chronic HCV infection perceive a decrease in functioning in aspects of daily life such as work, household functioning, sexual functioning and leisure.[207, 208] In a longitudinal study conducted alongside a randomized clinical trial, twenty-percent of sustained responders showed an improvement in the need to work shorter hours and the proportion of missed work days compared to treatment failures.[209]

Our study has several limitations. Awareness of viremia status has been associated with decreased quality of life.[211] Although we did not have data on the respondents’ awareness, 93% of responders completed questionnaires more than 90 days after the assessment of sustained response to antiviral therapy and 98% of treatment failures completed questionnaires 90 days after the end of therapy. The vast majority of patients were likely aware of their HCV viremia status. Although sustained responders had higher quality of life scores than treatment failures, we cannot rule out the possibility that quality of life prior to antiviral therapy was higher in this group, since quality of life measures were obtained at a single time point. However, although our quality of life measure is cross-sectional, the timing of the measurement is relevant and informative. Our cohort of more than 200 patients was assessed an average of 3.7 years following antiviral therapy indicating that the short-term benefit of successful therapy demonstrated in clinical trials is maintained over the long-term. Respondents provided information on productivity for the previous 90 days and it is unclear whether or not improvement in work productivity applies to the entire follow-up period.

Although treatment with antiviral therapy can result in viral clearance for more than 50% of patients, uptake of antiviral therapy among HCV infected patients is low.[323, 324] In our population, sustained responders to antiviral therapy had improved quality of life, higher employment rates, and better productivity at work, leisure, household activities and volunteering than treatment failures. These benefits should be considered by patients and providers as they make decisions about antiviral therapy. The results should also inform health care policy makers’ decision making about strategies to reduce the morbidity and economic impact of HCV infection.
## 26 Tables – Study 2

**Table 5.1** Demographic and Clinical Variables (Study 2 – Quality of Life Following Antiviral Therapy)

<table>
<thead>
<tr>
<th></th>
<th>Treatment failures (N=103)</th>
<th>Sustained Responders (N=133)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean, sd)</td>
<td>n 9</td>
<td>n 10</td>
<td>0.44</td>
</tr>
<tr>
<td>Male</td>
<td>69 68</td>
<td>62 47</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Married/Common-Law</td>
<td>60 59</td>
<td>74 56</td>
<td>0.72</td>
</tr>
<tr>
<td>White ethnicity</td>
<td>87 86</td>
<td>108 82</td>
<td>0.56</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attended high school</td>
<td>15 15</td>
<td>14 11</td>
<td></td>
</tr>
<tr>
<td>Completed high school</td>
<td>19 19</td>
<td>24 18</td>
<td></td>
</tr>
<tr>
<td>Attended college, university or trade school</td>
<td>32 31</td>
<td>33 25</td>
<td></td>
</tr>
<tr>
<td>Completed trade school/apprenticeship</td>
<td>13 13</td>
<td>16 12</td>
<td></td>
</tr>
<tr>
<td>Completed college or university</td>
<td>23 23</td>
<td>45 34</td>
<td>0.37</td>
</tr>
<tr>
<td>History of injection drug use</td>
<td>56 55</td>
<td>72 55</td>
<td>0.95</td>
</tr>
<tr>
<td>History of dependence on alcohol</td>
<td>33 37</td>
<td>33 31</td>
<td>0.51</td>
</tr>
<tr>
<td>History of mental health problems</td>
<td>63 62</td>
<td>76 58</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>Treatment failures (N=103)</td>
<td>Sustained Responders (N=133)</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------------</td>
<td>------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| Time since end of therapy (years)    | 3.5                         | 3                            | 3.9 2 0.34  
|                                      |                             |                              |  
| Infected (or previously infected)    | 69 77                       |                              | 60 53 p<0.0001  
| with genotype 1 or 4                |                             |                              |  
| Alanine aminotransferase level       | 86.8 67                     |                              | 35.5 42 p<0.0001  
| (ALT) (mean, sd)                    |                             |                              |  
| Liver biopsy                         | 71 70                       |                              | 84 63 0.37  
<p>| | | |
|                                      |                             |                              |<br />
| Fibrosis score 0                    | 2                           |                              | 1               |<br />
|                                      |                             |                              |<br />
| 1                                    | 11                          |                              | 15              |<br />
|                                      |                             |                              |<br />
| 2                                    | 36                          |                              | 45              |<br />
|                                      |                             |                              |<br />
| 3                                    | 17                          |                              | 17              |<br />
|                                      |                             |                              |<br />
| 4                                    | 5                           |                              | 6               |<br />
| Index of Coexistent Disease (ICED)   | 24 24                       |                              | 26 20 0.1      |<br />
| score                                |                             |                              |<br />
| 0                                    | 16                          |                              | 16              |<br />
|                                      |                             |                              |<br />
| 1                                    | 21                          |                              | 21              |<br />
|                                      |                             |                              |<br />
| 2                                    | 40                          |                              | 45 34 0.1      |</p>
<table>
<thead>
<tr>
<th>Charlson score Category</th>
<th>Treatment failures (N=103)</th>
<th>Sustained Responders (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>58</td>
<td>86</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>≥2</td>
<td>21</td>
<td>15</td>
</tr>
</tbody>
</table>

* The Index of Coexistent Disease (ICED) consists of two subscales: coexistent disease and physical impairment. The coexistent disease subscale identifies and scores the severity of the following conditions: ischemic heart disease cardiomyopathy, non-ischemic heart disease cardiomyopathy, primary arrhythmias and conduction problems, congestive heart failure, hypertension, cerebral vascular accident, peripheral vascular disease, diabetes mellitus, respiratory problems, malignancies/neoplasm/cancer, hepatobiliary disease, renal disease, arthritis, gastrointestinal disease and infectious disease. It classifies severity into five levels (0 - 4): 0 - absence of coexistent disease, 1 – a comorbid condition which is asymptomatic or mildly symptomatic, 2 - a mild to moderate condition that is generally symptomatic and requires medical intervention, 3 - an uncontrolled condition which causes moderate to severe disease manifestations during medical care, and 4 – an uncontrolled condition which causes severe manifestations during medical care. The physical impairment subscale assesses functional impairment in the following categories: circulation, respiration, neurological, mental status, urinary, fecal, feeding, ambulation, transfer, vision, hearing and speech. There are 3 levels of
impairment (0 – 2), where 0 indicates no significant impairment/normal function, 1 indicates mild or moderate impairment, and 2 indicates serious/severe impairment. The ICED score is based on the highest disease severity level and the highest physical impairment level. Scores range from 0 to 3, where 0 is absence of co-existent disease and no significant impairment, and 3 is serious/severe physical impairment combined with any level of disease severity. As noted in the methods section, the ICED score was modified for our study by assigning a weight of zero to hepatobiliary disease (coexistent disease subscale) and to mental status (physical impairment subscale).

** The Charlson score assigns the following weights for each condition that a patient has: 1 for myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes; 2 for hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia, lymphoma; 3 for moderate or severe liver disease; 6 for metastatic solid tumor or acquired immunodeficiency syndrome. Diabetes with end organ damage, metastatic solid tumor, and moderate or severe renal disease override diabetes, any tumor, and mild liver disease, respectively. Thus only the higher weight is assigned. The sum of the weights equals the score. As noted in the methods section, liver disease was not counted as a comorbidity and was assigned a weight of zero for this analysis.
Table 5.2: Work and productivity variables (Study 2 – Quality of Life Following Antiviral Therapy)

<table>
<thead>
<tr>
<th>Monthly income from all sources (mean, sd)</th>
<th>Treatment failures (N=103)</th>
<th>Sustained Responders (N=133)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Monthly income from all sources (mean, sd)</td>
<td>2470</td>
<td>3174</td>
<td>6583</td>
</tr>
<tr>
<td>Monthly income category</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$0</td>
<td>14</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Less than $1000</td>
<td>18</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>$1000 - $1999</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>$2000 - $3999</td>
<td>25</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>$4000 - $5999</td>
<td>18</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>$6000 or more</td>
<td>7</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Employed</td>
<td>52</td>
<td>51</td>
<td>89</td>
</tr>
<tr>
<td>Receiving social assistance income</td>
<td>37</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Treatment failures (N=103)</td>
<td>Sustained Responders (N=133)</td>
<td>p</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>----------------------------</td>
<td>-------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Due to Hepatitis C or treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missed Work</td>
<td>14</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Missed Volunteering</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Missed Chores</td>
<td>32</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>Missed Work, Volunteering and/or Chores</td>
<td>45</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Total hours of missed Work, Volunteering and/or Chores in the previous 3 months (mean, sd)</td>
<td>154</td>
<td>200</td>
<td>177</td>
</tr>
<tr>
<td>Difficulty working</td>
<td>15</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Difficulty with leisure</td>
<td>22</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Percent reduction in work capacity (mean, sd)</td>
<td>5.8</td>
<td>18</td>
<td>1.1</td>
</tr>
<tr>
<td>Percent reduction in leisure capacity (mean, sd)</td>
<td>10.7</td>
<td>24</td>
<td>3.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>82</td>
<td>81</td>
<td>90</td>
</tr>
</tbody>
</table>
Table 5.3: Comparison of mean quality of life scores among treatment failures, sustained responders and age and sex adjusted population norms (Study 2 – Quality of Life Following Antiviral Therapy)

<table>
<thead>
<tr>
<th>SF-36 Scalesa</th>
<th>Treatment failures</th>
<th>Sustained Responders</th>
<th>Population Norms*</th>
<th>p-value for the comparison between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>SF-36 Scalesa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>68</td>
<td>29.1</td>
<td>80.7</td>
<td>22.7</td>
</tr>
<tr>
<td>Role Physical</td>
<td>58.3</td>
<td>34.9</td>
<td>75.6</td>
<td>28</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>56.9</td>
<td>27.4</td>
<td>72</td>
<td>25.8</td>
</tr>
<tr>
<td>General Health</td>
<td>45.5</td>
<td>26.9</td>
<td>64.7</td>
<td>24.5</td>
</tr>
<tr>
<td>Vitality</td>
<td>42.3</td>
<td>24.8</td>
<td>55</td>
<td>22.7</td>
</tr>
<tr>
<td>Social functioning</td>
<td>60.5</td>
<td>30.4</td>
<td>74.4</td>
<td>26.2</td>
</tr>
<tr>
<td>Role emotional</td>
<td>63.6</td>
<td>31.6</td>
<td>77.5</td>
<td>26.2</td>
</tr>
<tr>
<td>Mental health</td>
<td>62.3</td>
<td>21.6</td>
<td>71.6</td>
<td>19.7</td>
</tr>
<tr>
<td>Physical component summary score</td>
<td>42.5</td>
<td>11.6</td>
<td>49.2</td>
<td>9.9</td>
</tr>
<tr>
<td>Mental component summary score</td>
<td>40.5</td>
<td>13</td>
<td>46.1</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>Treatment failures</td>
<td>Sustained Responders</td>
<td>Population Norms*</td>
<td>p-value for the comparison between groups</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional general scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic health distress</td>
<td>57.6</td>
<td>30.6</td>
<td>75.8</td>
<td>25.4</td>
</tr>
<tr>
<td>Positive well being</td>
<td>55.1</td>
<td>25.9</td>
<td>61.2</td>
<td>22.7</td>
</tr>
<tr>
<td>Hepatitis specific scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis-specific Limitations</td>
<td>61.3</td>
<td>34.4</td>
<td>85</td>
<td>25.3</td>
</tr>
<tr>
<td>Hepatitis-specific Health Distress</td>
<td>59.3</td>
<td>34</td>
<td>82.8</td>
<td>24.8</td>
</tr>
<tr>
<td>Utilitiesb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Utilities Index 3</td>
<td>0.58</td>
<td>0.34</td>
<td>0.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Health Utilities Index 2</td>
<td>0.74</td>
<td>0.2</td>
<td>0.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Short Form 6D</td>
<td>0.65</td>
<td>0.14</td>
<td>0.71</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Treatment failures</td>
<td>Sustained Responders</td>
<td>Population Norms*</td>
<td>p-value for the comparison between groups</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>TF versus SR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TF versus norms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR versus norms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time trade-off</td>
<td>0.84</td>
<td>0.24</td>
<td>0.89</td>
<td>0.18</td>
</tr>
</tbody>
</table>

a The Medical Outcomes Study Short Form 36 Version 2 (SF-36 V2) measures health related quality of life in 8 domains (physical functioning, role physical, bodily pain, general health perception, energy/vitality, social functioning, role emotional and mental health) along with a physical summary score (PCS) and mental summary score (MCS). Each of the 8 domains and the summary scores are scored out of 100, with higher scores indicating better quality of life.[317] The additional domains of the Hepatitis Quality of Life questionnaire (HQLQ) - generic health distress, positive well-being, hepatitis specific limitations and hepatitis-specific health distress – are also scored from 0 to 100 with higher scores indicating better quality of life.[171, 172]

b The Health Utilities Index Mark III (HUI3) scores can range from -0.36 to 1.00. The Health Utilities Index Mark II (HUI2) scores can range from -0.03 to 1.00. Higher scores indicate better quality of life and negative scores represent states considered worse than death. [177] The Short Form 6D utility scores can range from 0.3 to 1.[187] and the time trade-off (TTO) utility scores can range from 0 to 1. Higher scores indicate better quality of life.

* Canadian norms for the SF-36 were taken from Hopman et al. [319], Canadian norms for the HUI3 were taken from the Joint Canada/United States Survey of Health [318], Normative data for the SF-6D were taken from the National Health Measurement Survey [320]

TF indicates Treatment Failures, SR indicates Sustained Responder
Table 5.4: Results from regression models (Study 2 – Quality of Life Following Antiviral Therapy)

<table>
<thead>
<tr>
<th></th>
<th>HUI3 B*</th>
<th>95% CI</th>
<th>HUI2 B*</th>
<th>95% CI</th>
<th>SF6D B*</th>
<th>95% CI</th>
<th>TTO B*</th>
<th>95% CI</th>
<th>PCS B*</th>
<th>95% CI</th>
<th>MCS B*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR</td>
<td>0.08</td>
<td>(0.01, 0.15)</td>
<td>0.03</td>
<td>(-0.01, 0.07)</td>
<td>0.05</td>
<td>(0.02, 0.08)</td>
<td>0.05</td>
<td>(-0.01, 0.11)</td>
<td>5.73</td>
<td>(3.24, 8.22)</td>
<td>5.22</td>
<td>(2.07, 8.37)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0008</td>
<td>(0.002, 0.002)</td>
<td>0.002</td>
<td>(-0.01, 0.01)</td>
<td>-0.004</td>
<td>(-0.01, 0.005)</td>
<td>-0.01</td>
<td>(-0.03, 0.002)</td>
<td>-1.18</td>
<td>(-1.82, -0.54)</td>
<td>0.71</td>
<td>(-0.1, 1.53)</td>
</tr>
<tr>
<td>Male sex</td>
<td>-0.05</td>
<td>(-0.12, 0.02)</td>
<td>-0.04</td>
<td>(-0.09, 0)</td>
<td>-0.003</td>
<td>(-0.04, 0.03)</td>
<td>0.01</td>
<td>(-0.05, 0.07)</td>
<td>0.76</td>
<td>(-1.71, 3.23)</td>
<td>0.23</td>
<td>(-2.9, 3.36)</td>
</tr>
<tr>
<td>White ethnicity</td>
<td>-0.05</td>
<td>(-0.15, 0.04)</td>
<td>-0.04</td>
<td>(-0.1, 0.01)</td>
<td>-0.003</td>
<td>(-0.05, 0.04)</td>
<td>0.03</td>
<td>(-0.04, 0.11)</td>
<td>0.47</td>
<td>(-2.82, 3.75)</td>
<td>-0.77</td>
<td>(-4.93, 3.4)</td>
</tr>
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<td>Marital status</td>
<td>0.07</td>
<td>(-0.002, 0.14)</td>
<td>0.04</td>
<td>(0.008, 0)</td>
<td>0.04</td>
<td>(0.01, 0.07)</td>
<td>0.02</td>
<td>(-0.04, 0.07)</td>
<td>0.51</td>
<td>(-1.93, 2.94)</td>
<td>6.04</td>
<td>(2.95, 9.13)</td>
</tr>
<tr>
<td>Education</td>
<td>-0.04</td>
<td>(-0.12, 0.04)</td>
<td>-0.01</td>
<td>(-0.06, 0.03)</td>
<td>0.01</td>
<td>(-0.03, 0.04)</td>
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<td>(-0.07, 0.05)</td>
<td>-0.55</td>
<td>(-3.17, 2.08)</td>
<td>-0.29</td>
<td>(-3.62, 3.04)</td>
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<tr>
<td>Charlson Score</td>
<td>1</td>
<td>-0.07</td>
<td>(-0.16, 0.02)</td>
<td>-0.04</td>
<td>(-0.1, 0.01)</td>
<td>-0.03</td>
<td>(-0.08, 0.01)</td>
<td>-0.04</td>
<td>(-0.12, 0.03)</td>
<td>-3.02</td>
<td>(-6.14, 0.1)</td>
<td>-2.58</td>
</tr>
<tr>
<td></td>
<td>≥ 2</td>
<td>-0.14</td>
<td>(-0.25, -0.03)</td>
<td>-0.09</td>
<td>(-0.15, -0.02)</td>
<td>-0.04</td>
<td>(-0.09, 0.01)</td>
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<tr>
<td>ICED Score</td>
<td>1</td>
<td>0.1</td>
<td>(-0.02, 0.22)</td>
<td>0.03</td>
<td>(-0.04, 0.1)</td>
<td>0.02</td>
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<td>0.06</td>
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<td>1.65</td>
<td>(-2.52, 5.82)</td>
<td>2.08</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-0.19</td>
<td>(-0.29, -0.08)</td>
<td>-0.11</td>
<td>(-0.18, -0.05)</td>
<td>-0.1</td>
<td>(-0.15, -0.05)</td>
<td>-0.04</td>
<td>(-0.13, 0.04)</td>
<td>-3.85</td>
<td>(-7.48, -0.22)</td>
<td>-9.2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-0.26</td>
<td>(-0.37, -0.16)</td>
<td>-0.15</td>
<td>(-0.22, -0.09)</td>
<td>-0.12</td>
<td>(-0.17, -0.07)</td>
<td>-0.03</td>
<td>(-0.11, 0.05)</td>
<td>-8.79</td>
<td>(-12.45, -5.12)</td>
<td>-8.01</td>
</tr>
</tbody>
</table>
*Unstandardized coefficient

1 Results are difference in utility per 5 years of age

2 Marital status is a binary variable with 0 = not married or common-law, 1 = married or common-law

3 Education is a binary variable with 0 = completed high school or less, 1 = started or completed trade/college/university

4 The reference category is Charlson Score = 0

5 The reference category is ICED Score = 0

SVR, Sustained virological response; HUI3, Health Utilities Index 3; HUI2, Health Utilities Index 2; PCS, Physical component summary score; MCS, Mental component summary score; SF6D, Short Form 6D; TTO, Time trade-off; ICED, Index of Co-existent Disease
Chapter 6 Study 3 – Treatment of hepatitis C for substance abusers

Treatment of hepatitis C infection for current or former substance abusers in a community setting

27 Abstract

Substance abusers account for the largest number of hepatitis C infected cases in developed countries but in North America are least likely to be treated with antiviral therapy. We describe a care model for treating current or former substance abusers with antiviral therapy for Hepatitis C virus (HCV) infection. The care model involved hepatitis nurses, a psychologist, infectious disease specialist and primary care physicians. Clients’ use of alcohol and illicit substances was monitored with urine toxicology screens. The association between substance use, rates of completion of therapy and rates of response were assessed using multivariable regression analyses. A total of 109 clients (75 with genotype 1/4 and 34 with genotype 2/3) received at least one injection with pegylated interferon between November 2002 and January 2006. Treatment completion rates of 61% and 74% were achieved for genotypes 1/4, and 2/3 respectively. Rates of treatment response in an intention to treat analysis were 51% for genotypes 1/4 and 68% for genotypes 2/3. Whereas positive urine toxicology screen indicating use of illicit substances in the six months prior to initiation of antiviral therapy was significantly associated with lower rates of treatment completion but not lower rates of sustained virological response. A positive urine screen indicating use of alcohol was significantly associated with lower rates of completion and lower rates of sustained virological response. Overall rates of completion and response are comparable to those demonstrated in non-substance abusing populations. Antiviral therapy for hepatitis C infection can be successful within the context of ongoing care for substance abuse.

Keywords: delivery of health care, hepatitis C, methadone maintenance, substance abuse, treatment outcome.

28 Introduction

Hepatitis C is a blood-borne viral illness responsible for significant morbidity and mortality worldwide. In developed countries, the screening of the blood supply has virtually eliminated blood products as a source of infection and the majority of new infections occur in injection drug
users (IDUs). International estimates of the incidence of HCV among IDUs range from 11 to 42 per 100 person years. Prevalence of HCV infection among IDUs ranges from 29-88%.

HCV infection can be cured with interferon-based antiviral therapies. However treatment uptake among HCV infected patients is low, and uptake among current or former substance abusers is even lower. Low treatment uptake may be due to a lack of readiness, judgment that this is a low priority compared to other health concerns, perception that the harms of treatment outweigh the benefits or perceived stigma and discrimination by clinicians. Clinicians are reluctant to treat patients with coexisting psychiatric comorbidity and on-going substance abuse and until recently, clinical practice guidelines recommended against treating patients on methadone maintenance. Substance abusers may also face referral barriers because of limited availability of specialists. Better ways of managing side effect profiles, evidence of lower rates of re-infection following viral clearance and calls to action based on ethical concerns have resulted in an increased interest in treating patients who are current or former substance abusers.

The Ontario Addiction Treatment Centres (OATC) operates a network of twenty-six community-based methadone maintenance treatment programs (MMTP) for treating opiate addiction, located primarily in medium-sized cities and suburban areas of Ontario, Canada. Since its inception in 1995, the OATC has treated an estimated 10,000 methadone clients and treats current or former substance abusers for HCV infection. The primary objectives of this paper are to describe the model of care HCV care at the OATC and to assess the rates of completion of therapy and rates of sustained virological response (SVR) to antiviral therapy. Our secondary objective is to determine whether substance abuse prior to therapy is associated with decreased rates of treatment completion or response to therapy.

29 Methods

The study design was a retrospective review of electronic and paper medical records of all HCV infected clients treated with antiviral therapy at the OATC clinics. The criterion for Inclusion was receipt of at least one injection with pegylated interferon prior to January 2006, to allow enough time to observe treatment outcomes. The primary outcomes were rates of completion of antiviral therapy and sustained virological response (SVR). Treatment completion was defined as
no discontinuation in therapy longer than two weeks, with 80% of medications taken over the prescribed duration of therapy. SVR was defined as undetectable HCV ribonucleic acid (RNA <50 IU/mL) by qualitative polymerase chain reaction (PCR) assay (Cobas Amplicor HCV Test, v2.0) 24 weeks after completing antiviral therapy. Outcomes and the reasons for discontinuation of therapy were ascertained based on clinical notes and laboratory test results in the medical records, and follow-up with nurses that were present at the OATC at the time of the chart review. Urinalysis data were taken from the electronic medical records. The study represents all clients initiated on antiviral therapy at the OATC between November 2002 and January 2006, as identified in an electronic database.

Methadone Maintenance Treatment at the OATC

Each OATC clinic was served by a primary care physician, some certified in addiction medicine, a nurse and an addiction counselor. Some clinics had access to the clinical psychiatrist or psychologist on staff at the OATC. Clients were referred for methadone maintenance treatment (MMT) by clinical practitioners or were self-referred. Clients generally received MMT exclusively from one clinic. At intake, clients underwent routine history and physical examination, including interviews regarding alcohol and substance abuse history. Clients were screened for infection with human immunodeficiency virus, and hepatitis A, B and C viruses. Once enrolled, clients were monitored with urine toxicology screens to detect ethyl alcohol, indicating ingestion of alcoholic beverages, opiates and opiate metabolites, cocaine and its metabolites. Urinalysis was performed using the iMDx™ Prep MMT-3 Assay by NOVX® Systems. Opiates other than methadone or its metabolites were considered illicit. Screening frequency ranged from twice weekly to once every 2 weeks depending on the level of stability achieved by the patient as demonstrated by consecutively negative urine screens. While abstinence was the goal of MMT, clients often continued to use illicit drugs, albeit at a greatly reduced rate. Therefore we characterize all clients as “current or former substance abusers”.

Historical context of HCV treatment at the OATC

The HCV treatment programme arose due to unmet need as approximately 50% of clients were infected with hepatitis C. Clients were unwilling to access care from hepatologists, who were located primarily in urban centres and geographically remote for many patients. Hepatologists
frequently recommended liver biopsy which many clients were unwilling to undergo. Clients also perceived that they were stigmatized as a result of having contracted HCV from injection drug use. As a result, a care model was developed that would allow patients to receive therapy at the local OATC clinic.

HCV therapy inclusion and exclusion criteria

Clinical criteria for antiviral therapy included chronic HCV infection based on a history of positive HCV RNA for at least 6 months and compensated liver disease. Patients were not treated if they had serum alanine aminotransferase (ALT) level > 10 times upper limit of normal, serum creatinine level > 1.5 times the upper limit of normal, neutrophil count < 1000/mm3, hemoglobin < 10 g/L in males and < 9 g/L in females, unstable or uncontrolled thyroid disease, treatment with pegylated interferon-α and/or ribavirin within the previous 12 months, presence or past history of clinically significant co-morbid diseases (cryoglobulinemic vasculitis, autoimmune hepatitis, alpha-1-anti-trypsin deficiency, genetic hemochromatosis, Wilson disease, drug- or toxin-induced liver disease, alcohol-related liver disease, primary biliary cirrhosis, sclerosing cholangitis, chronic hepatitis B infection, HIV infection, hematological malignancy, unstable or deteriorating cardiac, pulmonary, renal disease or poorly controlled diabetes mellitus) or concurrent therapy with immunosuppressive drugs or cytotoxic agents, such as prednisone, cyclosporine, azathioprine or chemotherapeutic agents. Patients with a previous psychiatric diagnosis were not excluded, but patients with an active psychiatric disorder were not treated at that time. Clients were referred to a psychologist or psychiatrist for pre-treatment assessment based on the judgment of the infectious disease specialist or family doctor. All fertile males and females were required to use effective contraception during treatment and 6 months after treatment.

In addition to clinical inclusion/exclusion criteria, clients were required to demonstrate stability and readiness to receive antiviral therapy. Regular attendance at clinic appointments for pre-treatment assessment was considered the primary indicator of readiness to undergo antiviral therapy. To demonstrate stability, patients were encouraged to have at least two months of negative urine screens. However, while drug abstinence was an important marker of stability, other markers such as stable housing, marital and employment status were also considered.
Care model and treatment protocol

Antiviral therapy was administered at the OATC clinics by an infectious disease specialist who supervised three nurses designated as regional hepatitis C programme coordinators and primary care physicians trained in hepatitis C treatment. Pre-treatment screening and assessment (medical history, physical examination, laboratory and diagnostic testing, and counseling) was performed by the nurses over a series of visits. Clients that were candidates for antiviral therapy, as judged by the nurse, were seen by the infectious disease specialist or clinic physician on staff at the OATC. The infectious disease specialist performed at least one consultation prior to initiating therapy and was ultimately responsible for the decision to start treatment. Nurse coordinators and the infectious disease specialist traveled to OATC clinic locations for meetings and consultations.

Patients were treated with pegylated-interferon alpha-2a (1,000 mg or 1,200 mg per day according to body weight) or pegylated-interferon alpha-2b (1.5 mcg/kg/week) in combination with ribavirin (800 - 1200 mg/day). Patients infected with genotype 1 and 4 were treated for up to 48 weeks and genotype 2 and 3 for up to 24 weeks (standard of care). Follow up visits with the nurse occurred bi-weekly through weeks 1 to 12 and monthly thereafter. Patients were seen every 4-6 weeks by the infectious disease specialist or primary care physician. When adverse events occurred, the infectious disease specialist performed a consultation and determined further options for therapy such as dose reduction, specialist referral, concurrent therapies such as erythropoietin or granulocyte colony stimulating factor, or discontinuation. In the event that the infectious disease specialist could not meet with the patient, a primary care physician conducted consultations. Patients on MMT continued to receive methadone and urine toxicology screens. Patients were encouraged to achieve complete drug abstinence, but positive urine screens did not result in the cessation of antiviral therapy if patients continued to adhere to treatment protocols.

Financing of MMT and HCV therapy

In Ontario, medical services (consultations and diagnostic tests) are covered by the Ontario Health Insurance Plan. Methadone financing is provided by the Ontario Drug Benefit (ODB) program for patients on social assistance, private health insurance plans or paid for directly by the client. For antiviral drugs, Section 8 access provides complete funding for clients on social
assistance. The Trillium programme provides complete or partial funding for clients not on social assistance who do not have sufficient private insurance coverage.

Analysis

Descriptive statistics were used to characterize the patients, and characterize our primary outcomes, the rates of completion of therapy and response to therapy. We assessed differences between continuous variables using the student t-test and differences between categorical variables using Pearson’s chi-squared test and Fisher’s exact test where expected cell counts were less than 5. We tested the association among substance use variables using chi-square tests. Univariate logistic regression analyses were performed with therapy completion and SVR as the outcomes.

Our secondary objective was to determine whether substance use prior to therapy was associated with completion of therapy or response to therapy. Multiple logistic regression analyses were performed to adjust for prognostic factors identified in previous studies. With completion of therapy as the outcome the factors chosen a priori included age, sex and genotype.[332-335] Models with SVR as the outcome included age, sex, genotype, viral load and therapy.[10, 332, 333, 336] In multivariable regression analyses, mean log viral load and mean ALT were imputed to patients with missing values. All p-values < .05 were considered statistically significant. All p-values < 0.05 were considered statistically significant. All analyses were performed using R, version 2.3.0.[264]

Ethics

The research protocol was approved by the University of Toronto Research Ethics Board as well as the University Health Network Research Ethics Board.

30 Results

A total of 109 patients received at least one injection with pegylated interferon alpha between November 2002 and January 2006. Although detailed data are not available, based on an estimated 4,000 clients during the time period and estimated rates of HCV prevalence of 50% among clients, this represents a small proportion (<6%) of all HCV infected clients. The majority
of the treated clients were male, with an average of 2 years attendance at an OATC clinic prior to initiating antiviral therapy. (Table 6.1) Demographic information recorded at the time of intake into the OATC demonstrated that the majority of clients were single (divorced, separated or widowed, 60%) and had completed high school (55%). Of the 86 clients for whom information was available on living arrangement at intake, the majority lived in a permanent apartment or house of their own (72%), and the rest stayed with family or friends (n=19), lived in a shelter or halfway house (n=4), with one client initiating MMT while transitioning from jail to the community. Most clients had a criminal history (71%) and a smaller proportion a history of incarceration (52%). Smoking was common (83%) and 39% reported a history of excessive alcohol consumption.

Only 61 patients had information in the medical records on the year or age of first injection. The estimated mean duration of infection based on this information was 15 years, with 21 patients having an estimated duration of longer than twenty years. Among the 75 patients reporting a psychiatric history, many had a history of both depression and anxiety. Other psychiatric disorders included bipolar disorder, personality disorder, post-traumatic stress disorder and social anxiety disorder. Eleven patients had previously been treated with antiviral therapies such as interferon alpha-2a and ribavirin. The most common abnormality reported for the 38 patients that underwent an abdominal ultrasound was evidence of fatty liver. None of the 7 patients who underwent a liver biopsy had evidence of cirrhosis or bridging fibrosis.

Treatment outcomes

The number of patients treated with Pegetron (Peginterferon Alfa-2b and Ribavirin, Schering-Plough Corporation) was 107 and 2 patients were treated with Pegasys and Copegus (pegylated interferon alpha-2a and ribavirin, Hoffman La Roche Inc.). Rates of completion of therapy, complete follow-up (returning for 6 month follow-up) and rates of SVR are reported separately for genotype 1 and 4 patients, and genotype 2 and 3 patients. (Table 6.2) In an intention to treat analysis where any patient lost to follow-up was assumed to be a non-responder, the rates of response to treatment were 51% for genotypes 1 and 4 and 68% for genotypes 2 and 3. Of the 38 who discontinued therapy, 16 were withdrawn from therapy for clinical reasons (insufficient response at 12 weeks, adverse events, laboratory abnormality), 15 for non-clinical reasons (non-adherence, substance abuse, refusal to continue therapy), and for 7 the reason for discontinuation
could not be ascertained from the medical records. A total of 8 patients failed to return for the 6 month follow-up assessment.

Substance use

For the 103 patients that were on MMT, the mean dose at the start of antiviral therapy was 112 mg. Patients not receiving methadone had been weaned off methadone or attended the clinic to access other services such as counseling and support groups. The majority of clients (60%) had at least one urine screen positive for illicit opiates in the six months prior to initiating antiviral therapy, with a smaller proportion of clients having a positive cocaine screen (39%), positive screen for alcohol ingestion (32%) or no positive screens (19%). (Table 6.1) The distribution of the number of positive urine tests is displayed in Figure 6.1. Among patients with at least one positive urine screen in the 6 months prior to therapy, the median percentages of urine screens positive for illicit opiates, cocaine and alcohol ingestion were 8%, 10% and 4%, respectively. Among patients with at least one positive urine screen during therapy, the median percentages of urine screens positive for illicit opiates, cocaine and alcohol ingestion were 7%, 7% and 3% respectively. The association between one urine screen positive for illicit substances and a urine screen positive for alcohol ingestion in the six months prior to therapy was not significant. The association between a positive urine screen in the 6 months prior to therapy and a positive urine screen during therapy was not significant for either illicit substances (opiates or cocaine) or alcohol ingestion. Those with use of illicit opiates or cocaine prior to antiviral therapy had on average more urine toxicology screens in the 6 months prior to therapy (78 versus 64, p = 0.02). Patients with a urine screen indicating alcohol ingestion prior to therapy had more urine screens (82 versus 70, p = 0.02) and were less likely to be married (27% versus 48%, p=0.08).

Substance Use and Treatment Outcomes

Rates of treatment completion appeared to be lower in those with a positive pre-treatment urine screen for illicit opiates or cocaine (59% versus 80%, p = 0.08). The rate of SVR (54% versus 57%, p =0.98) did not differ. (Table 6.3) Patients with a urine screen indicating alcohol ingestion prior to therapy had lower rates of completion (52% versus 72%, p = 0.07) and lower rates of SVR (39% versus 62%, p=0.05). (Table 6.3) Neither a urine screen positive for illicit opiates or
cocaine, nor a urine screen positive for alcohol ingestion during antiviral therapy was associated with therapy completion or SVR. (Table 6.3)

Univariate logistic regression analysis revealed that higher viral load, use of illicit substances and ingestion of alcohol in the six months prior to antiviral therapy were significantly associated with decreased rates of therapy completion. (Table 6.4) Univariate logistic regression analysis demonstrated that males, non-smokers and those with higher viral loads were significantly less likely to have an SVR. Completion of therapy was a strong predictor of SVR. The only substance use variable significantly associated with SVR was a positive urine screen for alcohol ingestion in the six months prior to therapy. (Table 6.4)

After adjusting for known prognostic factors, having a urine screen positive for illicit drugs (cocaine or opiates) in the six months prior to therapy was significantly associated with lower rates of completion of therapy but not with lower rates of SVR. (Table 6.5) A urine screen indicating ingestion of alcohol in the 6 months prior to therapy was significantly associated with lower rates of completion of therapy and significantly associated with lower rates of sustained virological response. (Table 6.5) The association between a positive urine screen indicating alcohol ingestion and SVR disappeared when adjusting for completion of therapy, suggesting that alcohol ingestion prior to therapy may affect SVR rates through decreasing rates of therapy completion. (Data not shown) Female sex and infection with genotype 2 or 3 were significantly associated with higher rates of SVR, and a higher viral load was significantly associated with lower rates of SVR. (Table 6.5) Among the patients with a urine screen positive for alcohol ingestion prior to therapy that completed therapy, the rate of response to therapy was 67% for patients infected with genotype 2 or 3 and 36% for patients infected with genotype 1 or 4.

31 Discussion

Our study demonstrates that antiviral therapy for hepatitis C infection can be successful alongside ongoing care for substance abuse. Response rates of 51% and 68% were obtained for patients infected with genotype 1/4 and genotype 2/3 respectively, and these rates are comparable to non-substance abusing populations. Positive urine screens for alcohol or illicit substances in the 6 months before treatment were associated with lower treatment completion rates. Alcohol use before treatment was associated with lower rates of SVR, because those with
alcohol use prior to therapy were less likely to complete therapy. Positive urine screens for illicit substances before treatment were not associated with lower rates of SVR.

The results of this study add to a growing body of evidence that current or former substance abusers infected with HCV can be successfully treated in the context of ongoing care for substance abuse. Sylvestre et al reported SVR rates of 28% with 70 patients [152], Backmund et al reported SVR rates of 36% with 50 patients [4] and Van Thiel et al reported SVR rates of 35% with 120 patients.[337] Response rates in these studies were lower than at the OATC because they were conducted prior to the introduction of pegylated-interferon alpha but were comparable to response rates in non-substance abusing populations. More recently, a study of 50 substance abusers maintained with naltrexone implants demonstrated SVR rates of 53% for genotype 1 and 67% for genotypes 2 and 3.[338]

Previous studies have demonstrated results similar to ours relating illicit substance abuse to lower rates of HCV antiviral therapy completion and demonstrating a link between alcohol consumption prior to therapy and SVR rates. In 71 MMT patients, those who relapsed to regular drug use during therapy had lower adherence to therapy than those who did not.[339] Interestingly, in these patients cannabis use was associated with increased adherence and higher SVR rates.[340] On the other hand, a prospective study of 87 IDUs showed no difference in therapy completion rates and response rates between active and inactive users.[341] Heavy injection drug use prior to and during therapy was not associated with SVR in 50 Australian patients with naltrexone implants, however consumption of more than 100g of alcohol per day was associated with decreased SVR.[338] In a mixed group of psychiatric patients including former addicts and those on MMT, alcohol consumption before and during therapy was not related to SVR.[303] In liver clinic populations and veterans, lifetime alcohol use measured using standard instruments has been associated with decreased rates of SVR [342-344] and alcohol intake prior to therapy has been linked to decreased SVR [345] and decreased rates of therapy completion.[346] Our urine alcohol screen did not differentiate between low level consumption and intoxication, and it is not known how much alcohol was consumed by patients with positive tests. Also, the only information available on alcohol consumption prior to enrolment at the OATC clinic was the patient self-reported history of excessive alcohol consumption. Patient self-reported history of excessive alcohol consumption was not associated with treatment completion or SVR.
The OATC model of care has components similar to other models addressing current or former substance abusers, but is distinctive in several important ways: i) most existing programs are located in a single centre; ii) existing programs are in large urban settings such as Perth, Munich, San Francisco, Chicago and Vancouver; iii) existing programs involve clinical care delivered primarily by specialists. [4, 152, 337, 338, 346] The OATC is multi-centred, located in rural and suburban communities, and is administered by family physicians and registered nurses, with an infectious disease specialist functioning as a supervisor of other clinicians. The OATC model has similarities to a shared care model in Australia designed to increase the involvement of nurses and primary care practitioners and address a shortage of specialist physicians and their location in primarily urban regions.[347] Similar to the OATC, limited use of liver biopsy has also been incorporated into Australian treatment models as biopsy has been eliminated as a precondition for subsidized HCV treatment.[348]

Our study has several limitations. The generalizability of our findings may be limited; patients retained on MMT therapy are a distinct subset of patients with substance abuse problems, treated patients did not have HIV co-infection or active psychiatric disorders and treated patients were a subset of HCV infected patients at the OATC that met treatment readiness criteria including regular attendance at clinic appointments, stable housing, marital and employment status. Urinalysis does not provide information on route of administration, and certain sub-groups such as intravenous drug users may have different outcomes than patients that abuse oral opiates. Information on lifetime alcohol consumption was not standardized but based on patient self-report. Information on body mass index, patient ethnicity and the degree of liver fibrosis was not available and these factors may have a significant effect on SVR rates. However, even though ethnicity was not recorded in the medical record, patient photographs in the electronic medical record indicate that the vast majority of clients were Caucasian.

Our study demonstrates that HCV antiviral therapy can be successful in the context of on-going substance abuse therapy and lends support to a growing body of evidence that suggests that while substance abusers should not be automatically excluded from antiviral therapy, on-going drug and alcohol use should be addressed. The study also demonstrates that primary care nurses and practitioners can successfully deliver HCV-related care, even to difficult to treat populations. The importance of targeting antiviral therapy to current or former substance abusers is underscored by the fact that almost all new HCV transmission occurs in this marginalized
population. Reducing the number of infected substance abusers may reduce the spread of
disease, diminish the HCV epidemic and make a significant impact on the morbidity and
mortality associated with HCV infection in the world.
### Table 6.1 Patient characteristics (N=109) (Study 3 – Treatment of hepatitis C for Substance Abusers)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (sd) or N (%)</th>
<th>N missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (sd)</td>
<td>41 (8)</td>
<td></td>
</tr>
<tr>
<td>Mean time at the OATC in years (sd)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Number male</td>
<td>77 (71%)</td>
<td></td>
</tr>
<tr>
<td>Completed high school</td>
<td>47 (55%)</td>
<td>24</td>
</tr>
<tr>
<td>Married/common-law</td>
<td>43 (40%)</td>
<td>2</td>
</tr>
<tr>
<td>Employed</td>
<td>38 (36%)</td>
<td>3</td>
</tr>
<tr>
<td>Permanent apartment or house</td>
<td>62 (72%)</td>
<td>23</td>
</tr>
<tr>
<td>Ever incarcerated</td>
<td>56 (51%)</td>
<td></td>
</tr>
<tr>
<td>Criminal record</td>
<td>77 (71%)</td>
<td></td>
</tr>
<tr>
<td>Self-reported history of excessive alcohol consumption</td>
<td>42 (39%)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>91 (83%)</td>
<td></td>
</tr>
<tr>
<td>Mean estimated duration of infection in years (sd)</td>
<td>15 (10)</td>
<td>48</td>
</tr>
<tr>
<td>Genotype 1,4</td>
<td>75 (69%)</td>
<td></td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>34 (31%)</td>
<td></td>
</tr>
<tr>
<td>Mean baseline viral load, log scale (sd)</td>
<td>5.46 (1.07)</td>
<td>17</td>
</tr>
<tr>
<td>Mean baseline ALT level, IU/ml (sd)</td>
<td>82 (65)</td>
<td>33</td>
</tr>
<tr>
<td>Self-reported depression history</td>
<td>64 (59%)</td>
<td></td>
</tr>
<tr>
<td>Self-reported anxiety history</td>
<td>47 (43%)</td>
<td></td>
</tr>
<tr>
<td>Mean no. of urine screens 6 months prior to therapy (sd)</td>
<td>74 (27)</td>
<td>5</td>
</tr>
<tr>
<td>No. with ≥1 positive urine screen for illicit opiates</td>
<td>62 (60%)</td>
<td></td>
</tr>
<tr>
<td>No. with ≥1 positive urine screen for cocaine</td>
<td>41 (39%)</td>
<td></td>
</tr>
<tr>
<td>No. with ≥1 positive urine screen for alcohol</td>
<td>33 (32%)</td>
<td></td>
</tr>
<tr>
<td>No. with 0 positive urine screens</td>
<td>20 (19%)</td>
<td></td>
</tr>
<tr>
<td>Mean no. of urine screens during therapy (sd)</td>
<td>92 (54)</td>
<td>7</td>
</tr>
<tr>
<td>No. with ≥1 positive urine screen for illicit opiates</td>
<td>58 (57%)</td>
<td></td>
</tr>
<tr>
<td>No. with ≥1 positive urine screen for cocaine</td>
<td>33 (32%)</td>
<td></td>
</tr>
<tr>
<td>No. with ≥1 positive urine screen for alcohol</td>
<td>28 (27%)</td>
<td></td>
</tr>
<tr>
<td>No. with 0 positive urine screens</td>
<td>25 (25%)</td>
<td></td>
</tr>
</tbody>
</table>

sd indicates standard deviation

ALT indicates alanine aminotransferase
Table 6.2: Treatment outcomes (Study 3 – Treatment of hepatitis C for Substance Abusers)

<table>
<thead>
<tr>
<th>Rate of completion of antiviral therapy</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1,4</td>
<td>46 / 75</td>
<td>61</td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>25 / 34</td>
<td>74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. with complete follow-up</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1,4</td>
<td>52 / 75</td>
<td>69</td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>27 / 34</td>
<td>79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rates of sustained virologic response (intention-to-treat analysis)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1/4</td>
<td>38 / 75</td>
<td>51</td>
</tr>
<tr>
<td>Genotype 2/3</td>
<td>23 / 34</td>
<td>68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for discontinuation of therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient response at twelve weeks</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Psychiatric adverse event</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Clinical adverse event (e.g. Flu-like symptoms)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Laboratory abnormality</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Non-adherent to appointments</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-adherent to antiviral drug therapy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Refusal to continue therapy</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Failure to return for 6 months follow-up appointment</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
Table 6.3: Treatment outcomes stratified by urine screen results for illicit substances or alcohol intoxication (Study 3 – Treatment of hepatitis C for Substance Abusers)

<table>
<thead>
<tr>
<th>Urine screen positive for illicit opiates or cocaine 6 months prior to therapy</th>
<th>Number</th>
<th>Proportion completing therapy</th>
<th>p-value</th>
<th>Proportion with a sustained virological response</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>74</td>
<td>59%</td>
<td></td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30</td>
<td>80%</td>
<td>0.08</td>
<td>57%</td>
<td>0.98</td>
</tr>
</tbody>
</table>

| Urine screen positive for intoxication with alcohol 6 months prior to therapy | Yes | 33 | 52% | | 39% |
| No | 71 | 72% | 0.07 | 62% | 0.05 |

| Urine screen positive for illicit opiates or cocaine during therapy | Yes | 68 | 71% | | 60% |
| No | 34 | 56% | 0.21 | 44% | 0.18 |

| Urine screen positive for intoxication with alcohol during therapy | Yes | 28 | 61% | | 54% |
| No | 74 | 68% | 0.68 | 55% | 0.95 |
Table 6.4: Univariate logistic regression analyses with completion of therapy and sustained virological response as the dependent variables (Study 3 – Treatment of hepatitis C for Substance Abusers)

<table>
<thead>
<tr>
<th></th>
<th>Completion of therapy</th>
<th>Sustained virological response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mean age in years</td>
<td>0.98</td>
<td>(0.93, 1.04)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.42</td>
<td>(0.61, 3.34)</td>
</tr>
<tr>
<td>Mean time at the OATC in years</td>
<td>1.10</td>
<td>(0.87, 1.38)</td>
</tr>
<tr>
<td>Married/common-law</td>
<td>1.24</td>
<td>(0.55, 2.81)</td>
</tr>
<tr>
<td>Permanent apartment or house</td>
<td>1.26</td>
<td>(0.47, 3.37)</td>
</tr>
<tr>
<td>Employed</td>
<td>0.61</td>
<td>(0.27, 1.40)</td>
</tr>
<tr>
<td>Completed high school</td>
<td>1.55</td>
<td>(0.64, 3.78)</td>
</tr>
<tr>
<td>Criminal record</td>
<td>0.80</td>
<td>(0.33, 1.92)</td>
</tr>
<tr>
<td>Ever incarcerated</td>
<td>0.57</td>
<td>(0.25, 1.26)</td>
</tr>
<tr>
<td>Self-reported history of excess</td>
<td>1.59</td>
<td>(0.69, 3.64)</td>
</tr>
<tr>
<td>alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1.23</td>
<td>(0.43, 3.49)</td>
</tr>
<tr>
<td>Mean estimated duration of infection in years</td>
<td>0.98</td>
<td>(0.93, 1.04)</td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>1.75</td>
<td>(0.72, 4.27)</td>
</tr>
<tr>
<td></td>
<td>Completion of therapy</td>
<td>Sustained virological response</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI p-value</td>
</tr>
<tr>
<td>Mean baseline viral load, log scale</td>
<td>0.46 (0.23, 0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean baseline ALT level, IU/ml</td>
<td>1.00 (0.99, 1.01)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean no. of urine screens prior to therapy</td>
<td>0.99 (0.98, 1.01)</td>
<td>0.24</td>
</tr>
<tr>
<td>Self-reported depression history</td>
<td>1.47 (0.66, 3.25)</td>
<td>0.35</td>
</tr>
<tr>
<td>Self-reported anxiety history</td>
<td>0.77 (0.35, 1.70)</td>
<td>0.51</td>
</tr>
<tr>
<td>Urine screen positive for illicit opiates or cocaine 6 months prior to therapy</td>
<td>0.37 (0.13, 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Urine screen positive for alcohol 6 months prior to therapy</td>
<td>0.42 (0.18, 0.98)</td>
<td>0.05</td>
</tr>
<tr>
<td>Urine screen positive for illicit opiates or cocaine during therapy</td>
<td>1.89 (0.81, 4.45)</td>
<td>0.14</td>
</tr>
<tr>
<td>Urine screen positive for alcohol during therapy</td>
<td>0.74 (0.30, 1.83)</td>
<td>0.52</td>
</tr>
<tr>
<td>Completed therapy</td>
<td>NA  NA NA</td>
<td>5.84</td>
</tr>
</tbody>
</table>

ALT indicates alanine aminotransferase.
Table 6.5: Logistic regression analysis of the association between substance use 6 months prior to therapy with completion of therapy and sustained virological response (SVR), adjusting for prognostic factors (Study 3 – Treatment of hepatitis C for Substance Abusers)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completion of therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age</td>
<td>0.97 (0.92, 1.03)</td>
<td>0.36</td>
</tr>
<tr>
<td>Female Sex</td>
<td>0.69 (0.26, 1.84)</td>
<td>0.46</td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>1.92 (0.71, 5.17)</td>
<td>0.20</td>
</tr>
<tr>
<td>Urine screen positive for illicit opiates or cocaine 6 months prior to therapy</td>
<td>0.30 (0.10, 0.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>Urine screen positive for alcohol 6 months prior to therapy</td>
<td>0.37 (0.15,0.93)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Sustained Virological Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age</td>
<td>0.98 (0.92, 1.04)</td>
<td>0.44</td>
</tr>
<tr>
<td>Female Sex</td>
<td>3.47 (1.24, 9.72)</td>
<td>0.02</td>
</tr>
<tr>
<td>Genotype 2,3</td>
<td>2.50 (0.95, 6.55)</td>
<td>0.06</td>
</tr>
<tr>
<td>Log Viral Load</td>
<td>0.46 (0.24, 0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Urine screen positive for illicit opiates or cocaine 6 months prior to therapy</td>
<td>0.74 (0.28, 1.98)</td>
<td>0.55</td>
</tr>
<tr>
<td>Urine screen positive for alcohol 6 months prior to therapy</td>
<td>0.39 (0.15,0.98)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
33 Figure – Study 3

Figure 6.1: Distribution of the number of positive urine screens 6 months prior to antiviral therapy and during antiviral therapy (Study 3 – Treatment of hepatitis C for Substance Abusers)

a) illicit opiates or cocaine 6 months prior to therapy

x-axis indicates the number of positive urine screens

y-axis indicates the proportion of patients
b) illicit opiates or cocaine during therapy

x-axis indicates the number of positive urine screens

y-axis indicates the proportion of patients
c) alcohol 6 months prior to therapy

x-axis indicates the number of positive urine screens

y-axis indicates the proportion of patients
d) alcohol during therapy

x-axis indicates the number of positive urine screens

y-axis indicates the proportion of patients
Chapter 7
Conclusion and Implications

34 Summary of contribution

The work of this thesis makes several contributions to knowledge about chronic HCV infection and its impact, particularly pertaining to substance abusing populations.

Study 1 Summary

In the study entitled, “Natural History of Chronic Hepatitis C Viral infection obtained through injection drug use: A Bayesian Meta-Analysis,” we estimated the rate of progression to cirrhosis for populations who acquired infection through injection drug use. We identified a total of 47 published articles and performed a meta-regression on a subset of 44 in which biopsy data were used to diagnose cirrhosis. The meta-regression represented 6,457 patients. The estimated rate of progression to cirrhosis was 8.1 per 1000 person-years (95% Credible Region (CR), 3.9 to 14.7) corresponding to a 20-year cirrhosis prevalence of 14.8% (95% CR, 7.5 to 25.5). The proportion of male patients and the proportion consuming excessive alcohol were associated with faster progression. The proportion co-infected with HIV was not associated with faster progression. We also found no evidence that studies in settings with a high risk of referral bias were associated with faster progression.

Our study is the first we are aware of to investigate the natural history of chronic HCV infection focused only on this population. Our findings were consistent with other findings indicating that those acquiring infection through injection drug use have similar prognosis to those with HCV infection of other etiologies. The study had some important limitations.

- Using summary data from published analyses means that the estimates are best incorporated into clinical decision making and public policy planning on an aggregate level.

- While our unadjusted analysis confirmed previous findings that studies conducted in clinical settings were associated with faster progression rates than studies conducted in
non-clinical settings, we were unable to adjust for this in the meta-regression due to limitations of sample size.

- We were not able to explore the impact of different models of fibrosis progression on our rate estimates. Some evidence suggests that fibrosis progression rates increase with advanced stages of fibrosis. Approximately ½ of the studies in our analysis did not report biopsy stage distribution.

**Study 1 Implications**

Our study demonstrates that chronic HCV infection can be associated with significant morbidity and mortality in populations of patients who acquired infection through injection drug use. Natural history estimates from study 1 can contribute to forecasting efforts predicting the future burden of disease that may result from on-going HCV transmission among substance abusers. The factors associated with increased rates of progression – the proportion male and the proportion consuming excessive alcohol – are common in injection drug using populations. Forecasting progression to cirrhosis in this population, accounting for the prevalence of risk factors such as male sex and alcohol abuse, can allow policy makers and clinicians to weigh different options for preventing and treating HCV among substance abusers.

**Study 2 Summary**

In the study entitled, “Sustained responders have better quality of life and productivity compared to treatment failures long after antiviral therapy for hepatitis C”, we explored the association between sustained response to antiviral therapy and differences in quality of life in patients recruited from tertiary care clinics. Although few patients reported active substance abuse, approximately 50% of patients had previously injected illicit substances at least once. We found differences in quality of life between sustained responders and treatment failures that were both statistically significant and clinically significant. A total of 235 patients (133 responders and 102 treatment failures) completed questionnaires an average of 3.7 years after the end of treatment. Treatment failures had significantly lower scores on each of eight Medical Outcomes Study Short Form (SF)-36 domains, hepatitis specific domains and the summary component scores. Utility measures including the Health Utilities Index Mark 2/3 (HUI2/3), the SF-6D and time
The regression-adjusted difference in HUI3, SF-6D, PCS and MCS scores was 0.08 (p=0.04), 0.05 (p=0.004), 5.22 (p=0.001) and 5.73 (p<0.0001), respectively. Treatment failures were more likely to have missed work, volunteering or household activities in the last 3 months due to hepatitis C or its treatment (44% versus 9%, p<0.001).

Our study was the first we are aware of to assess quality of life and productivity long after therapy completion. We employed a significant number of quality of life measures and demonstrated consistency across the results. Using detailed reviews of patient medical records along with patient self-report, we were able to adjust for factors such as age, sex and co-morbid illnesses that might also impact quality of life. Even after adjustment for these factors, differences in quality of life between sustained responders and treatment failures remained.

Our study had several limitations. The study population may not be representative given that the questionnaire respondents were a convenience sample. The study design was cross-sectional. We were unable to measure quality of life prior to the start of antiviral therapy. As a result, we cannot rule out the possibility that sustained responders to antiviral therapy had better quality of life prior to therapy than treatment failures. We don’t know whether or not patients were aware of their therapeutic outcomes. While we suspect that most were aware, differences between the groups may account for differences in quality of life.

**Study 2 Implications**

The key implications of our study are that the quality of life improvement demonstrated in randomized clinical trials translates to a real-world clinic population and the improvements are maintained long after the short-term follow-up of clinical trials. The quality of life improvements are also associated with increased productivity and increased employment rates. The results of study 2 provide important information to patients and clinicians making treatment decisions. They also provide insights to policy makers about potential secondary benefits of addressing HCV through antiviral therapy, suggesting that individuals who clear antiviral therapy have greater productivity. These benefits should be considered by patients and providers as they make decisions about antiviral therapy. The results should also inform health care policy makers’ decision making about strategies to reduce the morbidity and economic impact of HCV infection.
Study 3 Summary

In the study entitled, “Treatment of Hepatitis C infection in patients on methadone maintenance in a community setting”, we demonstrated that despite ongoing use of illicit substances and alcohol, current or former substance abusers can be successfully treated. A total of 109 clients of the Ontario Addiction Treatment Centres (75 with genotype 1/4 and 34 with genotype 2/3) received at least one dose of antiviral therapy. Treatment completion rates of 61% and 74% were achieved for genotypes 1/4, and 2/3 respectively. Rates of treatment response in an intention to treat analysis were 51% for genotypes 1/4 and 68% for genotypes 2/3. A positive urine screen indicating at least one instance of illicit substance use in the six months prior to initiation of antiviral therapy was significantly associated with lower rates of treatment completion but not lower rates of sustained virological response. A positive urine screen indicating use of alcohol was significantly associated with lower rates of completion and lower rates of sustained virological response.

Our study is consistent with other publications describing HCV treatment programs for individuals with ongoing substance abuse problems. Antiviral therapy for chronic HCV infection can be successful in the context of multi-disciplinary care for substance abuse. Our study also demonstrates the possibility of employing minimal specialist services and optimizing the use of primary care physicians and nurses in treating chronic HCV. The care model employed by the OATC is one of only a few in the world that presents a potential solution to the shortage of specialist physicians in treating patients with chronic HCV infection.

The study had several limitations. We were unable to differentiate between low level consumption of alcohol and alcohol abuse. We had limited information on lifetime alcohol consumption, relying only on patient report for this variable. Limited biopsy information prevented us from assessing the degree of liver fibrosis of treated patients. Fibrosis stage is an important predictor of response to antiviral therapy which would have been optimal to include in the regression analysis we conducted. Other information that impacts on treatment response rates such as body mass index was also not available. While we did not have data on patient ethnicity, photographs contained in the medical record suggested that the vast majority were Caucasian. Recent evidence demonstrates that Caucasians frequently express a variant of the IL28B gene that confers an advantage in responding to antiviral therapy. Patients treated at the OATC were
also on average slightly younger by approximately 3 years than patients in other real-world clinic populations.\[123, 128] Age is a determinant of response to therapy and younger patients are more likely to respond. Thus the response rates we observed may be optimized compared to other populations. Some studies suggest that females are more likely to respond to antiviral therapy. The impact on response seems to be related to the lower body mass index of females and the adequacy of dosing with antiviral therapies.\[10, 349]

**Study 3 Implications**

Study 3 provides information that can be used to optimize the management of current or former substance abusers undergoing antiviral therapy. The key implications of our study are that:

- substance abusers should not be automatically excluded from antiviral therapy
- nurses, psychiatrists, counselors and other health care practitioners can successfully deliver HCV-related care to difficult to treat populations
- while on antiviral therapy on-going drug and alcohol use should be addressed because of the potential to decrease adherence to therapy and impact on response rates

**35 Future studies**

Injection drug use in North America is currently the most important risk factor for infection with HCV and new initiates to injection drug use continue to be infected at extremely high rates. As a result, even though rates of HCV infection have declined in the general population, the health burden due to end-stage liver disease will continue to rise in the future because a significant proportion of patients that acquire HCV infection through injection drug use will experience end-stage liver disease and there is no prophylactic vaccine available now or in the near future. The work of this thesis sheds light on some of the issues related to addressing chronic HCV infection for substance abusers. Several important questions arise from the work which can be potentially be addressed by future studies.
Natural history

One challenge arising from the work of this thesis is to improve on prognostic estimates from study 1. Study 1 estimates of the rate of progression to cirrhosis pertain to populations of patients. Improved estimates could shed light on understanding prognosis at the individual level. One approach to this problem would be to contact the authors on the 47 studies we identified and request access to individual level patient data. While it is not likely that it would be possible to obtain all of the patient data from each of the studies, even if data from a significant proportion of the more than 6,000 patients in the meta-analyses could be obtained, this would present a tremendous opportunity to quantify the impact of age, sex, alcohol consumption, ALT levels and HIV co-infection on the rate of progression to cirrhosis. With a significant amount of data, Bayesian modeling could be employed to represent the complex relationships in the data and separate individual effects on prognosis from study related effects such as setting and method of diagnosis.

Quality of life

More studies are required to confirm that successful antiviral therapy improves quality of life for substance abusers. The evidence suggests that HCV infection is only one of many factors contributing to low quality of life in HCV infected injection drug users. Further study of the quality of life impact of sustained response to antiviral therapy in substance abusers will likely require large sample sizes to isolate decrements in quality of life due to HCV from decrements due to substance abuse. Prospective analysis of quality of life in substance abusers undergoing antiviral therapy would also shed light on the quality of life response to antiviral therapy.

Cost-effectiveness analysis

The estimates of the rate of progression to cirrhosis generated by study 1 can be incorporated into forecasting analyses to assess the value for money of different options for minimizing HCV impact through treatment, prevention and harm reduction. Cost-effectiveness analysis should incorporate the following features:
- Estimated health impacts in terms of morbidity and mortality from cirrhosis, hepatocellular carcinoma, liver failure and transplantation

- Quality of life impacts and potentially impacts on productivity

- Competing risks of mortality in substance abusing populations. Even though HCV is expected to have an impact on the health and longevity of individuals with substance abuse issues, it is important to account for the increased morbidity and mortality of substance abusers at both young as well as an older age compared to the general population, when considering policy options. Other factors such as ethnic variation in rates of response to antiviral therapy should be considered.

- In addition to intervention costs (e.g. needle exchange, methadone maintenance, antiviral therapy), the costs of treating end-stage liver disease should be incorporated. Importantly, the costs of therapy for substance abusers should accurately reflect the realities of delivering treatment to this population. Multi-disciplinary care addressing both substance abuse and HCV infection requires additional specialties including addiction therapy specialists, counselors and psychologists in order to optimize treatment outcomes. Also, the cost of screening patients who are not eventually treated should be incorporated. Patients who undergo evaluation and are subsequently deemed ineligible for therapy, represent the sunk costs of treating the patients who eventually receive antiviral therapy. Understanding these “sunk” costs is an important factor in assessing the usefulness of various approaches to treatment in this population. The cost of treatment from the patient perspective should also be included. Patient costs incurred from travel, out of pocket drug expenditures, lost productivity and lost leisure, should be considered.

**Decision psychology**

Many studies indicate that only a small proportion of current or former substance users are treated with antiviral therapy, even in settings with comprehensive, multidisciplinary care. [323, 350] Understanding the factors that contribute to access and utilization of antiviral therapy and the extent to which these factors are modifiable, can assist in developing health policy to reduce the burden of disease among HCV infected patients by increasing access to antiviral therapy.
Expected utility theory posits that individuals trade-off benefits and harms associated with different options to maximize utility. One of the keys to understanding individual decisions is assessing both the trade-offs and the values that patients place on processes and outcomes, as well as individual orientation towards taking risks. Normative theories specify the decisions that individuals should rationally make based on the probabilities of benefits and harms and the values patients place on the harms. Decision psychology demonstrates that humans frequently act irrationally, due to cognitive deficits that make decisions subject to factors such as framing of decisions. [351]

Studies based in the academic discipline of decision psychology may shed light on the reasoning behind low treatment uptake among substance abusers. Decision analytic modeling of the patient decision to forego antiviral therapy can indicate the extent to which patients are acting rationally in deferring treatment. Decision analytic modeling can be used to explicitly express the tradeoffs and values of an individual patient using a model. Some evidence indicates that patients are satisfied with their decision to defer therapy when followed up one year later.[352] However the extent to which these decisions are rational has only been partially addressed. Analysis of quality of life tradeoffs demonstrated that disutility associated with antiviral therapy was too high compared to current health. [220]

Models of rational addiction view the actions of individuals who abuse substance through the lens of economics and psychology. Through the framework of the rational addiction model, the choices of addicts can be explained as rational decisions when taking into account certain factors. Addicts tend to be present-oriented rather than future-oriented. Addicts tend to have a short term vision of the future and heavily discount the negative future consequences of consuming substances, in light of the present rewards of consumption. Studies demonstrate that individuals who abuse substances seek to optimize utility on the basis of anticipated rewards that have been learned by doing. [353, 354] Therefore, addicts choose substance use because they seek to maximize utility in the context of a short-term view of the future. The time preference of substance abusers may impact the desire to undergo antiviral therapy. If substance abusers have a present-oriented view of life and discount future events related to liver disease, then they would be less likely to undergo antiviral therapy. It may be informative to compare the time preferences of substance abusers that opt to undergo antiviral therapy with those who are otherwise eligible but forego therapy. Methods for measuring time preference using tests and questionnaires can be
applied to assess the extent to which time preference is associated with decisions around antiviral therapy. Understanding the ways in which time preference impacts on treatment decisions may provide insights into ways to improve the uptake of antiviral therapy among substance abusers. Understanding time preference and the impact on treatment decisions may lead to a more efficient method for identifying patients for antiviral therapy.

**Communication needs and decision aids**

The low uptake of antiviral therapy among substance abusers and indeed non-substance abusing populations may also be related to communication difficulties among patients and providers that have been identified in the literature. Forty-one percent of HCV-infected patients report having difficulty communicating with physicians. Providers express concerns that patient questions related to HCV infection and treatment often go unanswered. Physicians describe outcomes in a confusing way and patients incorrectly comprehend the probability of sustained response to antiviral therapy by a large margin following clinical encounters. One study showed that an educational intervention improved patient knowledge and willingness to accept treatment. Thus decision aids may be useful for patients facing the decision of whether or not to undergo antiviral therapy for HCV infection.

Decision aids are tools designed to reduce decisional conflict by preparing patients for decision-making. The concept of decisional conflict was proposed by Janis and Mann and defined as follows: “Decisional conflict is a state of uncertainty about a course of action.” Decisional uncertainty is exacerbated when a person feels: 1) uninformed about alternatives, benefits and risks, 2) is unclear about personal values and 3) feels unsupported in making a choice or pressured to choose on a course of action. Decision aids help patients to clarify their values and assist patients in communicating with others in the process of making a decision. Decision aids can take several forms including pamphlets, audio and computerized formats, with the goal of enhancing the interaction between patients and clinicians and not substituting it.

Future work may focus on the communication needs of patients and providers with the goal of developing a decision aid. Although a clinical decision aid exists to help patients decide about hepatitis C antiviral therapy, the decision aid contains aspects specific to the United States including a discussion of health insurance coverage, and more importantly, no process for
assessing patient and provider decision support was included in its development.[364] Additional criticisms of the decision aid include a lack of individualized risk assessment for liver prognosis or response to antiviral therapy. The patient population most heavily impacted by chronic HCV infection includes current or former substance abusers, and a complex mixture of health services is required to optimally treat these patients. Assessing decision support needs specific to this population of patients and the providers with whom they interact is of particular importance in developing a clinical decision aid. Any assessment of patient and provider needs should encompass the broad range of health care professionals - nurses, general practitioners, addiction counselors, infectious disease and hepatology specialists – that play a significant role in delivering comprehensive health care to these patients.[256, 347, 365]

The use of decision aids has not been tested in patient populations including substance abusers. [366] The extent to which decision aids could be useful to this patient group is unclear. Although accessible reading language is the recommended practice in developing decision aids, patients with substance abuse problems and low socioeconomic status may have poorer literacy than the average population. Using computers to provide patients with individual prognosis risk and probability of response may not be feasible for patients with substance abuse problems. Patients may not have easy access to computers, and clinicians may not have resources to provide computers. Innovative approaches using cartoons and video clips may be considered. Despite concerns about decision aids, in low literacy and low numeracy populations, decision aids may be a worthwhile avenue to pursue in order to ensure that individuals infected with HCV make optimal decisions about antiviral therapy.

36 Conclusion

Although recent improvements in the safety of the blood supply have reduced the incidence of HCV from blood transfusion, cohorts infected prior to improvements in safety will still progress to end stage disease at a significant rate. Along with the on-going transmission of HCV among injection drug users, the health and policy issues associated with HCV remain. The work of this thesis has informed clinical and health policy related to substance abusers by estimating the expected rate of progression to cirrhosis, assessing the efficacy of HCV antiviral therapy for patients with ongoing substance abuse and assessing the association between successful therapy and quality of life. While the contributions of the thesis work have been significant, there is great
need for future work in this area to navigate complicated issues and further inform policy options for reducing the burden of illness in this population.
References or Bibliography


Appendices

Appendix 1: Questionnaire Booklets 1 & 2 - Quality of Life, Health History and Cost (Study 2)
Population-Based Estimates of Cost and Quality of Life in Community Dwelling HCV Patients

Questionnaire Booklet 1

Quality of Life and Health History

Please write your initials

First  Middle  Last

Please check today's date

<table>
<thead>
<tr>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
<th>Jul</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>21</td>
<td>22</td>
<td>23</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>29</td>
<td>30</td>
<td>31</td>
<td>2005</td>
<td>2006</td>
<td>2007</td>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Your Health and Well-Being

1. In general, would you say your health is:

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

2. Compared to one year ago, how would you rate your health in general now?

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports

b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

c) Lifting or carrying groceries

d) Climbing several flights of stairs

e) Climbing one flight of stairs

f) Bending, kneeling, or stooping

g) Walking more than a mile

h) Walking several hundred yards

i) Walking one hundred yards

j) Bathing or dressing yourself

<table>
<thead>
<tr>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
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<td>μ</td>
<td>μ</td>
<td>μ</td>
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<td>μ</td>
<td>μ</td>
<td>μ</td>
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<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

a) Cut down on the **amount of time** you spent on work or other activities

b) **Accomplished less** than you would like

c) Were limited in the **kind** of work or other activities

d) Had **difficulty** performing the work or other activities (for example, it took extra effort)

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

a) Cut down on the **amount of time** you spent on work or other activities

b) **Accomplished less** than you would like

c) Did work or other activities **less carefully than usual**

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

7. How much **bodily** pain have you had during the past 4 weeks?

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

8. During the past 4 weeks, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Did you feel full of life?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Have you been very nervous?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>d) Have you felt calm and peaceful?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>e) Did you have a lot of energy?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>f) Have you felt downhearted and depressed?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>g) Did you feel worn out?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>h) Have you been happy?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>i) Did you feel tired?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

<table>
<thead>
<tr>
<th>All of the Time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

11. How TRUE or FALSE are each of the following statements for you?

<table>
<thead>
<tr>
<th>Statement</th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) I seem to get sick a little easier than other people</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) I am as healthy as anybody I know</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) I expect my health to get worse</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>d) My health is excellent</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>
12. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th></th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Were you discouraged by your health problems?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Did you feel weighted down by your health problems?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) Was your health a worry in your life?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>d) Were you frustrated by your health?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

13. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th></th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Have you generally enjoyed the things you do?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Has your daily life been full of things that were interesting to you?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) Have you felt cheerful, lighthearted?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>d) Has living been a wonderful adventure for you?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

14. How much of the time during the past 4 weeks has your hepatitis limited you in:

<table>
<thead>
<tr>
<th></th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Your everyday physical activities such as walking or climbing stairs, carrying groceries or participating in sports?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Your daily work, both work outside the home and housework?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) Your normal social activities with family, friends, neighbors or groups?</td>
<td>μ μ</td>
<td>μ μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

Hepatitis Quality of Life Questionnaire (HQLQ™) © 1999 by QualityMetric Incorporated
15. How much of the time during the **past 4 weeks**...

<table>
<thead>
<tr>
<th></th>
<th>All of the Time</th>
<th>Most of the Time</th>
<th>A Good Bit of the Time</th>
<th>Some of the Time</th>
<th>A Little of the Time</th>
<th>None of the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Were you discouraged because of your hepatitis?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Did you feel weighted down by your hepatitis?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) Was having hepatitis a worry in your life?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>d) Were you frustrated because of having hepatitis?</td>
<td>μ</td>
<td>μ</td>
<td>μ</td>
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<td>μ</td>
</tr>
</tbody>
</table>

THANK YOU VERY MUCH FOR ANSWERING THESE QUESTIONS.

PLEASE GO TO THE NEXT QUESTIONNAIRE ON QUALITY OF LIFE.
Instructions
This questionnaire contains a set of questions which ask about various aspects of your health. When answering these questions please think about your health and your ability to do things on a day-to-day basis, during the past week. To define the past week period, please think about what the date was 7 days ago and recall the major events that you have experienced during this period. Please focus your answers on your abilities, disabilities and how you have felt during the past week.

You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

Please read each question and consider your answers carefully. For each question, please select one answer that best describes your level of ability or disability during the past week. Please indicate the selected answer by placing a check mark in the box beside the answer. Please make sure your check marks stay within the boxes.

All information you provide is confidential. There are no right or wrong answers; what we want is your opinion about your abilities and feelings.

1. Which one of the following best describes your ability, during the past week, to see well enough to read ordinary newsprint?
   - Able to see well enough without glasses or contact lenses.
   - Able to see well enough with glasses or contact lenses.
   - Unable to see well enough even with glasses or contact lenses.
   - Unable to see at all.

2. Which one of the following best describes your ability, during the past week, to see well enough to recognize a friend on the other side of the street?
   - Able to see well enough without glasses or contact lenses.
   - Able to see well enough with glasses or contact lenses.
   - Unable to see well enough even with glasses or contact lenses.
   - Unable to see at all.
3. Which one of the following best describes your ability, during the past week, to hear what was said in a group conversation with at least three other people?

- Able to hear what was said without a hearing aid.
- Able to hear what was said with a hearing aid.
- Unable to hear what was said even with a hearing aid.
- Unable to hear what was said, but did not wear a hearing aid.
- Unable to hear at all.

4. Which one of the following best describes your ability, during the past week, to hear what was said in a conversation with one other person in a quiet room?

- Able to hear what was said without a hearing aid.
- Able to hear what was said with a hearing aid.
- Unable to hear what was said even with a hearing aid.
- Unable to hear what was said, but did not wear a hearing aid.
- Unable to hear at all.

5. Which one of the following best describes your ability, during the past week, to be understood when speaking your own language with people who do not know you?

- Able to be understood completely.
- Able to be understood partially.
- Unable to be understood.
- Unable to speak at all.

6. Which one of the following best describes your ability, during the past week, to be understood when speaking with people who know you well?

- Able to be understood completely.
- Able to be understood partially.
- Unable to be understood.
- Unable to speak at all.
7. Which one of the following best describes how you have been feeling during the past week?

μ Happy and interested in life.
μ Somewhat happy.
μ Somewhat unhappy.
μ Very unhappy.
μ So unhappy that life was not worthwhile.

8. Which one of the following best describes the pain and discomfort you have experienced during the past week?

μ Free of pain and discomfort.
μ Mild to moderate pain or discomfort that prevented no activities.
μ Moderate pain or discomfort that prevented some activities.
μ Moderate to severe pain or discomfort that prevented some activities.
μ Severe pain or discomfort that prevented most activities.

9. Which one of the following best describes your ability, during the past week, to walk? Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

μ Able to walk around the neighbourhood without difficulty, and without walking equipment.
μ Able to walk around the neighbourhood with difficulty; but did not require walking equipment or the help of another person.
μ Able to walk around the neighbourhood with walking equipment, but without the help of another person.
μ Able to walk only short distances with walking equipment, and required a wheelchair to get around the neighbourhood.
μ Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and required a wheelchair to get around the neighbourhood.
μ Unable to walk at all.

© Health Utilities Inc. (HUInc), 2002.
10. Which one of the following best describes your ability, during the past week, to use your hands and fingers?

Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

µ Full use of two hands and ten fingers.

µ Limitations in the use of hands or fingers, but did not require special tools or the help of another person.

µ Limitations in the use of hands or fingers, independent with use of special tools (did not require the help of another person).

µ Limitations in the use of hands or fingers, required the help of another person for some tasks (not independent even with use of special tools).

µ Limitations in the use of hands or fingers, required the help of another person for most tasks (not independent even with use of special tools).

µ Limitations in the use of hands or fingers, required the help of another person for all tasks (not independent even with use of special tools).

11. Which one of the following best describes your ability, during the past week, to remember things?

µ Able to remember most things.

µ Somewhat forgetful.

µ Very forgetful.

µ Unable to remember anything at all.

12. Which one of the following best describes your ability, during the past week, to think and solve day to day problems?

µ Able to think clearly and solve day to day problems.

µ Had a little difficulty when trying to think and solve day to day problems.

µ Had some difficulty when trying to think and solve day to day problems.

µ Had great difficulty when trying to think and solve day to day problems.

µ Unable to think or solve day to day problems.
13. Which one of the following best describes your ability, during the past week, to perform basic activities?

- Eat, bathe, dress and use the toilet normally.
- Eat, bathe, dress or use the toilet independently with difficulty.
- Required mechanical equipment to eat, bathe, dress or use the toilet independently.
- Required the help of another person to eat, bathe, dress or use the toilet.

14. Which one of the following best describes how you have been feeling during the past week?

- Generally happy and free from worry.
- Occasionally fretful, angry, irritable, anxious or depressed.
- Often fretful, angry, irritable, anxious or depressed.
- Almost always fretful, angry, irritable, anxious or depressed.
- Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help.

15. Which one of the following best describes the pain or discomfort you have experienced during the past week?

- Free of pain and discomfort.
- Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.
- Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities.
- Frequent pain or discomfort; frequent disruption of normal activities. Discomfort required prescription narcotics for relief.
- Severe pain or discomfort. Pain not relieved by drugs and constantly disrupted normal activities.
16. Overall, how would you rate your health during the past week?

μ Excellent.
μ Very good.
μ Good.
μ Fair.
μ Poor.

17. How did you complete the questionnaire? Please select the one answer that best describes your situation.

μ By myself, without any help from anyone else.
μ By myself, except someone else circled the answers on the questionnaire form for me.
μ With the help of someone else.
μ This questionnaire was completed by a family member, without help from the subject or patient.
μ This questionnaire was completed by a nurse or other health professional, without help from the subject or patient. Please specify type of health professional: ______________________________
μ This questionnaire was completed by another person, without help from the subject or patient. Please specify relationship to subject or patient: ________________________

THANK YOU VERY MUCH FOR ANSWERING THESE QUESTIONS.

PLEASE GO TO THE NEXT QUESTIONNAIRE ON QUALITY OF LIFE.
TIME TRADE-OFF QUESTION

I would like you to think about your current health. This includes your physical and mental well-being, your relationships with people in your life, your energy level, your symptoms related to any illness, disability, or disease, etc.

Imagine that you have 20 years left to live. Imagine that you will live these 20 years in your current health state with all of the symptoms and problems that you are presently experiencing, including those related to your Hepatitis C or to any other illness, disability, or disease you may have. This is shown on the scale below with an “X” marked over the number 20 -

Your Current Health

OR

Imagine that you can choose to live a shorter period of time in perfect health, with no symptoms or problems whatsoever. Would you rather live less than 20 years in perfect health, or would you rather live 20 years as you are now? Think about this choice.

On the scale below, please mark an “X” over a number on the scale to indicate the number of years of perfect health (from 0 to 20, inclusive) that you think is of equal value to 20 years in your current health.

Perfect Health

Version 2: October 17, 2005
# Health Checklist

Please indicate which of the following health conditions you have experienced in the past or are currently experiencing. Please make sure your check marks stay within the boxes.

<table>
<thead>
<tr>
<th>Do you have…</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. High blood pressure?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) If you take medication, is your blood pressure higher than 160/100 while you are on medication?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>2. A history of angina (chest pain or chest tightness)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, is it due to prolonged physical activity?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Do you get angina or shortness of breath during normal daily activities?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) Do you get angina or shortness of breath while you are resting?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>3. A history of one or more heart attacks or coronary artery disease?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, have you had it in the last 6 months?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Did you have coronary artery bypass surgery?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>4. A history of rheumatic fever, narrowing of your heart valves, or inflammation of your heart?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) If you take medication, are your symptoms controlled while you are on medication?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>5. Irregular beating of your heart (e.g. fast or slow heartbeat)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) If you take medication, are your symptoms controlled while you are on medication?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) If your symptoms are not controlled, do you get recurring dizziness or fainting?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>d) Do you have a pacemaker?</td>
<td>μ</td>
<td>μ</td>
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<tr>
<td>6. A history of a single episode of congestive heart failure (CHF)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, do you have mild symptoms (e.g. mild swelling or mild shortness of breath)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Do you have more severe symptoms (e.g. major swelling, severe shortness of breath, heart enlargement, or chronic tiredness)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>Question</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>7. A history of more than one episode of congestive heart failure (CHF)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) IF YES, do you have mild symptoms (e.g. mild swelling or mild shortness of breath)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Do you have more severe symptoms (e.g. major swelling, severe shortness of breath, heart enlargement, or chronic tiredness)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>8. A history of peripheral vascular disease (blood clot in your veins or arteries)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, did you have an operation to unclog or bypass your veins or arteries?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Did your symptoms disappear due to your operation?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) If you still have symptoms, do you feel pain while you are walking?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>d) If you still have symptoms, do you feel pain while you are resting, or have any major swelling?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>9. A history of an aneurysm (ballooning of a vein or artery)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, do you have any remaining symptoms?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>10. A history of stroke warning symptoms (TIA)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, did your stroke warning symptoms last longer than 24 hours?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) Did you have more than one episode of stroke warning symptoms?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) Did you have a history of stroke?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>d) Do you have mild balance problems or mild skin sensations (e.g. burning, prickling, itching, or tingling)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>e) Do you have paralysis on one side of your body, the lower half of your body, or your entire body?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>11. Alzheimer's disease or any other type of dementia?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>12. Lung disease like asthma, emphysema, chronic bronchitis, or chronic obstructive lung disease?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) If you take medication, do you have shortness of breath while you are doing strenuous activities?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) If you take medication, do you have shortness of breath while you are resting?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>13. Arthritis like rheumatoid arthritis or osteoarthritis?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>b) If you take medication, are your symptoms controlled while you are on medication?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>c) Did you have a hip or knee replacement in the last 3 months?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>Question</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>-------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>14. Diseases that affect the muscles or joints like lupus, polymyalgia, polymyositis, dermatomyositis, or scleroderma?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>15. Mild gastritis, diverticulitis, or mild irritable bowel syndrome?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>b) If you take medication, are your symptoms controlled while you are on medication?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>c) Has there been any bleeding, blockage, or inflammation?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>16. Ulcerative colitis?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>b) If you take medication, are your symptoms controlled while you are on medication?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>c) Do you have any bleeding, blockage, or inflammation?</td>
<td>μμ</td>
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<tr>
<td>17. A current diagnosis of an active peptic ulcer, gastric ulcer, or duodenal ulcer?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>b) If you take medication, are your symptoms controlled while you are on medication?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>c) Do you have any bleeding, blockage, or inflammation?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>18. A history of a peptic ulcer, gastric ulcer, or duodenal ulcer in the last year that disappeared on its own or due to treatment?</td>
<td>μμ</td>
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</tr>
<tr>
<td>19. Hiatus hernia with inflammation of the esophagus?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>a) IF YES, do you take medication for it?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>b) If you take medication, are your symptoms controlled while you are on medication?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>c) Do you have any bleeding, blockage, or inflammation?</td>
<td>μμ</td>
<td>μμ</td>
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<tr>
<td>20. Removal of a polyp in the last month?</td>
<td>μμ</td>
<td>μμ</td>
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<tr>
<td>21. A history of hepatitis that disappeared on its own or due to treatment?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>a) IF YES, did it happen in the last year?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>22. Chronic hepatitis?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>23. Cirrhosis?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>a) IF YES, do you have any symptoms due to cirrhosis?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
<tr>
<td>b) Do you have symptoms including increased pressure in your liver, swelling of your abdomen, or bleeding in your stomach or esophagus?</td>
<td>μμ</td>
<td>μμ</td>
</tr>
</tbody>
</table>
### Do you have…

<table>
<thead>
<tr>
<th>Number</th>
<th>Question</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.</td>
<td>Diabetes?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td></td>
<td>a) IF YES, do you take medication for it?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td></td>
<td>b) If you take medication, is your blood sugar higher than 16.5 mmol/L (300 mg/dL) while you are on medication?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td></td>
<td>c) Has it caused nerve damage or gangrene?</td>
<td>μ</td>
<td>μ</td>
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<tr>
<td>25.</td>
<td>A history of a urinary tract infection?</td>
<td>μ</td>
<td>μ</td>
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<tr>
<td></td>
<td>a) IF YES, did your symptoms disappear with treatment?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>26.</td>
<td>A history of nephritis (inflammation of kidneys) in the last 3 months that disappeared on its own or due to treatment?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>27.</td>
<td>A history of surgery to remove kidney stones or gallstones or high-intensity ultrasound to break kidney or gallstones in the last 6 months?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>28.</td>
<td>A current diagnosis of nephritis, kidney stones, or mild renal artery stenosis?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>29.</td>
<td>Kidney problems (e.g. high creatinine blood test), kidney failure, moderate/severe renal artery stenosis, dialysis, or kidney transplant?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>30.</td>
<td>A history of any tumour or cancer (not including leukemia, lymphoma, or Hodgkin’s disease)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td></td>
<td>a) IF YES, has it been more than 5 years since your last treatment?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td></td>
<td>b) Did the cancer spread to other parts of your body, such as bone?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>31.</td>
<td>A current diagnosis of any tumour or cancer (not including leukemia, lymphoma, or Hodgkin’s disease)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td></td>
<td>a) IF YES, have you had treatment within the last year?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td></td>
<td>b) Did the cancer spread to other parts of your body, such as bone?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>32.</td>
<td>Leukemia?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>33.</td>
<td>Lymphoma or Hodgkin's disease?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>34.</td>
<td>HIV-positive (human immunodeficiency virus)?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>35.</td>
<td>AIDS (acquired immune deficiency syndrome), or AIDS-related complex?</td>
<td>μ</td>
<td>μ</td>
</tr>
<tr>
<td>36.</td>
<td>Other (specify):</td>
<td>μ</td>
<td>μ</td>
</tr>
</tbody>
</table>

THANK YOU VERY MUCH FOR ANSWERING THESE QUESTIONS.
PLEASE GO TO THE NEXT QUESTIONNAIRE.
Physical Impairment Checklist

This questionnaire is to help us understand any physical problems you might currently be experiencing. Please check only ONE answer for each question.

1. Which of the following best describes your circulation (heart, blood vessels, etc)?
   - No problems or symptoms
   - Chest pain, dizziness, shortness of breath while walking, using pacemaker or walking with the help of another person
   - Heart failure or confined to bed

2. Which of the following best describes your respiration (lungs, breathing, etc)?
   - No problems or symptoms
   - Chronic cough, shortness of breath, only able to walk one block
   - Chronic obstructive pulmonary disease, chronic bronchitis, emphysema, using an oxygen tank or using a respirator

3. Which of the following best describes your nervous system (brain, spinal cord, nerves, etc)?
   - No problems or symptoms
   - Dizziness, numbness, fainting or controlled seizures
   - Balance problems, partial paralysis, uncontrolled seizures, confined to bed

4. Which of the following best describes your mental status?
   - No problems or symptoms
   - Occasional forgetfulness, mild depression, or irrational thinking
   - Long-term depression, confusion, or psychosis

5. Which of the following best describes your bladder?
   - No problems or symptoms
   - Difficulty in controlling your bladder (hesitant, dribbling)
   - Unable to control your bladder

6. Which of the following best describes your bowels?
   - No problems or symptoms
   - Pain with bowel movements, chronic diarrhea or constipation
   - Unable to control your bowels
7. Which of the following best describes your ability to feed yourself?

- No problems
- Difficulty chewing or swallowing (needs food to be cut)
- Unable to eat or feed yourself or need tube feeding

8. Which of the following best describes your ability to walk?

- No problems
- Walking with a cane, walker or with the help of another person
- Using a wheelchair
- Confined to bed

9. Which of the following best describes your ability to transfer yourself out of bed?

- No problems
- Difficulty transferring out of bed by yourself or need the help of another person to transfer out of bed
- Confined to bed

10. Which of the following best describes your ability to see?

- No problems or able to see while wearing glasses or contact lenses
- Slight blurring, difficulty reading or driving (even with glasses)
- Severe blurring, unable to read or drive (even with glasses)

11. Which of the following best describes your ability to hear?

- No problems or able to hear while wearing a hearing aid
- Hard of hearing or able to hear in only one ear (even with hearing aid)
- Deaf (even with hearing aid)

12. Which of the following best describes your ability to speak?

- No problems
- Slurring, minor speech problems, or using a device
- Major speech problems or unable to speak

THANK YOU VERY MUCH FOR ANSWERING THESE QUESTIONS. PLEASE GO TO THE NEXT QUESTIONNAIRE.
Health History Questionnaire

This questionnaire is to help us understand the factors leading to your diagnosis of hepatitis C and the impact of hepatitis C on your health. Please check only one answer for each question.

**Transmission**
The following section helps us understand how you were exposed to hepatitis C and what led to your diagnosis.

1. Have you ever received a blood transfusion?
   - Yes
   - No (skip to Q3)

2. In what **year** did you receive your **first** blood transfusion? __________
   (Enter exact year or the approximate year if necessary)

3. Have you ever in your life, even once (even if it was many years ago), used a needle to take non-prescription drugs (e.g. injected heroin)?
   - Yes
   - No (skip to Q5)

4. In what **year** did you **first** use a needle to take drugs? __________
   (Enter exact year or the approximate year if necessary)

5. Have you ever in your life, even once, (even if it was many years ago), snorted cocaine through your nose?
   - Yes
   - No (skip to Q7)

6. In what **year** did you **first** snort cocaine through your nose? __________
   (Enter exact year or the approximate year if necessary)

7. How many **times** do you recall having injected or snorted drugs in your lifetime?
   - Never (skip to Q13)
   - 1 time only
   - 2-5 times
   - 6-20 times
   - More than 20 times
8. Have you ever seen anyone such as a doctor, psychiatrist, social worker, or counselor for treatment or counseling regarding your drug use?
   µ Yes
   µ No

9. Thinking back to the time when you injected or snorted drugs, did you ever become **dependent** on the drugs and take them on a daily basis for at least 4 weeks?
   µ Yes
   µ No

10. What was the total amount of time in your life that you injected or snorted drugs on a daily basis?
    µ Less than a month
    µ 1 to 6 months
    µ 7 months to 2 years
    µ 2 to 5 years
    µ More than 5 years

11. Do you currently inject or snort drugs?
    µ Yes
    µ No (skip to Q13)

12. Please estimate how often you currently inject or snort drugs. (Check only **ONE** answer)
    µ Everyday
    µ A few times a week
    µ A few times a month
    µ A few times a year

13. Have you ever had a tattoo applied to your skin?
    µ Yes
    µ No (skip to Q15)

14. In what **year** did you **first** have a tattoo applied to your skin? __________

15. Have you ever injured yourself with a needle (punctured your skin)?
    µ Yes
    µ No (skip to Q17)

16. In what **year** did you **first** get injured with a needle? __________
17. Have you ever had sex with someone of the opposite sex?
   - Yes
   - No (skip to Q19)

18. Please estimate how many sexual partners of the opposite sex that you have had in your lifetime:
   - 1
   - 2-10
   - 11-50
   - More than 50

19. Have you ever had sex with someone of the same sex?
   - Yes
   - No (skip to Q21)

20. Please estimate how many sexual partners of the same sex that you have had in your lifetime:
   - 1
   - 2-10
   - 11-50
   - More than 50

21. Have you ever had a sexually transmitted disease like chlamydia, gonorrhea, genital Herpes, genital warts, syphilis, HIV/AIDS, etc?
   - Yes
   - No

22. When did you first find out that you have hepatitis C?
   Enter the month or approximate month _____ (01 for Jan, 12 for Dec)
   Enter the year or approximate year __________

23. How were you informed that you have hepatitis C?
   - I received a letter from the blood bank
   - I was told by my family doctor
   - I was told by a public health nurse
   - I was told by a gastrointestinal or liver specialist
   - Other (please write answer) ______________________________
24. What was the reason that you went for the blood test that showed you have hepatitis C?
- I went for blood donation
- I had a routine blood test which showed abnormal liver enzymes, so my doctor tested me for hepatitis C
- I was worried that I may have been exposed to hepatitis C, so I requested to be tested
- I was not feeling well and my physician ordered the test
- Other (please write answer) _______________________

25. How do you believe that you acquired Hepatitis C? (Check only ONE answer)
- From a blood transfusion
- From surgery
- Through sex
- Through birth
- From snorting cocaine
- From injecting non-prescription drugs
- From getting a tattoo
- From injuring yourself with a needle
- From body piercing
- From acupuncture
- Other (write in answer) _______________________
- Don’t know

**Alcohol**

The following questions attempt to measure your lifetime alcohol use.

1 standard drink = 12 ounces or one can of beer
   = 1.5 ounces liquor (such as rum, gin, vodka) or one drink with a shot of liquor
   = 5 ounces or one glass of wine
   = 3 ounces fortified wine (such as sherry, port)

26. In your lifetime, have you ever drunk alcoholic beverages on a regular basis of at least one alcoholic drink per week for three months in a row?
- Yes
- No (skip to Q33)

27. What age did you start drinking? _______
28. During the last year, how often did you drink alcohol on average?
   ______ days per week and ______ alcoholic drinks per day

29. Have you ever gone to anyone such as a doctor, psychiatrist, social worker, counselor or Alcoholics Anonymous for treatment or counseling regarding your alcohol use?
   µ Yes
   µ No

30. Have you ever been hospitalized because of your drinking?
   µ Yes
   µ No

31. Thinking back to the phase of your life when you were drinking regularly, did you ever become dependent on alcohol?
   µ Yes
   µ No (skip to Q33)

32. What was the total period in your life in which you were dependent on alcohol?
   µ Less than a month
   µ 1 to 6 months
   µ 6 months to 2 years
   µ More than 2 years

Mental Health
The following section reviews your mental health history including depression, anxiety, and mood.

33. Have you ever been seen at a psychiatric or mental health clinic or gone to a doctor or social worker for help with an emotional problem?
   µ Yes
   µ No

34. Have you ever been hospitalized in a psychiatric facility for emotional problems?
   µ Yes
   µ No

35. Have you ever been treated for an emotional problem such as anxiety or depression with prescription medicine (such as xanax, prozac, zoloft, valium, or other anti-depressants)?
   µ Yes
   µ No (skip to Q37)
36. What was the total duration of time you were on these medications?
   - Less than 1 month
   - 1 to 6 months
   - 6 months to 2 years
   - More than 2 years

**Physical Symptoms**
The following questions are about physical symptoms in patients with hepatitis C

37. Please indicate which of the following symptoms you have consistently had at least once a week for the past 4 weeks, and the severity (mild, moderate, or severe) that they have most frequently been:

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>a)</td>
<td>Fatigue</td>
<td>μ μ μ μ</td>
<td></td>
</tr>
<tr>
<td>b)</td>
<td>Abdominal pain</td>
<td>μ μ μ μ</td>
<td></td>
</tr>
<tr>
<td>c)</td>
<td>Muscle cramps</td>
<td>μ μ μ μ</td>
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<tr>
<td>d)</td>
<td>Itching</td>
<td>μ μ μ μ</td>
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<tr>
<td>e)</td>
<td>Joint pains</td>
<td>μ μ μ μ</td>
<td></td>
</tr>
<tr>
<td>f)</td>
<td>Weakness</td>
<td>μ μ μ μ</td>
<td></td>
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<tr>
<td>g)</td>
<td>Nausea</td>
<td>μ μ μ μ</td>
<td></td>
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<tr>
<td>h)</td>
<td>Poor appetite</td>
<td>μ μ μ μ</td>
<td></td>
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<tr>
<td>i)</td>
<td>Dark urine</td>
<td>μ μ μ μ</td>
<td></td>
</tr>
<tr>
<td>j)</td>
<td>Jaundice</td>
<td>μ μ μ μ</td>
<td></td>
</tr>
</tbody>
</table>

THANK YOU VERY MUCH FOR ANSWERING THESE QUESTIONS.