EXAMINING HEPATITIS C PATIENT CARE PATHWAYS AND SERVICES IN CANADA – RESULTS FROM A NATIONAL SPECIALISTS' SURVEY

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EXAMINING HEPATITIS C PATIENT CARE PATHWAYS AND SERVICES IN CANADA – RESULTS FROM A NATIONAL SPECIALISTS' SURVEY

by

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A thesis submitted to the

School of Graduate Studies

in partial fulfillment of the

requirements for the degree of

Master of Science in Medicine

Division of Community Health and Humanities
Faculty of Medicine
Memorial University of Newfoundland and Labrador

May 2008

St. John's Newfoundland

ABSTRACT

Background and Aims: This study was designed to examine management practices of Canadian physicians trained in the specialties of infectious diseases, gastroenterology and hepatology in order to increase understanding of how people living with the Hepatitis C Virus (HCV) receive treatment across Canada. Approximately 170-175 million people worldwide are infected with HCV and the current prevalence of HCV in Canada is approximately 0.8%. It is known that treatment outcome and hence management strategies differ based on factors such as genotype and viral load, liver histology, body weight, co-infection with HIV and adherence. Canadian hepatologists have varied perspectives towards treating HCV patients [1]. The purpose of the study was to examine health care services provided to HCV patients by HCV health care providers (infectious disease specialists, hepatologists, gastroenterologists) and to see if there is variation in treating HCV in Canada. It is hypothesized that regional variation in treatment exists because of unequal access to care across Canada and that staffing capacity will be a major barrier to care.

Methods: A nationwide anonymous postal survey was conducted to determine if treatment varies by geographical location. HCV health care providers were identified through the Canadian Medical Directory [2]. A cover letter outlining study objectives and a questionnaire were sent to all eligible HCV health care providers. The survey requested information regarding health care provider demographics, referral pathways, treatment

eligibility, pattern of drug prescribing, barriers to providing high quality service, and the role of physicians in providing treatment.

Results: A structured questionnaire was sent to 562 physicians and 222 returned completed questionnaires with an adjusted response rate of 42%. Forty-three percent of respondents provided a comprehensive service (included treatment and follow-up), 33 % provided a diagnostic and investigative service (followed by referral to dedicated HCV service), and 24 % had no role in the management and diagnosis of people with HCV. The estimated number of patients managed by the total number of comprehensive service providers was over 27,000 with an increasing trend over the previous years. Regional variation was observed between comprehensive care providers across Canada, including the size of practice community, number of patients, and type of service provided. The majority of comprehensive service providers indicated that they would not provide treatment to a current injection drug user; the provinces most likely to provide treatment were Alberta and Nova Scotia. Key barriers to quality of care identified by the majority of comprehensive service providers were funding for treatment and patient non-attendance.

Conclusions: Survey respondents revealed that there are regional variations across Canada at many levels of the patient pathway, which could contribute to inequalities in health care services provided to patients with HCV. The results provide a baseline assessment of the overall HCV services across Canada. Services involving a

multidisciplinary clinic setting need to be expanded and regional networks should be formed in order to allow for a more comprehensive approach to the identification of HCV patients and health care delivery of HCV antiviral therapy.

ACKNOWLEDGEMENTS

I wish to thank the many individuals who have helped in the preparation of this thesis. I appreciate the interest shown by the physicians who took the time to complete the questionnaires. Without their responses my study would not have prevailed.

The financial support of the Atlantic Interdisciplinary Research Network and the National Canadian Research Training Program in Hepatitis C, which enabled me to conduct my research, is gratefully acknowledged. Moreover, the guidance and encouragment that I have received from both organisations over the past few years has been immensely appreciated.

It has been a pleasure to be associated with the faculty, staff, and graduate students of the Division of Community Health and Humanities. Their friendship and advice were invaluable. Thank you to Dr. Peter Wang, Dr. Gerry Mugford and Dr. Murray Krahn for serving on my supervisory committee and providing encouragment and sound advice over the years.

My sincere thanks go to my co-supervisors, Dr. Peter Wang and Dr. Gerry Mugford, for their excellent teachings and assistance as well as their confidence in my work. It was an enjoyment working with them and getting to know them throughout my Masters program.

Finally, I would like to thank my parents and brother and sisters for their unrelenting support and encouragement.

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LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
CMD	Canadian Medical Directory
CSP	Comprehensive Service Provider
DIP	Diagnostic Investigative Provider
DNA	Deoxyribonucleic Acid
DOT	Directly Observed Therapy
EVR	Early Virological Response
GI	Gastroenterologist
GP	General Practitioner
HAART	Highly Active Antiretroviral Therapy
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HIC	Human Investigation Committee
HIV	Human Immunodeficiency Virus
ID	Infectious disease specialist
IDUs	Injection Drug Users
IFN	Interferon
PCR	Polymerase Chain Reaction

PEG	Pegylated
PVR	Partial Virological Response
QoL	Quality of life
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic Acid
RVR	Rapid Virological Response
SVR	Sustained Virological Response
TCPS	Tri-Council Policy Statement
TMA	Transcription Mediated Amplification

CHAPTER 1: INTRODUCTION

1.1 Description of the Problem

The treatment of patients with Hepatitis C in Canada is a population health issue and is therefore of utmost importance to all Canadians. Successful treatment of Hepatitis C will greatly decrease the general population's risk of acquiring the infection. Furthermore, untreated patients can pose a threat to general public health.

It is estimated that approximately 175 million people worldwide are infected with the Hepatitis C virus (HCV) [3]. In Canada, HCV is associated with excess mortality and infected individuals are more likely to have a reduced quality of life (QoL) [4]. The estimated prevalence of HCV in Canada is 0.8% to 1%, which continues to be a dire economic and medical burden to Canadians [5]. In industrialised countries injection drug use is the leading risk factor for HCV infection [6]. Even though there is universal screening of the blood supply (eliminating this source of new cases of HCV infection), there are still over 4,500 new infections per year [5]. The risk of transmission is associated with sharing injection equipment such as needles and syringes as well as spoons, cottons and other injection paraphernalia [7]. In Canada, we do not have a sense of how each province is providing HCV treatment to patients. In order to develop comprehensive strategies to address the HCV epidemic, it is vital to understand physician factors associated with HCV-related practice patterns. Thus, an inaugural nationwide survey was conducted to examine management practices of physicians trained in the specialties of infectious diseases, gastroenterology and hepatology.

1.2 Purpose of the Study

The present study has been undertaken to examine the pathways and services provided by HCV health care providers in the ten provinces of Canada[1] and the barriers that HCV health care providers might encounter while providing HCV treatment to patients.

1.3 Research Question

I propose to assess HCV health care providers' (hepatologists, gastroenterologists and infectious disease specialists) clinical practice patterns and how people living with HCV are managed in the health care system (i.e. referral patterns, diagnosis and treatment). It is hypothesized that regional variation in treatment exists because of unequal access to care across Canada and that staffing capacity will be a major barrier to care.

1.4 Rationale

The aim of the above research is to examine the HCV management and treatment employed by physicians throughout Canada and determine if there is geographical variation in treating HCV patients. Early treatment of HCV is essential to impede the progression of liver disease and the study will evaluate practices and understanding of physicians who treat HCV patients. Results derived from this study will be able to identify regional variations in HCV practice, which has implications for improving HCV care. A national survey of current practices and service design needs to be conducted in

[1] The Northwest Territories, Yukon, and Nunavut were excluded from the study

order to establish baseline information to plan future services for people living with HCV.

In order to assess the geographical variation of HCV treatment in Canada, there is a need for a systematic approach to the identification, testing, referral, selection for treatment and follow-up of HCV positive patients.

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

2.1 Hepatitis C Overview

Hepatitis C Virus was identified in 1989 as 'non A, non B' hepatitis and is the most prevalent of the recognized hepatitis viruses in Canada and the United States [8]. There are a total of six viruses (A, B, C, D, E, and G) that account for the majority of viral hepatitis [9]. HCV belongs to the flaviviridae family and is a single-stranded ribonucleic acid (RNA) virus [10]. HCV has a narrow host range and only infects humans and chimpanzees.

HCV viral RNA and monostructural proteins have been found in the liver of infected patients as well as in experimentally inoculated chimpazees, confirming that the liver is the site of HCV replication [12]. There is also strong evidence that HCV can replicate in peripheral mononuclear cells, both *in vivo* or in experimentally infected B- and T-cell lines [12]. The HCV replication cycle is based primarily on analogies, due to the lack of a convenient animal model [12]. A hypothetical model of HCV replication can be summarized as follows (refer to Figure 1): (1) penetration of the host cell and liberation of the genomic RNA from the virus particle into the cytoplasm; (2) translation of the input RNA, processing of the polyprotein and formation of a replicase complex associated with intracellular membranes; (3) utilization of the input plus-strand for synthesis of a minus-strand RNA intermediate; (4) production of new plus-strand RNA molecules which in turn can be used for synthesis of new minus strands, polyprotien expression or packaging into progeny virions; (5) release of virus from the infected cell.

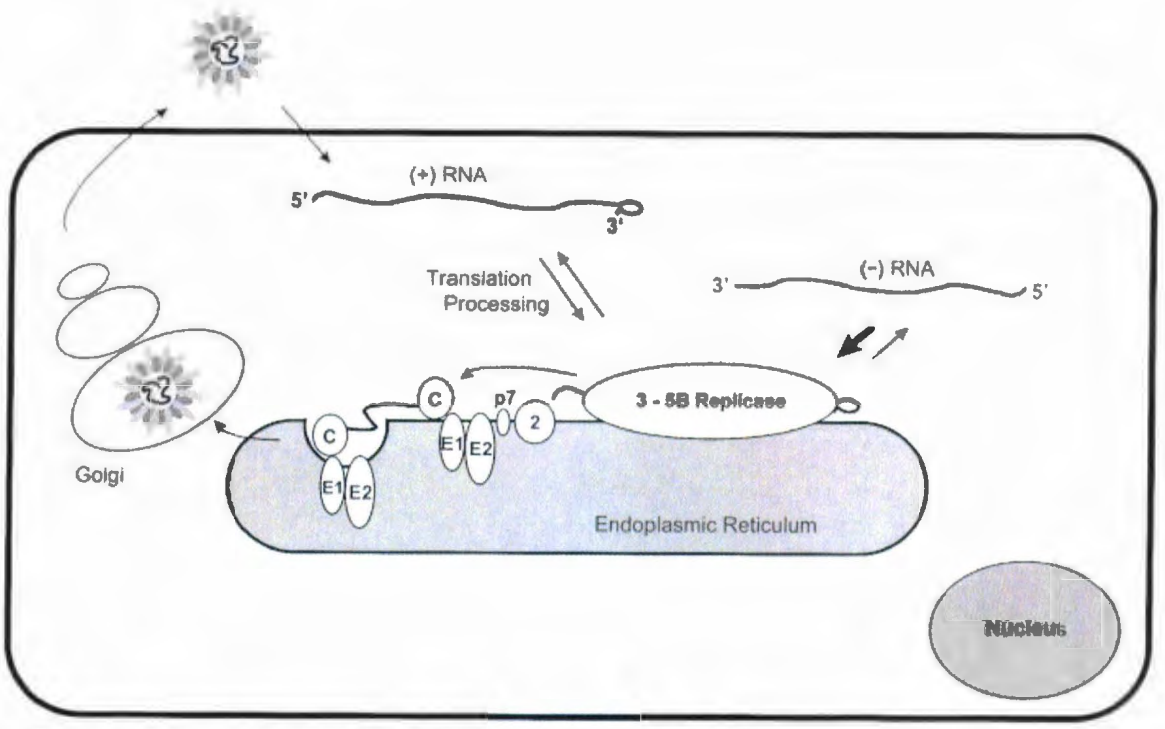

Figure 1: Hypothetical model of the HCV replication cycle [12]

There is a high mutation rate in HCV that allows for a noticeable amount of genetic heterogeneity in the genome. Consequently, there are 6 major HCV genotypes (with over 50 subtypes), with genotype 1 being the most widespread, followed by gentoypes 2 and 3, found in approximately 10%-20% of HCV patients in North America [11]. A genotype is the genetic make up of a cell, individual, or organism. The genotypes identified differ in viral pathogenicity, reponse to treatment, and overall prognosis [9].

The quasispecies nature of HCV has been proposed as a mechanism of viral persistence [13]. Viral quasispecies refers to closely related (but not identical) mutant and recombinant viral genomes subjected to continuous genetic variation, competition and selection [14]. "Quasi" means resembling each other, and a quasispecies is created when RNA polymerase makes a mistake during HCV reproduction. These mistakes can create mutations, some of which are able to survive and therefore form HCV microvariants. The

production of variants is primarily due to the high error rate of the viral RNA-dependent RNA polymerase (RdRp), which is expected to be in the range of 10^{-4} [12]. Errors are randomly introduced into the genome by the RdRp and because of the lack of proofreading function in these enzymes, errors remain uncorrected [10]. The quasispecies of HCV is suggested to be the mechanism by which HCV evades the control of the humoral and cellular immune responses, allowing for a persistent infection to prevail [13].

HCV is transmitted through contact with blood and blood products [15]. Presently, the primary cause of transmission is injection drug use, which accounts for roughly 60% of new and existing cases [16-18]. In addition, other modes of HCV transmission can occur through methods such as needle-stick injuries, blood transfusion, body piercing, tattooing, higher risk sexual behaviour, and maternal-infant spread [19, 20]. Moreover, HCV is often incorrectly perceived as dangerous and contagious to the community and is also falsely classified as a sexually transmitted disease[2] [21, 22].

The primary risk factors are well known, and they include blood transfusion before 1992, intravenous or intra-nasal drug use, and imprisonment (due to its reationship with drug use) [15, 23]. HCV is notably more infective than HIV following a needle-stick injury (3% compared to 0.3%) [9]. In addition, it can take up to 6 months for seroconversion to occur in HCV; therefore, rigorous follow-up must be in place for patients at risk of contracting the virus. [9]. The disease can remain asymptomatic for many years. However, cirrhosis can develop unobtrusively in 20%-30% of chronically

[2] It should be noted that HCV is associated with higher-risk sexual behaviour (i.e. multiple partners, if partner is HIVcoinfected or exposure to blood during intercourse through trauma, mucosal tears etc.).

infected individuals over a period of 20-30 years [8, 24]. HCV-related cirrhosis has become the leading cause for liver transplantation in North America [11]. At present, there are no effective vaccines available for HCV [11].

2.1.2 Background of Therapy for Hepatitis C

The initial selection of interferon alfa (IFN-α) as a possible treatment for chronic HCV was empirical. The agent behind 'non-A, non-B' hepatitis had yet to be confirmed, and specific drugs could not be designed because nothing was known about the virus' virological characteristics [25]. The following sections chronicle HCV treatment discoveries over the years, from monotherapy with IFN to specific HCV inhibitors.

2.1.2.1 From Monotherapy to Combination

The main objective for treatment is to annihilate the virus and prevent any complications from chronic HCV infection. The current treatment and standard of care for HCV is a combination of peginterferon and ribavirin [15]. In 1986, IFN-α demonstrated beneficial effects in patients with HCV before the virus was even identified [26]. IFNs are a class of cytokines produced by white blood cells that regulate the immune system and are involved in host defense [27]. Treatment with IFN-α subsequently led to a decline in HCV RNA, and successful responses were observed when HCV RNA was no longer detectable by currently available assays and chronic infection had been resolved [28]. IFN-α has antiviral activity but does not directly target the virus or any specific part of its replication cycle. IFN-α acts by inducing IFN-stimulated genes that are able to form a non-virus specific state within the cell [29, 30]. Nevertheless, monotherapy with IFN-α did not have a high sustained virological response (SVR) rate. An SVR occurs when a patient has a negative HCV viral load test 6 months after the completion of HCV therapy. This response determines whether

treatment has been effective at clearing HCV. A 6-month course of therapy led to a sustained response of 6-12%, and a 12-month course raised the rate to only 16-20% [31].

2.1.2.2 The Addition of Ribavirin

Ribavirin was the first drug to be offered as an oral treatment for HCV [32]. Ribavirin was created in 1970 as a guanasine analogue but was also observed to possess characterisitics that act upon RNA and DNA viruses [33]. It should be mentioned that the exact mechanism that ribavirin uses to increase the response rate in combination with IFN-α remains unknown [25, 33, 34]. It is thought that ribavirin acts on the production of viral deoxyribonucleic acid (DNA) and RNA, thus interfering with the replication and the survival of the virus [35]

In the early 1990s, HCV monotherapy with ribavirin demonstrated improvements in serum aminotransferase levels in 50% of patients. However, viral load did not decrease and patients did not clear HCV, even after prolonged treatment [36, 37]. Alanine aminotransferase levels (ALT) decreased in all patients taking ribavirin. However, once treatment terminated they increased to pretreatment concentrations [32].When the antiviral agent ribavirin was combined with IFN-α, treatment was improved and the sustained response rate doubled to 35-40% [25, 38]. Ribivirin was then approved for therapy to treat chronic HCV patients but only in combination with IFN-α. The treatment regimen consisted of IFN-α three times per week and a daily dose of ribavirin. In 1999, the European Association for the Study of the Liver Consensus Conference approved ribavirin and IFN-α combination therapy as the standard treatment for HCV [39]

2.1.2.3 The Development of PEG-IFN-alpha

Another major advancement was the creation of pegylated interferon (PEG-IFN). PEG-IFN was developed by attaching poly(ethylene glycol) to recombinant IFN-α, which led to a molecule with a longer half-life and a better rate of virological response [40-42]. The formation of PEG-IFN-α enabled treatment to be given once a week as opposed to three times, thus allowing for better adherence to treatment. There are two different forms of PEG-IFN available: PEG IFN-alpha-2a[3] and PEG-IFN-alpha-2b[4]. The size of the polyethylene glycol molecules bound to the IFN molecule is what distinguishes the two forms from each other. Although the two forms have not been specifically evaluated to compare their effectiveness, they appear to obtain equivalent responses to therapy [4].

When PEG-IFN and ribavirin were given in combination the sustained response was increased to 54-56% [43, 44]. This can be seen as a major improvement. Nevertheless, these response rates have only been examined on selected populations and rarely do they include patients with co-morbidities and co-infections [45]. In 2002, the National Insitutes of Health Consensus Developement Conference changed the standard of treatment for HCV to PEG-IFN-α combined with ribavirin.

2.1.2.4 The Future of Therapy

Through the unveiling of the 3D structure of HCV, it is now possible to examine various functional viral elements (i.e. HCV proteins and genome structures). This discovery has made it possible to target specific elements of HCV in order to screen and

[3] PEG IFN-alpha-2a is developed by Hoffmann-La Roche and is called Pegasys
[4] PEG-IFN-alpha-2b is developed by Schering-Plough and is called Pegetron.

develop specific small inhibitory molecules [46]. Thus, it is imaginable that specific inhibitors could be targeted for all steps of the HCV life cycle [25]. Current targets consist of the HCV internal ribosome entry site (the RNA structure that initiates HCV polyprotein translation), HCV NS3 proteinase (the enzyme that ensures polyprotein processing downstream of the NS3-NS4 junction), and HCV RNA-dependent RNA polymerase (the enzyme that catalyzes HCV replication) [25].

There are many small molecule inhibitors currently being evaluated which directly target HCV replication and have been shown to interfere with the ability of HCV to evade IFN. For instance, VX-950 specifically acts upon the NS3-4A protease of HCV and has antiviral activity in vitro. In a study conducted by Reesink et al. [47] it was demonstrated that after 14 days of treatment with VX-950 all patients had at least a 2-$\log_{10}$ decrease from baseline HCV RNA and two patients achieved undetectable levels. More notably, VX-950 was able to reduce viral load in a population of patients, 79% of which were previously non-responders to interferon based regimens [47].

The main cause of treatment failure when using specific inhibitors to target viruses, apart from non adherence to therapy, has been viral resistance [25]. Consequently, it is forseeable that viral resistance will occur if the small molecule inhibitors are used alone rather than in combination. There are a number of ways to evade viral resistance, such as reducing virus production by using highly potent antiviral molecules and using a combination of drugs with different viral targets [48].

2.1.3 Hepatitis C Therapy Side Effects

Patients undergoing HCV therapy need to be closely monitored because the side effects associated with PEG-IFN and ribavirin therapy can be severe and life-threatening [4]. The adverse effects can affect a patient's ability to remain on treatment, lower their chances of attaining viral clearance and lessen their health-related quality of life [25]. Treatment is discontinued in 20-40% of patients due to severe dose-dependent side effects. In some cases doses are reduced, which effectively decreases the chance of achieving an SVR [49]. Monitoring side effects is paramount because it can help to avoid unnecessary treatment morbidity in patients who react poorly to therapy [50].

There are many medical contraindications for treatment with PEG-IFN and ribavirin (refer to Table 1). Ribavirin is teratogenic[5] in males and females and therefore contraception is advised during therapy and up to 6 months after therapy [51]. Other complications with combination treatment include hepatic decompensation in patients with cirrhosis and renal failure [52]. The two most common side-effects associated with ribavirin are hemolysis and anemia [52]. PEG-IFN side effects are linked to fatigue, muscle aches and psychological disorders such as depression, irritability, anxiety and sleep disturbance [52]. Moreover, interferon can also initiate pancytopenia, a reduction in red and white blood cells as well as platelets [44, 53]. Autoimmune thyroiditis has been observed to be the most common autoimmune reaction to therapy [53, 54].

More serious side-effects include mood changes and depression [41, 43, 44, 53]. If the symptoms are mild, they can be addressed by administering selective serotonin

[5] Able to disturb the development of an embryo or fetus

reuptake inhibitors [55]. Conversely, treatment must be discontinued if more severe depression or suicidal tendencies develop. Irregular side-effects include hair thinning and loss, hearing impairment, insomnia, visual disorders, interstitial pneumonia, pancreatitis, and colitis [53, 56].

Table 1: Common side effects of hepatitis C treatment

Pegylated-Interferon	**Ribavirin**
Flu-like symptoms -fever -chills -muscle and joint aches -nausea and loss of appetite Reduction in red and white blood cells Hair loss Depression	Anemia Hemolysis Birth defects Cough Shortness of breath Rash Insomnia

A study was recently conducted by Dan, Crone et al. [57] that assessed anger as a neuropsychiatric side effect of INF-α therapy. Results found that HCV patients demonstrated less control over their anger while taking IFN-α treatment, and angry reaction scores altered over the course of therapy [57]. The study observed a link between anger and depression, thus emphasizing the importance of monitoring patients receiving IFN-α treatment [57].The study also showed that there was an association between anger resulting from the treatment and a negative effect on patients' health-related quality of life [57]. This study illustrated the need to assess proactive treatment of these neuropsychiatric side-effects in order to examine whether or not intervention will affect a patient's adherence to treatment and improve their well-being.

2.1.4 Responses and Strategies of Treatment

A liver biopsy is able to measure the extent of disease most effectively and is the only way to stage HCV accurately [58]. However, the practice of obtaining a liver biopsy is currently being debated [59]. General recommendations indicate that a biopsy should be performed regardless of ALT levels because ALT is not a good predictor of hepatic fibrosis when the results will influence whether or not treatment is recommended, however, it is not essential to initiate treatment [59]. Nevertheless, the liver biopsy can be seen as a barrier to treatment for a number of patients [25]. Due to the fact that 75%-90% of patients with genotype 2 or 3 will clear the virus with treatment [43, 44], in 2002 the National Institutes of Health recommended that, in the absence of any contraindications, patients with genotype 2 or 3 do not have to undergo a liver biopsy and should begin treatment with PEG-IFN and ribavirin [60]. Six responses to therapy have been observed and defined:

(1) Rapid virological response (RVR)
(2) Early virological response (EVR)
(3) Partial virological response (PVR)
(4) Sustained virological response (SVR)
(5) Relapse
(6) Non-response

An *RVR* represents a vital part of the treatment phase because it helps determine the duration of treatment and is the best predictor of achieving an SVR [4]. An RVR occurs when HCV RNA is tested at week 4 and is undetectable. Therapy can then be shortened to 24 weeks for patients with genotype 1 and 12-16 weeks for patients with genotypes 2 and 3 [4]. An *EVR* occurs when there is non-detectable HCV RNA at week 12 of therapy [59]. A *PVR* occurs when a 2 log drop in HCV RNA is observed at week

12, however, HCV RNA is still detectable [59]. An *SVR* refers to no detectable hepatitis C ribonucleic acid 6 months after completion of therapy and represents the goal of therapy [59]. One major factor that decreases a patient's chance of obtaining an SVR is advanced fibrosis or cirrhosis [61, 62]. A *relapse response* occurs when viremia disappears and transaminases normalize but relapse within 6 months of the end of treatment [33]. A relapse response happens in 10-25% of patients and the cause is not well understood but could be related to inadequate or absent doses of ribavirin [33]. It is possible to achieve an SVR in patients who have relapsed. However, this usually occurs using a longer course of treatment or higher doses [63]. *Non-response* occurs in approximately one-third of patients with chronic HCV and these patients never become HCV RNA negative[33].

Treatment strategies differ based on viral factors such as genotype, baseline viral loads, quasispecisies diversity and acute versus chronic infection. Host factors include sex, race, age, stage of fibrosis, body weight, body mass index, and co-morbidities [33]. The current treatment regime includes a combination of PEG-IFN and ribavirin for 24 or 48 weeks [31]. Viral genotype is the major predictor of SVR rates [50]. Genotype 1 has an SVR range from 42% to 46%, whereas SVR rates for gentoypes 2 and 3 range from 76-80% [33, 43, 44]. In addition, a low baseline viral level has been observed to have improved rates of achieving an SVR [44]. Furthermore, HCV response rates have been seen to differ in terms of ethnic groups. For example African Americans infected with HCV have a reduced chance of achieving SVR [64]. The basis for this observation currently remains unknown.

2.1.5 Hepatitis C Diagnostic Tests

Diagnostic tests are essential to determine the course of HCV treatment. The common approach is to first test for HCV antibodies (anti-HCV) and then to use HCV RNA to confirm viremia [59]. A qualitative test is used to determine a positive or negative results; another quantitative test gives the viral load. It is very important to be consistent when using these assays because there is considerable inter-assay and intra-assay variation with HCV RNA testing [65]. The qualitative test can detect HCV RNA in the blood using techniques such as polymerase chain reaction (PCR) or transcription-mediated amplification (TMA). The quantitative test uses target amplification (PCR, TMA) or signal amplification techniques to determine the amount of HCV RNA in the blood [59].

Quantitative HCV RNA tests have allowed physicians to evaluate the prognosis of HCV therapy and identify patients who are nonresponders early on, as well as patients who will conceivably achieve an SVR [59]. Moreover, HCV RNA tests can be used to identify acute infection because HCV RNA can be detected 1-2 weeks after exposure, while antibodies are usually detected 8 weeks after exposure [66, 67]. Furthermore, HCV RNA testing can be implemented when a patient receives a negative anti-HCV test and they have already established conditions associated with a diminished antibody production such as HIV infection [68]. This situation occurs when a person fails to mount the appropriate host immune response due to immunodeficiency, which leads to a false negative anti-HCV. Consequently, the HCV RNA test must be used to confirm infection.

Patients who test positive for HCV antibody are usually then offered additional tests to confirm the results. The presence of circulating virus is commonly confirmed by viral load measurements and HCV polymerase chain reaction. A qualitative HCV RNA test at week 4 is used to determine whether or not a RVR has been achieved. A week 12 quantitative HCV RNA test is used to assess EVR, which is at least a 2-log drop in HCV RNA concentration from baseline. The Canadian guidelines state that this rule does not need to be applied rigorously because there is an inherent variability of 0.5 logs in the HCV RNA assays. Therefore, the guidelines accept a 1.8 log decline in HCV RNA concentration from baseline, which represents an EVR [50]. If a negative sensitive RNA test is obtained in a person who tested positive for HCV antibodies, it is most likely that HCV infection has been resolved. This occurs when previous chronic HCV infection is either resolved spontaneously or is treatment-induced [59].

The week 12 test is performed on patients with genotype 1, and failure to achieve an EVR initiates treatment withdrawal. It is now common practice to omit the week 12 assessment of an EVR for genotypes 2 and 3 because almost all patients achieve one [50]. The Canadian guidelines also recommend a week 24 qualitative HCV RNA test for patients who achieved a PVR. If HCV RNA is detected at this time, treatment should be stopped at week 24 [50].

2.1.6 Dose and Duration of Treatment

As mentioned above, the current treatment for HCV is a combination of PEG IFN alpha (2a or 2b) and ribavirin. There are six major genotypes [69] which can effectively predict the chance of responding to treatment and help determine the duration of

treatment [43, 44]. For instance, 48 weeks of therapy is given for genotypes 1,4,5 and 6. The treatment regimens are as follows: a weekly injection of 180 µg of PEG-IFN-alpha 2a or 1.5 µg/kg of PEG-IFN-alpha 2b [4]. Ribavirin is given in a dose of 800mg/day for patients with genotypes 2 and 3 and is dosed according to body weight for genotype 1. The medication is taken orally in two divided doses. If an EVR has not been achieved after 24 weeks, treatment is stopped because the chance of achieving an SVR is minimal. Furthermore, genotypes 2 and 3 only require 24 weeks of therapy [4]. Recently it has been suggested that a shorter duration of treatment (12 weeks) might be permitted for some patients infected with genotype 2 or 3 [70]. This alteration in treatment regimen has great implications for decreasing the prevalence of the disease because it could allow for more people to be willing to undergo HCV therapy.

Adverse side-effects can lead to dose reduction. The most common reasons for dose reduction of ribavirin and PEG-IFN- α include neutropenia, thrombocytopenia and anemia [44, 53]. The main drawback of reducing the dosage of medication is that it could jeopordize the antiviral therapy outcome, thus having a negative effect on viral eradication [34].

2.1.7 Acute and Chronic Hepatitis C

Acute HCV is an interesting occurence in the progression of HCV. Most cases are asymptomatic and rarely diagnosed. This stage can go unnoticed and is usually observed only under specific circumstances, such as when there is documented seroconversion and a known exposure [4]. It is very difficult to conduct studies on patients with acute HCV-infection because most of them do not develop symptoms, and therefore do not seek

medical attention and cannot be traced in medical records [59]. Furthermore, the HCV acutely infected patients that do have symptoms will most likely spontaneously clear the virus [66]. In general, high rates of spontaneous clearance have been observed following acute symptomatic infection [71]. Patients with acute HCV have a high rate of response to antiviral therapy and many become HCV RNA negative regardless of their viral load or genotype [72]. Thus, it can be suggested that non-response to therapy is acquired during chronic infection [33]. It is recommended that treatment for symptomatic acute HCV be delayed for the first 12 weeks, to allow for spontaneous clearance to occur and to avoid any unnecessary treatment [59]. However, treatment for asymptomatic acute HCV-infected patients should be started as soon as possible [59].

Testing for chronic HCV infection should be conducted on patients who have any risk factors for coming into contact with the virus. Risk factors include past or current injection drug use, blood transfusion before 1991, and immigration from countries of high prevalence [73, 74]. Patients with chronic HCV should be assessed on an individual basis to determine whether or not therapy should be offered. Many factors need to be taken into consideration before treatment is initiated. These factors include risk of disease progression to end stage, risk of adverse effects with therapy, and comorbid conditions. As well, other medical conditions need to be examined, such as history of past or current psychiatric disease, seizures, cardiac or renal disease, autoimmune disease, and alcohol or drug addiction [4]. Approximately 20% of chronically infected patients will develop cirrhosis over the next 20 years following acute infection, and roughly 3-5% of these patients will develop hepatocellular carcinoma (HCC) [34].

2.1.8 Characteristics of Hepatitis C Patients

The prognosis of chronic HCV is not well defined and varies on a case by case basis. Nevertheless, a number of patients will eventually develop cirrhosis and HCC [65]. The lifetime risk of cirrhosis in HCV carriers is estimated to be between 20-50%, with factors such as alcohol consumption identified as increasing the risk [34, 65].

As mentioned previously, the primary risk factor for HCV is injection drug use and studies have shown that exposure to HCV occurs in approximately 90% of injection drug users (IDUs) [75]. Despite this high prevalence rate, very few IDUs with HCV have actually been treated with interferon-based antiviral therapy [76, 77] and prior to 2002 current IDUs were not typically considered for treatment [78]. This was due to the fact that in 1997 the National Insitutes of Health (NIH) revealed in a consensus statement on the management of HCV that IDUs should have a period of illicit drug use abstinence for 6 months prior to HCV treatment[6] [79]. It should also be mentioned that the incidence of HCV infection is also high in non-injection drug users compared to the general population, due to the sharing of non-injection equipment such as, pipes and straws [34].

The majority of HCV patients often have high rates of comorbidity which can include psychiatric illness, alcoholism and psychosocial instability [18, 34, 80]. Studies have demonstrated that many HCV patients have also concurrent diagnoses of mental health disorders such as depression, post-traumatic stress disorder, psychosis or anxiety [81-83]. HCV patients are more likely to have these co-occuring illnesses when

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[6] The NIH Consensus Statement: March 24-26, 1997 stated "treatment of patients who are drinking significant amounts of alcohol or who are actively using illicit drugs should be delayed until these habits are discontinued for at least 6 months."79. *National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 1997--March 24-26, 1997* 1997 [cited October 2nd 2007]; Available from: http: consensus.nih.gov 1997 1997HepatitisC105html.htm.

compared to the overall population. This can be seen as a major barrier to providing HCV treatment [80]. HCV patients should undergo psychiatric screening and counselling before commencing HCV therapy [80]. The Beck Depression Inventory is a screening tool used to monitor patients for depression and has been shown to perform the best in this type of analysis.

In addition, many people living with HCV are coping with social issues such as homelessness, lack of support and high mobility [4]. Subsequently, many of these "typical" patients were considered unsuitable for treatment because of concerns with adherence and stability and have been omitted from clinical trials. This omission is unjustifiable and studies have shown that only a mere 10% of HCV IDUs who are eligible for treatment actually receive therapy [4, 76]. Furthermore, successful treatment of HCV in IDUs may greatly decrease the general population's risk of acquiring the infection [84]. In 2002[7] the NIH declared that eligibility for HCV treatment should be determined on a case-by-case basis [60]. Consequently, there should be an individualised approach to delivering HCV therapy to patients. For instance, the decision to treat should be based on patient willingness to commence treatment, social conditions which can affect a patient's stability and other medical comorbidities that may hinder treatment [85].

[7] The National Institutes of Health Consensus Statement: June 10-12, 2002 stated "many patients with chronic hepatitis C have been ineligible for trials because of injection drug use, significant alcohol use, age, and a number of comorbid medical and neuropsychiatric conditions. Efforts should be made to increase the availability of the best current treatments to these patients." Moreover, "it is recommended that treatment of active injection drug use be considered on a case-by-case basis, and that active injection drug use in and of itself not be used to exclude such patients from antiviral therapy." 60. *National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002.* Hepatology, 2002. **36**(5 Suppl 1): p. S3-20.

Furthermore, it is suggested that adherence to antiviral therapy will be increased if patients are enrolled in interdisciplinary programs where there is collaboration between a hepatologist and an addictions counsellor in addition to stringent patient follow-up by a multidisciplinary team [86]. Regardless of whether or not a patient is an IDU or a non-IDU a shared-care model offers a broader scope of care and is essential to improve the delivery of HCV treatment. The shared-care model involves a coordinated care team consisting of a hepatologist, family physcian, nurse specialist, and psychiatrist [87, 88].

2.1.9 Hepatitis C in Injection Drug Users

There is no guideline as to how to manage and treat HCV "real world"[8] patient who is addicted to drugs and also coping with other complex medical conditions. These patients "may have poor adherence to health care regimens, high rates of comorbid psychiatric illness, psychosocial instability, and poor health literacy" [89]. HCV-related service needs are not uniformly addressed because clinics and community health centres do not have a set national guideline for the treatment of HCV individuals who have multiple morbidities. This is a serious gap in care, which needs to be examined more thoroughly.

Numerous studies have revealed that IDUs have had simliar compliance and treatment response rates compared to non-IDUs [84, 86, 87, 90-92]. For instance, Jeffrey, MacQuillan et al [87] revealed an SVR rate of 62% among 50 HCV patients undergoing opiate detoxification, which is comparable to large controlled clinical trails of pegylated

[8] An HCV real world patient tends to have advanced liver disease, lengthy disease exposure, continuing drug use and is affected by psychosocial issues, such as housing, conditions, legal services, psychiatric disorders, and addictions.

PEG-IFN-α and ribavirin where the SVR rate was 54% and 63% [43, 44]. This study provided naltrexone implants for opiate dependency treatment. Naltrexone is a long acting opiate antagonist that is non-addictive and produces no euphoria [93]. Despite the fact that methadone maintenance treatment is more commonly used than naltrexone it does not prevent people from using illicit drugs even years after starting the therapy [87].

These studies indicate that a rigid pretreatment abstinence duration should not be enforced. This will allow for willing and motivated HCV patients to receive therapy before achieving the designated 6 months sobriety, as long as they are supported by clinical and social support resources [92]. Moreover, it has also been demonstrated that patients who do not completely abstain from alcohol can also be successfully treated [94]. In addition, methadone maintenance clinics offer an excellent resource to screen for HCV, thus identifying new patients for HCV therapy [80]. Consequently, the future of HCV treatment must recognize the "typical" patient and allow for treatment to be provided regardless of current or former injection drug use.

Directly observed therapy (DOT) is another approach that has been taken for the treatment of HCV-infected IDUs. A study conducted by Grebely, Raffa et al. [85] revealed that 55% of participants achieved an SVR even though many patients continued to use illicit drugs during the course of their therapy. IFN-α injections were directly observed and allowed for patients to receive continuity of care and access to education and support provided by the nurses administering the treatment [85]. The mode of delivering HCV treatment to IDUs must meet their complicated social needs and DOT programs can provide a source of social support by providing a link to existing community-based organisations [95]. Consequently, pertinent issues such as housing and

food can also be addressed, allowing for HCV-infected IDUs to continue treatment. DOT can also act as a mode to enhance a trusting relationship between the patient and health-care provider and facilitate patient engagement in harm reduction [95].

The fears surrounding provision of treatment to IDUs such as compliance and re-infection are not well substantiated [92]. Furthermore, there are no studies that show abuse of drugs reduces the effectiveness of interferon and ribavirin therapy [92]. Despite the fact that re-infection is a potential risk of ongoing injection drug users, studies have shown that it does not occur as often as perceived [96, 97]. Adherence is vital in order for the course of therapy to be effective and is enhanced when the patient receives treatment from a multidisciplinary setting [4]. Even though effective HCV therapy is available, less than one-third of patients in large HCV clinics have received treatment [98]. It is suggested that substance use behaviours should be stabilised prior to treatment because HCV is generally not an emergency to treat and the outcome of treatment will most likely be improved [92]. Nevertheless, this all depends on the advancement of liver disease because 20% of active HCV cases will develop cirrhosis after 20-30 years of infection [60].

It is important to acknowledge the fact that HCV is not the only medical condition from which many patients suffer. Addiction is also a medical condition for which patients must receive treatment. Methadone and buprenorphine are very effective at reducing drug use and can help to stabilize patients. Nevertheless, it is important to recognize the neurochemical backbone[9] of addiction and the fact that neurochemical changes are slow

[9] A neurochemical backboneof addiction relects the long term abuse of psychoactive substances which can cause neurochemical changes. A neurochemical is an organic molecule that participates in neural activity.

to resolve and in some cases are irreversible [89]. However, this should not deter providing care to HCV infected IDUs as drug use alone is not a barrier to successful HCV treatment outcomes [89]. Thus, when providing treatment to HCV patients, a myriad of medical conditions must also be treated in order for HCV treatment to be effective.

2.1.10 Obstacles to Providing HCV Treatment to People Using Injection Drugs

Injection drug users are underrepresented when compared to other patients receiving treatment for HCV infection [77, 99]. The reason for this imbalanced provision of care has to do with the fact that IDUs face multiple barriers to receiving treatment. These barriers manifest themselves on different levels: (1) the individual level; (2) the provider level [77]; and (3) the environmental level [100, 101].

2.1.10.1 The Individual Level

A chaotic lifestyle can be an obstacle when attempting to provide HCV treatment to IDUs. For instance IDUs who were dependent on alcohol were much less likely to seek treatment for HCV infection [102]. Furthermore, adherence to treatment is another barrier that is often brought up when examining whether or not IDUs should be allowed treatment. HCV treatment regimens are arduous and require long-term dedication. Studies have shown that IDUs adhere poorly to treatment [103, 104]; studies also show that they adhere as well as other patients (non-IDUs) [105, 106]. Therefore, it is important to assess each IDU individually as they differ considerably from one to the

other. There are numerous other individual factors which affect the treatment of IDUs, such as depression, psychological stress, and lack of social support.

A study conducted by Strathdee, Latka et al.[102] examined reasons why IDUs were interested in seeking treatment. Patients who had a usual source of medical care were significantly more likely to be interested in treatment. This emphasizes the importance of continuity of care among patients having to face important decisions with regards to HCV treatment. Moreover, more IDUs sought treatment when a doctor had told them that HCV could cause liver damage or liver cancer [102]. Therefore, it is important to increase the use of health care in the IDU population in order to enhance the uptake of treatment.

Low patient motivation can act as a deterent to seeking treatment. This may occur because patients are apprehensive about starting a toxic treatment that requires injections, which may not ultimately result in a "cure". Moreover, IDUs may not be aware of the long-term effects of HCV due to the fact that it can take many years to have symptoms. Thus, they are not concerned about seeking treatment [107]. An unstable lifestyle can impede treatment initiation and success. An addict can go through stages of their life when they are stable and drug free, to periods when they are heavy into alcohol and drugs. Furthermore, factors such as inconsistent income, unstable housing, frequent incarceration and lack of basic life essentials such as meals, medications, and transportation all contribute to disorder and instability in one's life. Therefore, it can be difficult to commence and adhere to treatment when acute problems need to be addressed first. Active injection drug use has been a major barrier to providing HCV treatment and as a result numerous clinical trials have excluded individuals who are actively injecting

drugs. Nevertheless, studies have shown that treatment can be successfully provided to patients who are still injecting drugs [84]. Alcohol use is another barrier to care, as it is associated with the rapid progression of chronic hepatitis [99, 107].

2.1.10.2 The Provider Level

Re-infection is often a reason for withholding treatment from IDUs with HCV. However, it has been found that spontaneous clearance of HCV may actually award protection against re-infection, thus providing a stronger impetus to treat IDUs [108]. Timing of treatment is another factor to consider when examining IDUs with HCV. Therefore, treatment must be assessed on an individual basis. For instance, it might be more appropriate for some patients to address their drug use before providing HCV therapy. For other patients, it might be more pertinent to begin HCV treatment before the disease progresses any further [77].

Patient discrimination in the healthcare setting is another obstacle that can impede IDU HCV treatment. A study conducted in Australia revealed that many physicians believe that IDUs should not be provided HCV treatment due to concerns about adverse effects, adherence to treatment and re-infection with HCV [34]. Most physicians withhold treatment from HCV infected alcohol or injection drug users until a 6-month period of abstinence has been achieved [109]. This is an impractical condition considering the fact that patients with substance use disorders are subject to relapse [34]. In addition, some physicians still believe that current IDUs are unable to gain access to government funded treatment for HCV, which was the case in Australia until May 2001. Currently they are able to gain access to government funded treatment, but uptake has

remained low [34, 110]. Moreover, a provider may not supply treatment if a patient is HIV/HCV co-infected as it could be burdensome and ineffective, thus compromising the HIV treatment [107].

2.1.10.3 The Environmental Level

Environmental barriers exist even when individual and provider barriers are not apparent. These can consist of lack of access to basic needs, such as housing, transportation, childcare, and a primary health care physician. Low rates of HCV treatment for IDUs may also be due to the lack of access to primary healthcare. IDUs often use emergency rooms as their primary source for healthcare, and therefore may have limited opportunities to enter into HCV treatment [107].

2.1.11 Psychiatric Conditions

Therapy should not be withheld from patients who are at risk of becoming depressed while taking the treatment. Moreover, it has been shown that comorbidity of HCV infection and psychiatric disorder did not negatively influence the adherence to HCV therapy and treatment outcomes [111]. Many studies have shown support for the use of IFN-based therapy for HCV patients who also have active psychiatric illnesses and/or subtance use disorders [84, 96, 112-114].

If patients are depressed before they commence therapy, they are at a higher risk of experiencing worse symptoms [4]. Nevertheless, if patients become depressed, treatment should not be terminated because antidepressants can treat the symptoms effectively, allowing for the full course of therapy to be undertaken [4]. Recent studies

have shown promising results; pretreatment with antidepressants appears to be an effective method for minimising IFN-related depression [115, 116]. Moreover, if HCV patients with a history of depression are engaged in the shared-care model, a planned approach to preexisitng or IFN-induced psychiatric disorders can be taken [87]. This can be in the form of prophylatic antidepressant therapy, which can allow for more patients to complete HCV treatment and achieve an SVR [85, 87]. Conversly, there are serious situations in which therapy must be withdrawn, and these include suicidal thoughts and development of mania.

It is very difficult to engage HCV-infected patients in treatment. Several studies have indicated that no-show rates for initial appointments are roughly 50%, and many of those patients who do attend their appointment are not considered ideal candidiates due to comorbid psychiatric or substance use diagnosis [98, 117]. Consequently, changes in the method for which treatment is provided need to be made in order to increase the number of patients with comorbidities receiving HCV therapy. Hence, HCV treatment needs to be inclusive and allow for management of psychiatric and substance use disorders in HCV patients and not isolate the treatment regimen to exclusively antiviral therapy [34].

2.1.12 HIV/HCV Coinfection

Each patient coinfected with HIV/HCV must be approached with an individualized therapy in mind, allowing for extensive monitoring of side effects and treatment efficacy [118, 119]. Roughly 20% of HIV-infected patients are also coinfected with HCV [120]. The duration of HCV treatment is different for patients coinfected with HIV/HCV. For genotype 2 or 3, treatment should be more than 6 months; for genotype 1

or 4, treatment should last for more than 12 months [121, 122]. SVR rates for coinfected patients range from 43% to 62% in genotypes 2 and 3 and from 16% to 38% in genotype 1 after 48 weeks of therapy [4].

Prior to treatment initiation, CD4+ cells counts must be examined. If the patient is already on highly active antiretroviral therapy (HAART) and factors such as HCV genotype, severity of liver disease, viral load and degree of suppression of HIV replication are taken into consideration, the patient can initiate HCV treatment as long as their CD4+ cell counts are between 200 and 350 cells/μl [121, 122]. HIV carriers with cell counts less than 200 cells/μl tend to have a low response rate to anti-HCV therapy. Moreover, IFN based therapies cause a decline in CD4+ cell count, which can put patients at risk for developing opportunistic infections [123]. Consequently, HCV treatment cannot begin until CD4+ cell counts have increased [121, 122].

The timing of treatment depends on the stage of both diseases. If a patient has not yet been treated for either virus, it is recommended that HIV treatment should be delayed and HCV should be treated first [124]. Treating HCV first, could potentially decrease liver toxicity and improve the ultimate outcome of antiretroviral therapy [124]. However, HCV treatment must coincide with a CD4+ cell count that will allow for an effective response. Otherwise, HIV should be treated first with HAART therapy, which will hopefully allow for a better response to the HCV treatment once HIV has been stabilized [119] [124].

Drug-drug interaction should be taken into consideration when developing treatment for a person coinfected with HIV/HCV. Ribavirin may interact with other nucleoside reverse transcriptase inhibitors used in treatment of HIV such as didanosine

and cause mithochondrial toxicity. Cases of lactic acidosis and pancreatitis have been reported [122]. Therefore, in order to avoid this adverse reaction didanosine should not be used when treating patients with PEG-IFN and ribavirin[122]. In addition, stavudine and zidovudine should also be avoided because they have shown to be associated with an increased risk of hyperlactaemia or anaemia [125].

2.2 Hepatitis C: Current Situation in Canada

Chronic hepatitis C will become a major economic and medical burden in Canada over the next 10-20 years as people who are symptomatic with the disease advance to end-stage liver disease and develop hepatocellular carcinoma [65]. There are no large scale studies that have revealed the prevalence of chronic HCV in Canada [4]. However, the number of persons infected with HCV in Canada is estimated to be 240,000 or 0.8% of the total population, 0.96% in males and 0.53% in females [5]. It is estimated that approximately 5,000 new infections are expected to occur each year, although the incidence could be as high as 8,000 [126]. In January 1999 HCV was reported in all provinces and territories across the country [127]. Aboriginal populations in Canada have a 15%-20% percent positive rate for anti-HCV antibodies, compared to less than 1% for the general population [126]. Injection drug users represent an at-risk population with the highest rate of acquiring HCV infections [5]. Approximately one third of people infected with HCV in Canada do not know they have HCV because they have not been tested [128].

In Canada, HCV was first reported in British Columbia in 1992; gradually, other provinces started to report the disease [129]. It is estimated that 90,000 to 160,000

Canadians were infected with HCV through infected blood or blood products between 1960 and 1992 [130]. Presently, the primary route of transmission in Canada is injection drug use [126, 131]. Approximately 60% of injection drug users (IDUs) carry HCV, with some cities having prevalence rates ranging as high as 90% in IDU populations [126]. Approximately 2,700 HCV positive Canadian women give birth annually [126]. Vertical HCV transmission from mother to child can carry a risk of 5 to 10% [126]. However, if the mother is co-infected with HIV this risk is increased by up to 60% [126].

The management of HCV treatment varies throughout Canada. This can be seen in the responses to a survey conducted by Wang, Yi et al [1]. This study revealed that Canadian hepatologists have varied perspectives towards treating HCV patients [1]. Moreover, there is a lack of liver specialists in Canada, creating considerable treatment challenges [132]. Treatment intensity varies significantly by province. For example, only 14% of Ontario residents who acquired HCV through blood transfusion between 1986-1990 were treated. In contrast, 32% of the Manitoba residents were treated [133]. In addition, people living with HCV endure many barriers to treatment. For example, some provinces such as British Columbia will deny treatment to patients unless their liver enzyme levels test at more than 1.5 times normal. This is despite the fact that some biopsies show significant liver damage but normal liver enzyme levels [126]. Consequently, this can lead HCV patients to try and increase their liver enzyme levels through dangerous means, such as drinking excessive quantities of alcohol [126].

Treatment of HCV has shown to be extremely cost effective. Every $1 spent on HCV combination therapy results in medical cost savings of approimately $4 [126]. The Canadian Institues of Health Research indicates that HCV costs the Canadian health care

system $500 million annually [126]. This cost could be reduced if more HCV patients were treated with PEG-IFN and ribavirin combination therapy. It is known that early detection and treatment are associated with better treatment outcomes [126]. It is predicted that approximately 20% of infected Canadians will develop serious complications from HCV, such as cirrhosis, liver failure and hepatocellular carcinoma (HCC) [24]. As a result, treatment and medical care will become more complex and expensive. It is estimated that $1 million is spent on an HCV patient from time of diagnoses to death, including medical costs and the economic loss for that individual [126]. Anti-viral medications can cost $20,000 per course of treatment, whereas liver failure can cost $50,000 with a transplant exceeding $100,000 [126]. Therefore, the cost-effectiveness of HCV treatment far outweighs treatment of end stage liver disease, and more importantly reduces transmission of the virus to other people.

2.3 Treatment – Health Implications and Quality of Life

Advancements in treatment have led HCV to be deemed a "curable" disease [126, 134]. PEG IFN and ribavirin enhances SVR; however, this therapy has drawbacks. Nevertheless, the advancements made by using the drugs in combination are two to threefold times higher than what was previously achieved by using interferon monotherapy [43, 44].

There are many health implications with HCV. These can include hepatic cirrhosis, liver failure, and HCC. In many cases, the only remaining option for survival is a liver transplant. Unfortunately, there is a limited number of livers available for

transplantation on an annual basis[10] [126]. In addition, many complications are associated with a liver transplant, including HCV infection of the transplanted liver.

More importantly, the major impact of the disease is chronic ill health [135]. These symptoms can include lassitude, nausea, headaches and problems with memory and concentration, which all compromise the quality of life (QoL) of a person living with HCV [135, 136]. These ailments can cover the entire HCV disease spectrum from mild to more advanced liver disease [135]. These reductions in QoL have a deleterious effect on a person living with HCV because it can affect their physical, social and occupational functioning [137]. Canadian HCV patients have significantly lower health-related QoL scores on a physical and mental level, when compared with age-matched Canadian norms [137].

The side effects of HCV medications can indeed worsen the QoL of a person living with HCV. There is an association between therapy with alpha interferon and multiple psychiatric side effects, which include sadness, depression, anxiety and irritability [138]. These side effects are a major reason for early discontinuation of therapy, as 20-30% of patients develop some degree of depression during therapy [43, 44]. The coping abilities of the individual living with HCV will determine whether or not they are able to continue with treatment [139]. HCV patients tend to prefer the side effects of therapy sooner rather than later, especially if they will return to normal health after the treatment [139].

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[10] There are approximately 400 livers available for transplantation each year 126.*Rationale and recommendations for a Canadian hepatitis C strategy*. 2004 [cited; Available from: http: www.canhepc.net pdf canhepc_strategy_mar12.pdf.

Despite the notable benefits of treatment, there is an immense lack of financial support for medication. Almost 90% of people infected with HCV do not have access to effective treatment [126]. The drugs cost over $20,000 for a 48-week course of treatment, and in most cases the drugs are simply unaffordable for patients without private insurance. However, obtaining treatment is only part of the challenge towards restored health. The side-effects from the medication, as mentioned above, can lead patients to terminate treatment and in extreme cases commit suicide [126]. Completion of treatment is an arduous task and certain measures, such as adequate nutrition, housing and support need to be in place in order for it to be successful.

There is limited information on physicians' perceptions of QoL for people living with HCV. In a study conducted by Patil, Cotler et al. [140] a utility analysis was used to assess physicians' perceptions of HCV-related health states and how their perspectives on HCV affect the advice they give patients about the disease. The respondents in the study felt that HCV causes a dramatic reduction in health status and even without symptoms or cirrhosis they thought that HCV carried a 12% decrement from lifespan without HCV [140]. Moreover, time spent on therapy was judged to be associated with a 53% reduction from good health [140].

2.4 Determinants of Health

The determinants of health must be addressed when determining what leads to risk behaviours, sub-optimal health status, and lack of access to HCV treatment. The Public Health Agency of Canada lists key factors, such as income and social status, gender, education and literacy, and employment as part of the complex interactions that affect one's health status [141]. Very few IDUs enter HCV treatment programs [126]. This may be due to the fact that other needs, such as hunger and homelessness, must be met before treatment is sought. Therefore, in order to address the issue of treatment it is pertinent to examine the impact of the determinants of health and the complex interactions that are involved when evaluating HCV treatment accessibility.

2.5 Discrimination and Stigmatization of People Living with HCV

HCV is a chronic, transmissible, slowly progessive disease that is frequently associated with injection drug use [142]. It is due to this association that HCV infection can lead to stigmatizing experiences [20]. The stigima of HCV can be related to concerns about job loss, insurance, mortgages, friendships, and prejudices and discrimination directed at the children of people living with HCV [126].

Furthermore, it is important to note that discrimination is most common in the health-care setting [126, 143]. It is known that some General Practitioners (GPs[11]) restrict access to health care for patients that inject drugs [144]. This can lead to reduced contact between IDUs and health-care services. As a result, beneficial services such as health promotion, HIV and HCV testing, hepatitis B vaccination (HBV) and entry into

[11] General Practitioners are also known as Primary Care Physicians and Family Practitioners

drug treatment cannot be provided [20, 143]. It is therefore crucial for health care workers who manage HCV patients to be aware of the impact that their attitude has on the treatment outcome of their patients. Consequently, the QoL of people living with chronic HCV can be affected by perceived social stigmitization [142].

Stigmitization can occur in many constructs. It was found that people living with HCV reported stigmitization in the form of internalized shame, financial insecurity and social rejection [142]. This can lead to isolation, anxiety, and trouble coping with the disease [20]. In addition, HCV patients face negative stereotyping, especially since the disease tends to be associated with criminal behaviour [20]. A sense of helplessness and loss of control leads people living with HCV to envision a bleak future. Moreover, private relationships with family can deteriorate, leading to a loss of social support. This can have a negative affect on QoL and the ability to cope with the disease.

Furthermore, stigmitization has also led to a lack of public awareness with regards to disease prevention and control. People living with HCV come from diverse backgrounds, and ethnicity, race, education, occupation, age, gender and social status do not act as barriers to transmission [145]. Nevertheless, there is a general lack of support for programs to aid people with mental illness, substance users, prison populations and other marginalized populations [126]. As a result, treatment accessibility has been marred by the stereotyping and prejudices associated with HCV, consequently adversely affecting efforts to treat people living with HCV.

2.6 Literature Review – Hepatitis C Management Surveys

The high prevalence of HCV has led many countries, such as France, Australia, Turkey, Italy, the United Kingdom, and the United States to assess the screening and management of HCV by community-based practitioners [23, 146-150] and primary care (internal medicine and family practice) physicians [151]. Primary care providers have been designated the 'gatekeepers' for HCV care and will increasingly be the first to encounter patients with HCV infection [146, 151]. However, a number of studies demonstrate that primary care providers only care for a few HCV patients and refer the majority to sub-specialists [149, 150, 152].

A number of studies surveyed GPs and their knowledge and education needs surrounding HCV treatment, as well as their diagnosis and management of HCV infection [23, 144, 146, 147, 149, 150]. GPs have a vital role in the health system as they must be able to effectively identify patients at risk for HCV [148, 152]. This is an important task for GPs because the early stages are often asymptomatic. In addition, they should be able to perform the proper diagnostic tests and make the appropriate referrals [148, 152].

Results from previous studies showed that there is a need for targeted education for physicians concerning HCV, and that HCV management strategies need to be tailored to the identified needs of the general practitioner [23, 147-149]. For instance, physicians surveyed by Peksen, Canbaz et al. [146] erroneously identified sexual and vertical transmission as being major risk factors for HCV, and respondents demonstrated poor knowledge of treatment options for chronic HCV. It is quite common for a person infected with HCV to not be aware of their infection, and as a result GPs need to be

cognizant of the impact of HCV in order to reduce the burden of the disease on the health care system in terms of morbidity costs [148]. In summary, the studies revealed that GPs have demonstrated a poor knowledge base and practice patterns when dealing with the treatment of HCV patients [23, 144, 146, 149, 151, 152]. For example, Coppola, Karakousis et al. [151] observed that primary care residents tested for HCV in inappropriate situations and were unclear about current HCV treatment regimens. This lack of adequate knowledge has evidently led to lower rates of therapy [153].

In a study conducted by Shebab, Sonnad & Lok [149], it was shown that the majority of GPs correctly identified the major risk factors of HCV; however, an unsettling number of GPs (25%) still considered blood transfusion in 1994 a significant risk factor for HCV infection. In addition, 19% of GPs that responded to the survey considered casual household contact to be a significant risk factor for HCV infection [149]. Other disconcerting findings revealed that only 59% of the respondents reported that they ask patients for HCV risk factors, and only 70% of the GPs would conduct tests on patients with risk factors for HCV, which could lead to under- diagnosis [149]. In relation to treatment of HCV, only 52% of the respondents recommended combination therapy with interferon and ribavirin, despite the fact that large trials have revealed the effectiveness of interferon and ribavirin therapy, in contrast to interferon monotherapy [54].

The first national study of GPs in Australia about HCV was conducted by Gupta, Shah et al. [154]. Results revealed that GPs identified the need for hospital and specialist support. Moreover, the importance of hospital-based multidisciplinary clinics was declared to be useful in the management of HCV care by 55% of respondents since the

majority of HCV patients were referred to specialists. The study also identified specific educational and resource needs to incorporate into HCV educational programs for GPs, such as therapeutics, interpretation of tests and pre- and post-test counselling. Another crucial finding revealed that only one third of respondents stated that they would discuss psychosocial aspects as part of initial management of patients with HCV. Consequently, the need to address social and mental health issues will also have to be added to educational strategies for GPs treating HCV. The data from the study has allowed for more effective models of HCV care to be explored and addressed.

Another Australian study that surveyed GPs who serve large non-English speaking migrant populations attempted to assess knowledge of risk factors, complications, currently recommended antiviral therapy, referral practice to specialists and difficulties encountered by practitioners and patients in accessing information about HCV [155]. This study was conducted because Australia receives many migrants from countries with a high prevalence of HCV infection. The findings revealed a number of important issues pertaining to GPs' current management of chronic HCV infection and their knowledge base of HCV risk factors. The majority felt that they were well informed, however, almost half of the respondents agreed that lifetime immunity occurred or that they were uncertain about immunity. There were discrepancies about providing HBV and Hepatitis A Virus (HAV) vaccinations; for instance, 33% reported that they would only immunize against HBV and 10% stated that no immunization was required [155]. Furthermore, the GPs surveyed incorrectly listed sexual transmission and vertical transmission of HCV as being important risk factors when the estimated transmission risk is 5% [156]. All respondents indicated that IDU was a risk factor, but only 34% stated

that HCV could be spread through the use of shared injecting paraphernalia. In terms of providing referrals to specialists, most GPs referred patients when ALT levels were elevated or when abnormal liver function tests were observed. It was noted that 30% of respondents did not refer patients if they were not willing to undergo HCV antiviral therapy. This demonstrates that some GPs view specialist liver clinics as solely treatment providers. In contrast, these clinics also offer counselling and education; therefore, GPs should seek advice from specialists at any stage of the diagnosis. The majority of respondents (47%) stated that interferon and ribavirin therapy was the best treatment available. Conversely, 25% listed interferon monotherapy or lamivudine (commonly used in the treatment of HBV), which shows that physicians need regular updates on current treatments [155]. The study concluded that physicians require continuing access to the most up-to-date and accurate information on HCV treatment advances and care. It was suggested that different forms of communication, such as succinct bulletins, lectures and Internet websites be adapted in order to focus on the management of HCV in high-risk ethnic groups [155].

A study of HCV in Canada was presented at the *Navigating Life with Hepatitis C Conference,* held in Halifax, Nova Scotia between March 7-9 2006 [157]. The study evaluated physicians and HCV perceptions. A national survey of 789 family physicians was conducted, and stratified random sampling was used with the College of Family Physicians database. The aim of the survey was to describe the current knowledge and attitudes regarding HCV care and affected patients. It was determined that less than 50% of family doctors offer basic or advanced HCV care, despite the fact that family physicians believed that HCV screening is something that all family doctors can do. In

addition, it was noted that IDUs do not present a problem for them. However, the physicians were less confident in their ability to treat and follow-up dependent patients, and they expect poor results. Moreover, they view provision of HCV care as part of family practices but believe resources such as tests and investigations necessary to evaluate and treat patients are not easily accessed. The study had a response rate of 33%.

Another Canadian study surveyed practicing hepatologists about their attitudes and practices regarding interferon and ribavirin combination therapy for HCV patients in Canada [1]. An anonymous fax/postal survey was sent out. The questions examined the likelihood of treating a patient with certain clinical characteristics and opinions regarding how the physician's treatment decision is influenced by other factors. It was concluded that there is substantial variation in opinion among Canadian hepatologists toward HCV patients. In a general survey, however, respondents appear to follow published guidelines in their practice. The response rate was 86.4 %.

A recent study conducted by Litwin, Kunins et al. [158] evaluated HCV-related management practices carried out by substance abuse physicians. A survey instrument adapted from a study by Shehab, Sonnad et al. [152] was used to assess physician, practice, and patient characteristics and HCV-related practice patterns with an overall response rate of 52%. Three major findings were revealed from the study. The first found that substance abuse treatment physicians promote important areas of HCV-related care, such as screening IDUs for HCV, recommending HAV and HBV vaccinations to non-immune HCV-infected patients and referral of HCV patients for treatment. Despite this finding, only half of the surveyed physicians referred their HCV-infected patients for treatment. Moreover, only 45% of physicians recommended HAV vaccinations and 35%

recommended HBV. The second finding stated that substance abuse treatment physicians who also provide primary medical care are more likely to screen for HCV antibodies, recommend HAV and HBV vaccinations and refer to HCV specialists than physicians who do not provide primary care. Lastly, only 9% of surveyed substance abuse treatment physicians stated that they directly treat HCV-infected patients; however, a third said that they were willing to provide HCV antiviral treatment if they were provided with the necessary resources and education [158]. Another crucial finding from the study reported that 39% of physicians do not screen most IDUs for HCV antibodies. Consequently, these poor screening practices will cause infected IDUs to remain unaware of their HCV status. The overall findings from the study provided support for integrating substance abuse treatment and primary medical care to maximize care for chronic HCV [158].

A few studies have specifically surveyed gastroenterologists, hepatologists and infectious disease specialists [159, 160]. In a study conducted by Everhart, Stolar et al. the target population for the survey was practitioners most familiar with the management of HCV infection [160]. The reason for surveying specialists as opposed to general practitioners was because the specialists can be considered leaders who have the most influence to guide the management of patients with HCV. Furthermore, a study conducted in the UK by Parkes, J., P. Roderick, et al.[159] aimed to determine workload, configuration and care processes of current UK services available to manage patients with chronic HCV infection. Four specialties were targeted -Gastroenterology, Genito-Urinary Medicine, Hepatology and Infectious Diseases. A postal questionnaire was sent out, and it revealed that there is inequity and variation in the management of people with chronic HCV in the UK. The key barriers to care were staffing and funding of treatment.

The response rate for this study was 71%. The methods used in the UK study were adapted as a model for the current study on HCV management in Canada.

2.6.1 Coordinated Pathways of Care for Hepatitis C

Communication amongst the various disciplines integrated into pathways of HCV care is vital so that patients complete the full course of antiviral therapy. The multidisciplinary coordinated pathway of care includes many players in the health field, such as specialty nurses, addictions counsellors, psychiatrists, and primary care providers. The primary care providers, as mentioned above, are key to recommending HCV therapy and therefore need to receive continuing education about the history and treatment of HCV to provide optimal advice to their patients [140]. Moreover, primary care providers often decide whether or not to refer patients to specialists. Therefore, physicians in specialities such as hepatology need to understand other physicians' perspectives on HCV so that treatment concerns can be adequately addressed, allowing for more patients to receive treatment [140].

Pathways of care for patients diagnosed with HCV were examined by Irving, Smith et al. [161]. The impetus for the study came about because it was reported that only 55% of patients diagnosed with positive anti-HCV were referred to a specialist clinic for follow up tests [162]. The study set out to examine failures to identify, refer, and manage patients with chronic HCV. More specifically, drop out rates at all stages of the management pathway were examined, as well as reasons for non-referral of patients with anti-HCV positive tests to specialty care facilities [161]. The study determined that less than 50% of anti-HCV positive patients were referred to a specialist treatment facility

[161]. Therefore, recommendations were made for all anti-HCV positive patients to be referred to specialists for further management. The one exception for this referral is patients who are anti-HCV positive but HCV RNA negative, and this circumstance occurs in approximately 20% of people with HCV because of spontaneous clearance of HCV. The study revealed that there is a need for "innovative multidisciplinary approaches" to manage the numerous medical conditions and social issues in which many "real world" HCV patients have. Furthermore, by identifying the reasons for patient discontinuation of care, treatment strategies can be implemented to increase patient advancement into treatment.

2.6.2 Management of HCV Infection: Specialist Centres or General Practice?

There are many complex challenges when providing treatment to patients living with HCV. In most cases patients are referred to specialists, such as a hepatologist, in order to receive treatment [163]. Dusheiko [163], argues that hepatologists have a strong understanding of the complex nature of the disease and are therefore able to provide excellent care to minimise the morbidity of the disease.

Dusheiko states that HCV care should remain in a specialist centre in order to avoid treatment failure through delay and to minimise unnecessary treatment for those who do not progress to chronic disease. Furthermore, many aspects of managing patients with HCV involve experienced clinical interpretation of liver biopsies and for the physician to be able to determine the trajectory of the disease in a chronically infected patient. Specialists also oversee development of the guidelines for the management of HCV care, including the National Institute of Health and European Association for the

Study of the Liver guidelines. Moreover, hepatologists also monitor patients' response to therapy and any complications that they might have such as resistance, relapse or non-response. Hepatologists are at the forefront of providing care to HCV patients. They play an essential role in the diagnosis and management of HCC and have also begun to manage co-infections with HIV and HCV (or HBV).

Despite the pivotal role the hepatologist plays in managing HCV care, many factors appear to indicate that care should also be provided by non-specialist centres due to the large proportion of people living with HCV [164]. Brown, JL [164] refutes Dusheiko by stating that clinical guidelines have been distributed to all gastroenterologists in the United Kingdom and diagnostic tests are available to them as well. Consequently, the high prevalence of HCV demonstrates that care must become more widespread and allow for general practitioners (GPs) to be able to diagnose and treat the disease. GPs should familiarize themselves with some of the major contraindications of the treatment. Moreover, it is vital for GPs to be aware of their practice population. For example, if a patient comes to them with abnormal liver enzyme levels but no known risk factors, the physician should have an understanding of the patient's indigenous place of birth, drug use history, blood product histories so that they can help identify patients at-risk for HCV. Furthermore, it is important for GPs to have effective communication channels with specialists centres in order to provide up-to-date information about HCV to their patients in addition to having access to specialty care when needed [9].

GPs have a crucial role in the overall care and management of HCV patients. People living with HCV may be uncertain about the virus, methods of transmission, and

the fact that it is a silent, on-going infection. Consequently, GPs need to act as "gate-keepers" of information to inform their patients of the risks and current treatment regimes available [9]. The treatment of HCV lies in both the specialty and non-specialty fields. In order for this to work, there must be efficient communication between the physicians to secure effective management and care of HCV patients.

CHAPTER 3 RESEARCH DESIGN AND METHODS

3.1 Methodology

This quantitative research study used a questionnaire to gain insight about the HCV treatment services that exist in Canada. The following sections give an overview of the approach that was taken, as well as the methodology of developing the questionnaire that was used in the study.

3.1.2 Surveys

Surveys are essential tools in health services research in that they provide information on knowledge, attitudes, and patterns of care of practicing physicians. Physician surveys tend to have an average response rate of 54%, which is 13% lower than surveys administered to non-physician groups [165]. Physicians receive numerous questionnaires to complete and often have little time to devote to filling them out. The main reasons that have been found for physicians not being able to complete surveys are that they were too busy with other work or that the survey got lost in a pile of paper [166]. It is worth paying attention to physician low response rates because physicians have a vital role in service planning and provision [167].

A low response rate can adversely affect a study because of potential non-response bias. Non-response bias is the effect of a set of respondents who refuse or choose not to participate in research. Non-response bias is affected by two factors: the percentage of the sample not responding and the degree to which non-responders differ from the study population [167]. Responders and non-responders can be compared in

terms of demographic differences and other characteristics; however, this cannot assist in determining if the survey responses are in fact representative of the sampling frame being evaluated.

The proposed study employed various survey techniques in order to reduce the effect of non-response. The "Tailored Design Method" developed by Dillman [168] has five major components of survey design and administration: (1) enclosure of a token, prepaid, financial incentive; (2) design of a respondent friendly questionnaire (short questionnaire with closed ended questions); (3) use of four contacts by first class mail and one additional special contact (e.g. telephone call); (4) enclosure of a return envelope with first class stamp; and (5) addition of elements that increase personalization, such as a thank you card. [168]. The five components combined will help to achieve a higher response rate, however, the use of financial incentives has consistently been found to be the most effective [169].

Specific survey methods that are able to increase response rates have been identified. These include: (1) monetary incentives; (2) short questionnaires; (3) personalized questionnaires and letters; (4) coloured ink; (5) recorded delivery; (6) use of stamped return envelopes; (7) first class post; (8) contacting participants before sending questionnaires; (9) origin of questionnaire[12] [170]. Furthermore, evidence shows that using an actual stamp on the return envelope as opposed to a business reply stamp envelope can increase response rates [168]. It is difficult for many people to throw away

[12] University questionnaires are more likely to be returned than questionnaires from other sources, such as commercial organisations

something that has monetary value so they are therefore more compelled to send the questionnaire back.

Response rates are also affected by the survey mode selected for the study. Various studies have indicated that when physicians were offered the choice of four response modes - mail, internet, phone and fax - the majority chose to respond to the mail mode survey [169]. Mixed-mode surveys that allow respondents to be surveyed by interview, mail questionnaires, telephone or internet can also help overcome the difficulties of obtaining adequate response rates rather than using a single method.

The components of the "Tailored Design Method" can drastically increase the cost of a study. The use of prepaid financial incentives, certified mail, telephone calls, stamps on return envelopes, and multiple contacts require a compatible budget. In contrast, it is important to employ these techniques because the response rates received from a study directly affects the study's validity. In effect, it is important to achieve response rates that are able to demonstrate that the results from the study do not merely reflect a biased-sub sample of the population [169].

3.2 Methods

Using the methodology described above, a cross-sectional postal survey questionnaire was conducted that included a selection of the recommended methods used to increase response rates. Due to the financial constraints of the study, only two mail outs could be undertaken. The following sections are comprised of the methods that were used to carry out the survey-questionnaire. The survey was administered using the following instruments: a pre-notification letter (Appendix A); a survey package

containing a cover letter (Appendix B), the survey-questionnaire (Appendix C), and a thank-you card (Appendix D); and follow up telephone call (Appendix E).

3.2.1 Survey Development

The 14-page questionnaire (Appendix C) used in this study was adapted from research conducted by Parkes, Roderick et al. 2006 [159] and included items designed to assess the workload, configuration and care processes of services in Canada available to manage patients living with HCV. The questionnaire was directed at specialists (hepatologists, gastroenterologists, infectious disease specialists) in order to evaluate their understanding of concepts regarding diagnosis, referral practices, access to tests, barriers to treatment, treatment eligibility/ineligibility, HCV care management, and drug prescribing regimes.

The survey was distributed to members of the Atlantic Interdisciplinary Research Network: Social and Behavioural Issues in Hepatitis C and HIV/AIDS, as well as the National Canadian Research Training Program in Hepatitis C for comments and suggestions. The survey was then modified based on their feedback. Dillman's mail survey techniques were adapted for use in this study to create an effective approach to delivering the survey to respondents [168].

3.2.2 Target Population

Practitioners most familiar with management of HCV infection were selected for an investigative study of HCV service provision (i.e. patterns of healthcare delivery, referrals, coordinated care teams) in Canada. These specialists were found in the

Canadian Medical Directory (CMD) [2] under the titles of hepatologist, infectious disease specialist and gastroenterologist. The reason for selecting this population was because these specialists can be deemed the leaders who provide insight and recommendations that most influence the management and care of patients with HCV in their communities.

It is imperative to note that the treatment of HCV patients can include members of a comprehensive care clinic, which can be made up of hepatologists, psychologists, psychiatrists, infectious disease specialists, immunologists, nurse practitioners, and drug and alcohol addictions counsellors. In assessing the treatment provided to people living with HCV, it would be advantageous to evaluate the entire comprehensive care clinic in order to receive a complete account of HCV treatment in Canada. Unfortunately, due to time and budget constraints it is unfeasible to contact the entire clinic. Moreover, accessing contact lists for the HCV care clinics and all the members associated with treating people living with HCV would be an arduous task, especially if there are no common directories made available. Therefore, it is important to acknowledge that HCV health providers constitute a broad group of professions. However, for the sake of this study HCV health care providers will represent physicians who provide treatment to people living with HCV, such as hepatologists, gastroenterologists, and infectious disease specialists.

For the purpose of this study, the sample population was divided into three groups based on the type of service that the physicians provide to their patients. Respondents were asked to choose from the following three categories: (1) no role in the management and diagnosis of patients with HCV; (2) Diagnosis +/- initial investigations followed by

referral to dedicated HCV service; (3) Provision of a dedicated HCV service (diagnosis, investigation, treatment and follow-up).

3.2.3 Study Participants

The total number of physicians in the 2006 CMD [2] listed under the designated specialties of hepatology, gastroenterology and infectious diseases was 723. This number consisted of 562 English-speaking physicians and 160 French-speaking physicians. The CMD list was examined to verify that it was up to date. Fifty physicians were randomly selected from the list and were called to check that they were still in fact practicing. It was found that 46/50 physicians contacted from across Canada are practicing gastroenterologists, hepatologists or infectious disease specialists. Respondents were contacted if they met the following inclusion criteria and exclusion criteria.

Inclusion Criteria

1. Physician in one of the designated specialties: hepatology, gastroenterology, infectious diseases as indicated in CMD
2. Designated as English speaking in the CMD

Exclusion Criteria

1. Physicians in specialties other than hepatology, gastroenterology, infectious diseases
2. Designated as French speaking in the CMD

3.2.4 Survey-Questionnaire Design and Content

The survey-questionnaire (Appendix C) consisted of four sections:

(1) Health care provider demographics

(2) Identification of HCV patients

(3) HCV treatment

(4) HCV service configuration

In general, the question format consisted of closed questions with multiple choice and true/false answers and took approximately 5-10 minutes to complete.

3.2.4.1 Variables

Data was categorized into three groups, based on the type of service provided by the physician. The questionnaire started with health care providers having to describe their role in the management of patients with HCV. They had to select from three descriptions: (1) No role in the management of hepatitis C infection; (2) Providing diagnostic and investigative service but not treatment (diagnostic investigative provider-DIP); (3) Providing diagnostic testing, investigations, treatment and follow-up of patients (comprehensive service provider-CSP). If respondents chose the first description, they did not have to proceed to the other parts of the survey. They needed to simply check the box stating that they do not provide a role in HCV management, mention the consultant who provides the HCV service, and return the questionnaire. However, if respondents chose the other two options they were directed to further questions on designated pages of the questionnaire.

Geographical locations and regions were also coded. Regions were grouped together according to the Natural Resources of Canada website Atlas on Canada [171]. The four regions are as follows: (1) Atlantic region: Newfoundland, Nova Scotia, New Brunswick, Prince Edward Island; (2) Central region: Ontario and Quebec; (3) The Prairies: Manitoba, Saskatchewan and Alberta; (4) Western Canada: British Columbia.

The territories, Nunavut, Northwest Territories and Yukon were excluded. These regional groupings were done to examine whether or not differences could be observed on a regional basis as well as a provincial basis, allowing for a broader sense of HCV services in Canada.

3.2.4.1.1 Demographic Variables

Respondents who categorized themselves in the DIP or CSP category were then classified by age and sex. They were asked to select from 5 age groups (< 30, 30-39, 40-49, 50-59 and 60 or older). Respondents had to indicate the size of the community in which they practice. They had 4 choices: ≤ 25,000; > 25,000 but < 100,000; 100,000 to 500,000; and >500,000. Respondents also had to indicate their practice type and could select more than one option (solo practice, multiple-specialty group, academic, other). Finally, respondents were asked to describe the population that is best served by their clinical practice or hospital [urban (wholly), urban (predominantly), mixed urban (more urban than rural), mixed rural (more rural than urban), rural (predominantly), rural (wholly), other].

3.2.4.1.2 Variables for Diagnostic Investigative Providers

Diagnostic Investigative Providers (DIPs) were asked to fill out information regarding the management of HCV patients in their practice or hospital. DIPs had to indicate the proportion of patients diagnosed with HCV who are managed by a selection of physicians (hepatologists, gastroenterologists, infectious disease specialist, internist and other). They also had to indicate how many patients they diagnosed with HCV in

2005 (<10, 10-19, 20-29, 30-39, 40-49, and >50). Moreover, they had to indicate the percentage of patients diagnosed and subsequently referred to a specialist HCV service (<10%, 10-24%, 25-49%, 50-74%, 75-90%, and >90%). Finally, DIPs were asked to state if they had access to specific tests either in-house or external (qualitative PCR, viral load measurement, HCV genotyping and specialist liver histopathology). DIPs were then asked if they ever treat patients with HCV and the name of consultant(s) who provide a specialist HCV service for their patient population.

3.2.4.1.3 Variables for Comprehensive Service Providers

The section for Comprehensive Service Providers contained all of the above information that was filled out by the DIPs in addition to asking about:

(1) Prevalence of HCV in the respondent's practice

(2) Referrals

(3) Diagnostic tests and counselling

(4) Treatment regimens

(5) Service configuration of practice

(6) Barriers in the management of patients with HCV.

CSPs were asked to state the total number of patients with known HCV under their care and the approximate number of new HCV patients seen in the years 2003, 2004, 2005. They could select from four categories of patients (<10, 10-19, 20-30, and ≥40).

Respondents were also asked the approximate percentage of new patients who miss their initial appointment and could choose from six categories (0-4%, 5-9%, 10-24%, 25-

49%, 50-74%, ≥75%). They were also asked the percentage of time that they spend on clinical management of HCV patients (0-4%, 5-9%, 10-24%, 25-49%, 50-74%, ≥75%).

The source of referrals was also evaluated by asking respondents to indicate how many HCV patients came to them already diagnosed (0-4%, 5-9%, 10-24%, 25-49%, 50-74%, ≥75%). If the initial diagnosis was made before referral, CSPs were also asked to indicate the approximate percentage of referral from the following sources (primary care, prison healthcare, drug and alcohol service, hepatology, gastroenterology, infectious diseases, internist, and other). Moreover, respondents were asked to indicate the source of referral when the respondents themselves made a diagnosis of HCV (primary care, prison healthcare, drug and alcohol service, hepatology, gastroenterology, infectious diseases, internist, and other). Furthermore, CSPs were asked to indicate if they refer HCV patients to colleagues for further management and to state the circumstance in which they do so (treatment, follow-up, complex clinical issues relating to HCV, joint management, transplantation, patients desire for a second opinion).

CSPs were asked to indicate whether or not they have access to specific diagnostic tests, either in-house or external (qualitative PCR, viral load measurement, HCV genotyping and specialist liver histopathology) and if counselling services are available for their patients.

The section on patient treatment examined the criteria used to determine which patients are eligible for treatment (age, gender, genotype, severity of hepatitis, severity of fibrosis, history of substance use/abuse, co-morbidities, extrahepatic manifestations[13]) and whether or not the physicians would offer treatment under specific circumstances,

[13] An extrahepatic manifestation means diseases or conditions that affect organs other than the liver.

such as normal ALT, severe hepatitis and patient awaiting transplantation. In addition, main reasons for patient ineligibility (i.e. ongoing drug use, ongoing alcohol use, psychiatric disorder) were asked. They were also asked to indicate the proportion of new patients with HCV seen in 2005 who were eligible for treatment (0-5%, 6-9%, 10-24%, 25-49%, 50-74%, 75-89%, ≥90%) and the proportion of eligible patients who actually received treatment (0-5%, 6-9%, 10-24%, 25-49%, 50-74%, 75-89%, ≥90%).

The pattern of drug prescribing (i.e. interferon alone, pegylated interferon & ribavirin in combination) was also asked, as well as criteria used to end treatment. Respondents were asked to indicate if they follow dose reduction guidelines and the proportion of patients who receive a pre-treatment liver biopsy. A section on refusal of treatment asked the reasons given by eligible patients who refuse therapy (i.e. cost, inconvenient to start treatment due to work pressures, lack of concern over future). In addition, another question asked respondents to indicate the percentage of patients who stop treatment prematurely (0-5%, 6-9%, 10-24%, 25-49%, 50-74%, 75-89%, ≥90%) and their reasons for stopping. (i.e. no response to treatment, loss to follow up, side effects).

The section on service configuration of the practice asked respondents to indicate if they have a coordinated management strategy for HCV patients and if they work in a multidisciplinary team setting. If they did work in a team setting they were then asked to select the members from a list of disciplines (i.e. internist, radiologist, specialist nurse etc.).

The final section examined barriers to providing care, and respondents had to rank specific barriers (i.e. biopsy waiting times, staffing capacity, patient non-ttendance) and

then write any additional comments. Moreover, CSPs had to indicate the number of patients awaiting treatment, appointments, funding decisions, and investigations.

3.2.5 Survey Method

The following sections outline the implementation of the survey-questionnaire. Beginning with the format used to distribute the survey, followed by the return of the surveys and follow-up.

3.2.5.1 Questionnaire Distribution

The distribution and follow up proceeded in the following format:

(1) Pre-notification letter mailed out (Appendix A)

(2) Survey packaged mailed out: Cover letter (Appendix B); Survey-questionnaire (Appendix C); Thank you card (Appendix D)

(3) Follow-up telephone call to a random sample of physicians who had not returned questionnaire: Telephone script (Appendix E).

Surveys were mailed to 562 physicians at their sites of practice. A pre-notification letter (Appendix A) was sent a week before the package in order to notify the respondents of the study. The first letter, which introduced the participants to the study, was mailed out on January 25th 2007. The letter contained information outlining the objectives of the study as well as the affirmation of confidentiality and how informed consent is obtained. This was followed by the survey package (Appendix B and C), which was sent out on January 31st 2007. Questionnaires were given code numbers and mailed to each potential respondent with a covering letter and business reply stamped return envelope or a real

stamped return envelope. Half of the survey packages contained business reply stamps and the other half received real postage stamps on the return envelopes to evaluate whether or not the response rate would be affected by the type of reply stamp placed on the envelope. The package also included a thank you card (Appendix D).

3.2.5.2 Questionnaire Return

Participants were asked to place the completed questionnaire in a pre-addressed, pre-paid envelope. Anonymity was maintained because each survey was coded. Upon receipt of completed questionnaires, the geographical area and specialty of the physician was written on the front page and the code number was removed and replaced with a new number.

3.2.5.3 Telephone Follow-Up

The telephone follow-up call did not prove to be an effective method of contacting physicians to remind them to fill out the questionnaire. Only 2 of the physicians who were contacted later returned the questionnaire. Numerous obstacles arose when phoning: (1) the phone number provided by the CMD was a hospital and not a direct line to the physician; (2) mail boxes were often full so messages could not be left; (3) physicians were rarely spoken to directly. It is for this reason that so few physicians received a follow-up call. Moreover, the lag time from when the letter was sent out to the time the follow-up calls were made was too long, which possibly led for the questionnaire to be misplaced, lost, or forgotten.

3.3 Data Entry and Analysis

The data was first entered into Microsoft Access Version 11.0. A copy of the survey was created in Access and once all of the surveys were entered, the database was analyzed using the Statistical Package for Social Sciences (SPSS) Version 15.0 for Windows. Descriptive statistics including frequency tables and cross-tabulations were used to analyse data. Data was cleaned by coding answers. For instance, when respondents provided answers to open-ended questions the answers were coded to allow for an overall view of the respondents' answers. This occurred when participants had the option of providing a different response from the list provided. In this case, like-responses were grouped together. For example, participants were asked in question 23 to state which source provided the initial HCV diagnosis if it was made prior to referral. Participants could choose from a list of responses that included such disciplines as primary care, prison healthcare, and hepatology. If a source was not listed, participants could specify the *other* source such as, psychiatric hospital. These *other* sources were then coded by combining the specified sources into group so that they could be given a coding number and then analysed.

3.4 Ethical Considerations

Permission to conduct the study was granted by the Human Investigation Committee (HIC) of the Faculty of Medicine, Memorial University. When conducting any form of research involving humans the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS) must be applied. The TCPS ensures

respect for human dignity. The welfare and integrity of participants are of primary concern during the research process. Respect for privacy and confidentiality was employed throughout the study. This was addressed in terms of the protection towards the access, control and dissemination of personal information of research subjects. The surveys are kept in a locked storage area and access is limited. Moreover, computer files are password protected. In addition, the requirement of free and informed consent was put into effect so that all participants were fully aware of the intentions of the study. Completion of the questionnaire was taken to indicate individual consent. The study was conducted by policies on ethics outlined by HIC. An HIC application for the study was submitted in September 2006 and approved on January 22nd 2007 (Appendix F).

CHAPTER 4: RESULTS

4.1 Introduction

The following section presents detailed results obtained from the analysis of data collected by the national survey of Hepatitis C services in Canada, 2006. The respondents were 222 physicians selected from the CMD under the specialties of gastroenterology, infectious diseases, and hepatology. French speaking physicians were excluded from the survey.

4.2 Response Rate

From the initial list of 562 physicians, 25 were deemed ineligible for the study due to the following reasons: returned to sender (e.g. moved, does not treat HCV patients) (n=17), emailed to state they do not treat HCV patients (n 5) and retired (n 3). A random sample of 36 physicians who had not yet returned the questionnaire received follow-up telephone calls a month and a half after the survey package was distributed. Of the physicians who were phoned, 9 were deemed ineligible for the study as follows: do not treat HCV patients (n=4); no time to fill out survey (n 1); moved (n 2); on holiday (n=1); on maternity leave (n=1). In total, 34 physicians were deemed ineligible from the initial list of 562. Therefore, of the eligible 528 physicians, 222 returned completed questionnaires (42% response rate). There was no significant difference observed between the respondents who received a business reply stamped envelope and an envelope with a real postage stamp. Almost half of the respondents who replied (50.9%) had a real stamp, and just less than half (49.1%) had a business reply stamp.

Forty-three percent of respondents provided a comprehensive service (included treatment and follow-up), 33% provided a diagnostic and investigative service (followed by referral to dedicated HCV service), and 24% had no role in the management and diagnosis of people with HCV. Table 2 presents the response rates by specialty.

Table 2: Response rates & management role in the care of patients with chronic Hepatitis C by specialty

	Number in initial survey	Number in survey after correcting for ineligible respondents N (%)	Overall responding N (% total)	No role N (%)	DIP N (%)	CSP N (%)
GI	330 (58.7)	308 (58.3)	119 (38.6)	31 (58.5)	35 (47.9)	53 (55.2)
ID	172 (30.6)	162 (30.7)	78 (48.1)	21 (39.6)	35 (47.9)	22 (22.9)
Hepatology	60 (10.7)	58 (11.0)	25 (43.1)	1 (1.9)	3 (4.1)	21 (21.9)
Total	562 (100)	528 (100)	222 (42.0)	53 (100)	73 (100)	96 (100)

DIP= diagnostic & investigative provider
CSP= comprehensive service provider
GI=Gastroenterologist
ID=Infectious disease specialist

The medical practice of the respondents was approximately 54% (119/222) gastroenterologists, 35% infectious disease specialists and 11% hepatologists. Coordinated Service Providers (CSPs) made up of 84% (21/25) of the hepatologists who responded, 28% of infectious disease specialists, and 45% of gastroenterologists. The majority of infectious disease specialists provided no role or a diagnostic investigative provider (DIP) service (72%). Slightly over half of the gastroenterologists provided no role or a DIP service (55%). Infectious disease specialists had the highest response rate of 48%, followed by hepatologists (43%) and gastroenterologists (39%); however, the differences were not statistically significant, (χ^2=3.93, d.f=2, P 0.1374) (refer to Table 2).

4.3 Socio-demographic Characteristics

The distribution of the socio-demographic characteristics for the DIPs and CSPs are summarized in Table 3.

Table 3: Socio-demographic characteristics of DIPs (N=73) and CSPs (N=95)

Variable	Total DIPs (N=73)	Total CSPs (N=95)
Age group		
<30	0	0
30-39	30.1% (22)	15.8% (15)
40-49	39.7% (29)	42.1% (40)
50-59	21.9% (16)	29.5% (28)
60 +	8.2% (6)	12.6% (12)
Missing data	0	1% (1)
Sex		
Male	66.7% (48)	82.1% (78)
Female	33.3% (24)	17.9% (17)
Missing data	1% (1)	1% (1)
Years in Practice		
<5	21.4% (15)	7.4% (7)
5-9	17.1% (12)	18.9% (18)
10-19	34.3% (24)	38.9% (37)
≥ 20	27.1% (19)	34.7% (33)
Missing data	4% (3)	1% (1)
Size of community where they practice		
≤ 25,000	0	2.1% (2)
>25,000 but <100,000	4.1% (3)	6.3% (6)
100,000 to 500,000	17.8% (13)	44.2% (42)
> 500,000	78.1% (57)	47.4% (45)
Missing data	0	1% (1)
Practice Type*		
Solo practice	11	44
Multiple-specialty group	11	16
Academic	54	40
Other	1	2

*Respondents could indicate more than one practice type
Multiple-specialty group Patients managed by a team (i.e. HCV nurse and gastroenterologist) that coordinates care
Academic University based

The age group most represented by DIPs and CSPs was 40-49 years. The distribution of males versus females for DIPs was 66.7% and 33.3% respectively, and for CSPs the distribution was 82.1% males and 17.9% females. DIPs were mostly practicing in districts of over 500,000 people and the majority had between 10-20 years in practice. Moreover, the majority of DIPs were practicing in academic centres.

Overall, the CSPs had between 10-20 years of practice and were practicing in communities with 100,000 to more than 500,000 people. In addition, CSPs were primarily practicing in academic centres or in solo practice.

4.4 Management of HCV Patients by Diagnostic Investigative Providers

The majority of the populations being served by the clinical practice or hospital of DIPs was predominantly urban followed by mixed urban (more urban than rural) (refer to Figure 2). Patients diagnosed with HCV in the practice or hospital served by DIPs are managed as follows: Overall DIPs indicated that gastroenterologists, infectious disease specialists and internists manage HCV patients less than 50% of the time.

Question 7 of the survey asked DIPs to estimate the proportions of patients diagnosed with HCV in their practices who were managed by different types of specialists (hepatologists, gastroenterologists, infectious disease specialist). Just over half of the DIPs indicated that hepatologists managed HCV patients more than 50% of the time and 20% indicated that gastroenterologists managed patients more than 50% of the time. This demonstrates that HCV patients are for the most part managed by hepatologists, followed by gastroenterologists (refer to Table 4).

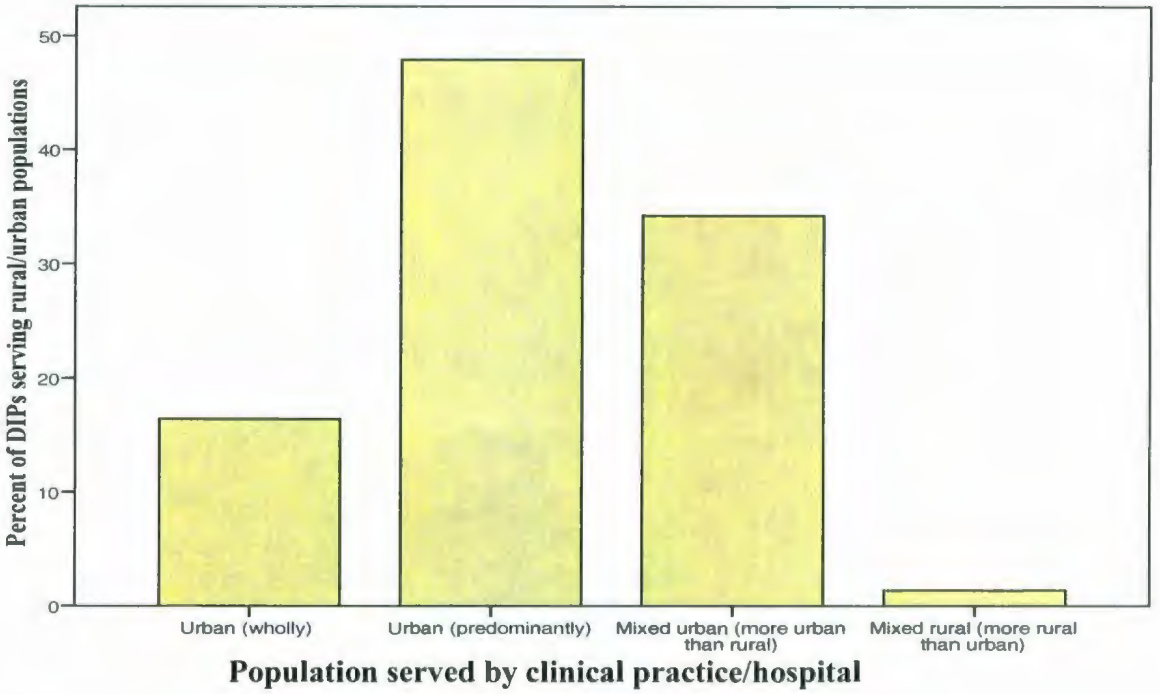

Figure 2: Distribution of the population served by DIPs clinical practice or hospital

Participants were asked to indicate approximately how many patients they diagnosed with HCV in 2005. Most DIPs cared for a small number of patients with HCV infection, with 72% diagnosing less than 10 patients with HCV (2005) and 92% diagnosing less than 20 patients (refer to Figure 3). Moreover, over 90% of the time the majority of patients diagnosed with HCV by DIPs are referred to a specialist HCV service (refer to Figure 4).

Table 4: DIPs identification of specialties that manage patients diagnosed with HCV

	Proportion of DIPs indicating which specialties manage HCV patients			
Proportion of patients managed (%)	**GI (N=69)**	**Hepatologist (N=69)**	**ID (N=69)**	**Internist (N=67)**
≤ 50	79.7%	49.3%	89.9%	100%
>50	20.3%	50.7%	10.1%	

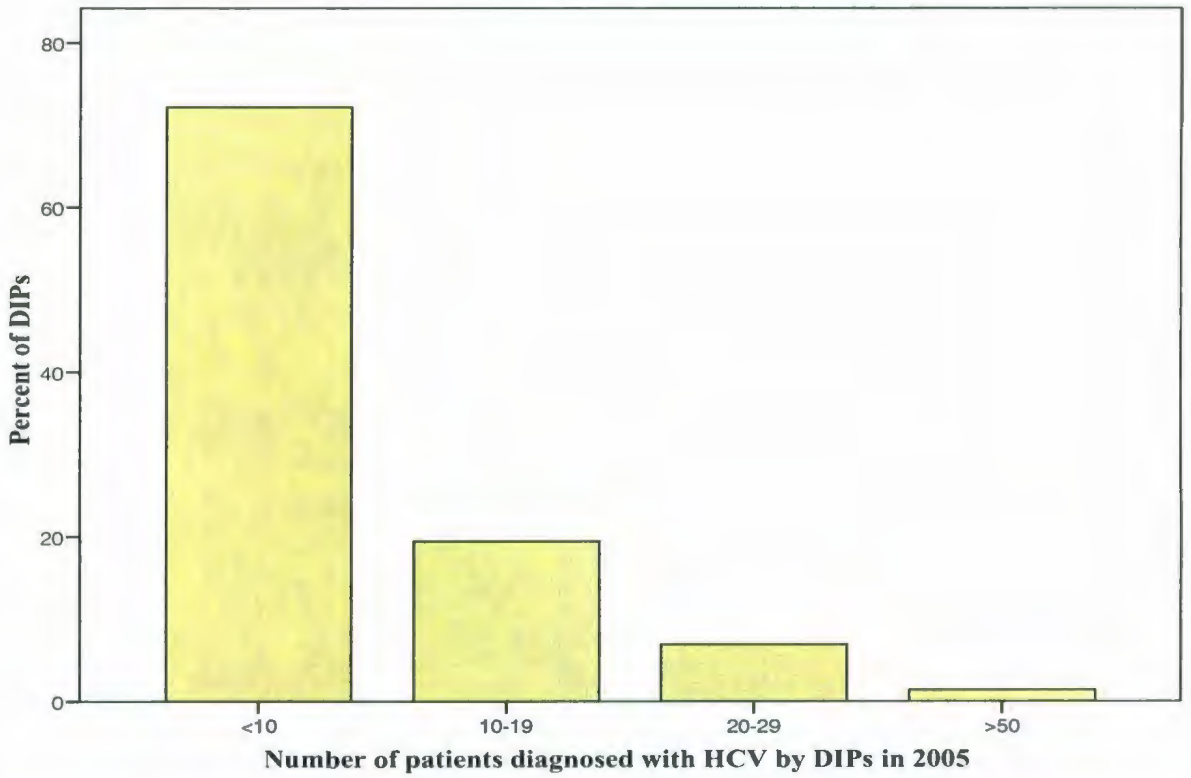

Figure 3: Number of patients diagnosed with HCV by DIPs in 2005 –results based on 72 DIP respondents

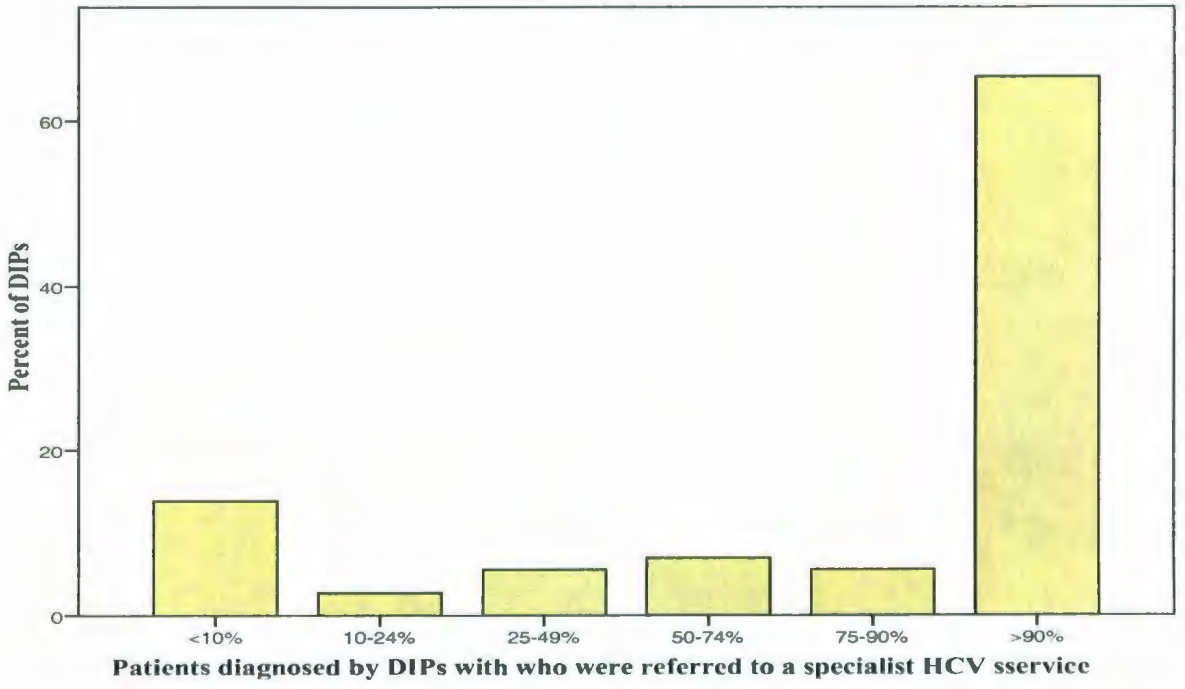

Figure 4: Percentage of patients diagnosed with HCV by DIPs who are referred to a specialist HCV service - results based on 72 DIPs respondents

DIPs have access to diagnostics tests either in-house or external (refer to Table 5). The majority of DIPs do not treat HCV patients (76%) and Figure 5 summarises the hospitals that provide a specialist HCV service to their patients. The majority of DIPs (91%) indicated the name of the hospital to which they refer their patients.

Table 5: Diagnostic tests available to DIPs

	Percentage of DIPs* with access to diagnostic services	
Service	**In-house**	**External**
Qualitative PCR	52.9% N=70	47.1% N=70
Viral load measurement	44.9% N=69	57.1% N=70
HCV genotyping	40.6% N=69	58.0% N=69
Specialist liver histopathology	67.1% N=70	34.8% N=69

***Totals can exceed 100% as more than one response**

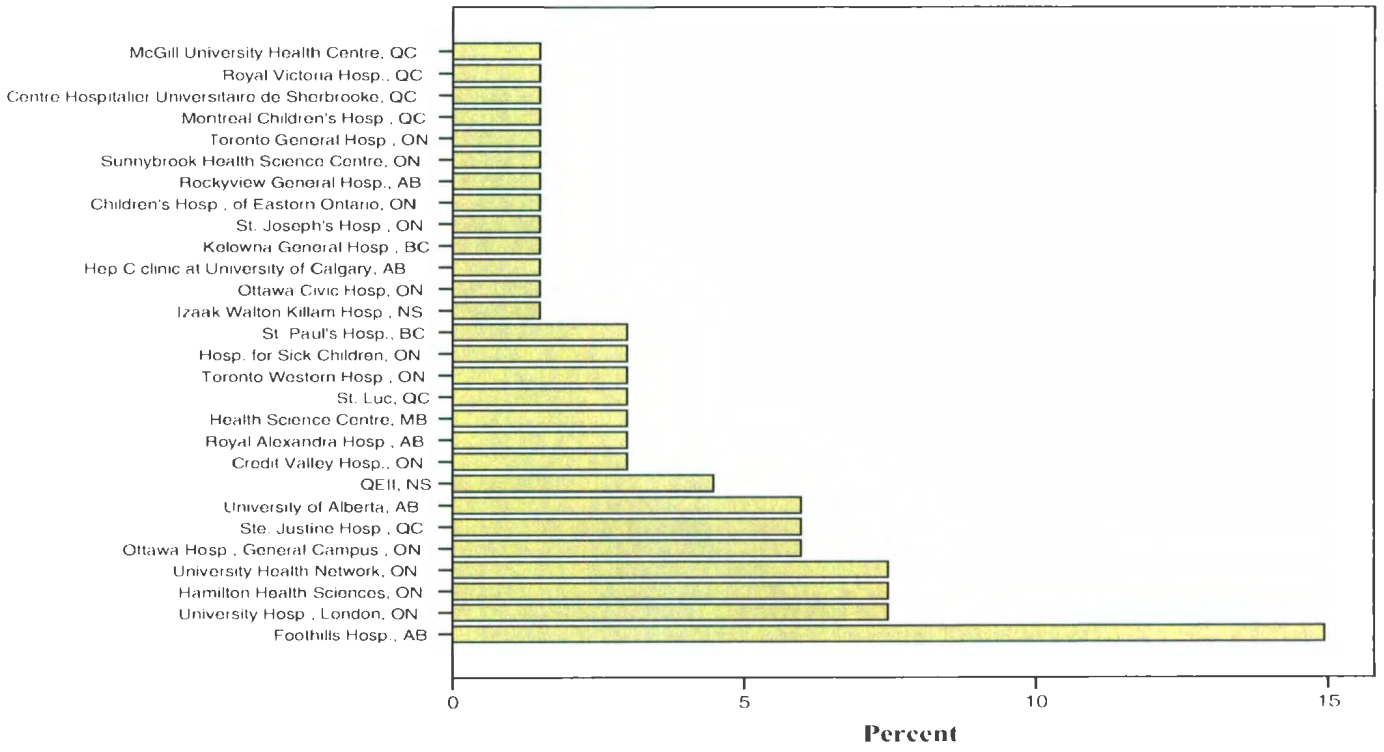

Figure 5: Hospitals referred to by DIPS that provide a specialist HCV service to their patients (N=67)

4.5 Management of HCV Patients by Comprehensive Service Providers

Comprehensive Service Providers were asked to specify the description that best fits the population served by their clinical practice/hospital. The majority of the populations being served by the clinical practice or hospital of CSPs was mixed urban (more urban than rural), followed by predominantly urban (refer to Figure 6).

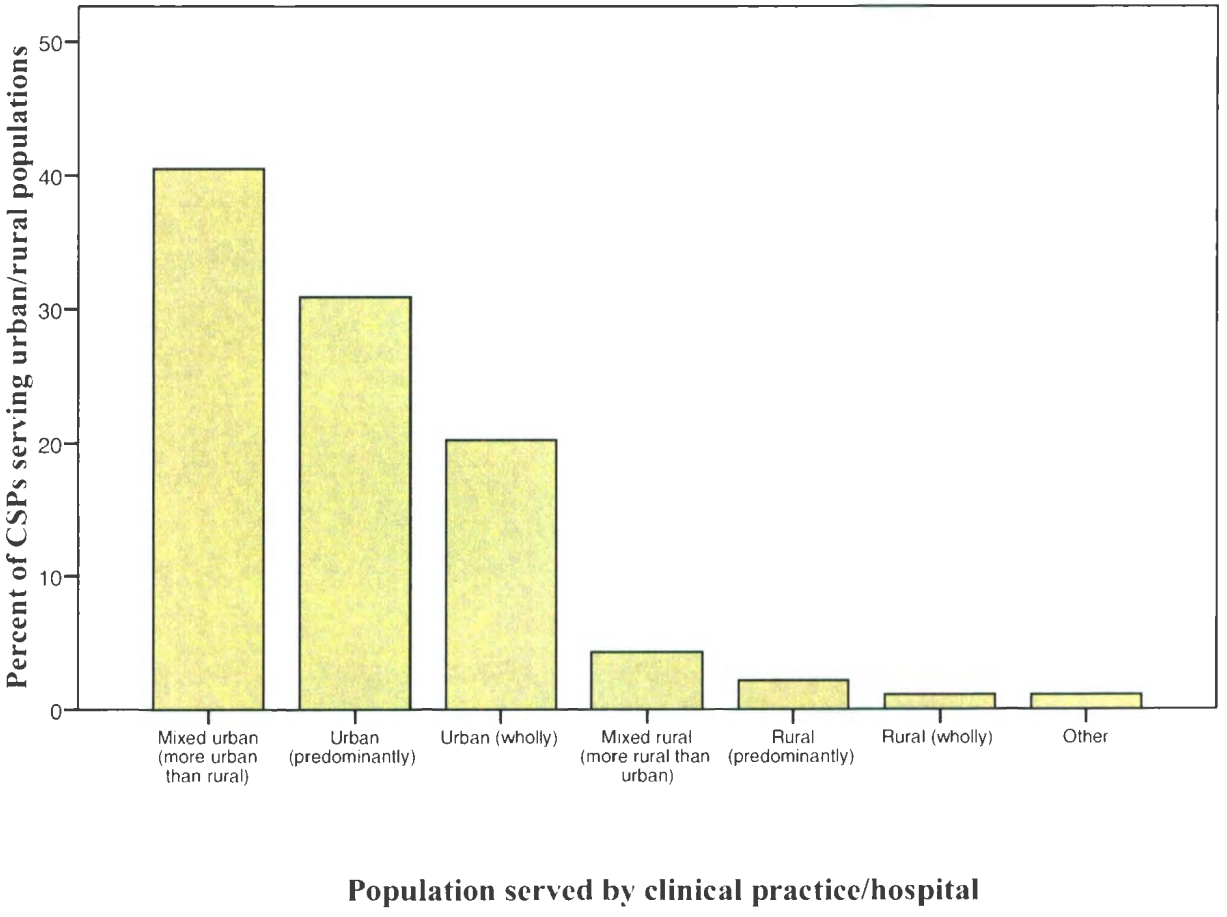

Figure 6: Distribution of populations served by CSPs clinical practice or hospital

Question 18 asked CSPs to indicate the total number of patients with known HCV currently under their care. The total estimated prevalent population of patients with HCV managed by the responding CSPs was 27, 652, of which 62% were managed by hepatologists (17,095/27,652), 20% were managed by gastroenterologists (5643/27,652) and 18% were managed by infectious disease specialists (4914/27,652). The number of prevalent patients varied between CSPs, the average number of patients under the care of CSPs was approximately 346. At the extremes, nine CSPs managed fewer than 20 cases in total and six CSPs were managing more than 1000 patients in total.

Table 6 shows the mean number of patients seen by CSPs by specialty. The median number of patients under the care of the hepatologists who responded was 900. Gastroenterologists had a median number of 134 under their care and infectious disease specialists had a median number of 259 patients under their care. Furthermore, 60% of the CSP respondents (48/80) had over 40 patients under their care (refer to Table 7). The information in Table 7 also reveals that a hepatologist or infectious disease specialist tended to care for more HCV patients than a gastroenterologist (χ^2=6.09, P 0.0476).

Table 6: Number of patients with known HCV under the care of CSPs by specialty

	N	Minimum	Maximum	Mean	Std. Deviation
Hepatologist	19	15	4000	899.74	1295.330
Gastroenterologist	42	3	1200	134.36	224.748
Infectious disease	19	20	1500	258.63	393.242

Table 7: Proportion of CSPs who have over 40 patents with HCV under their care by specialty (N=80)

		Number of CSPs who see less than 40 patients	Number of CSPs who see more than 40 patients	Total
		≤40	>40	
Specialty	Gastroenterology	22	20 (52%)	42
	Infectious diseases	6	13 (68%)	19
	Hepatology	4	15 (79%)	19
Total		32	48	80

Figure 7 shows the number of HCV patients under the care of CSPs divided by province. The province with the most CSPs who care for over 40 patients is Ontario, followed by British Columbia, Alberta, Quebec, New Brunswick, Saskatchewan, Nova Scotia and Newfoundland.

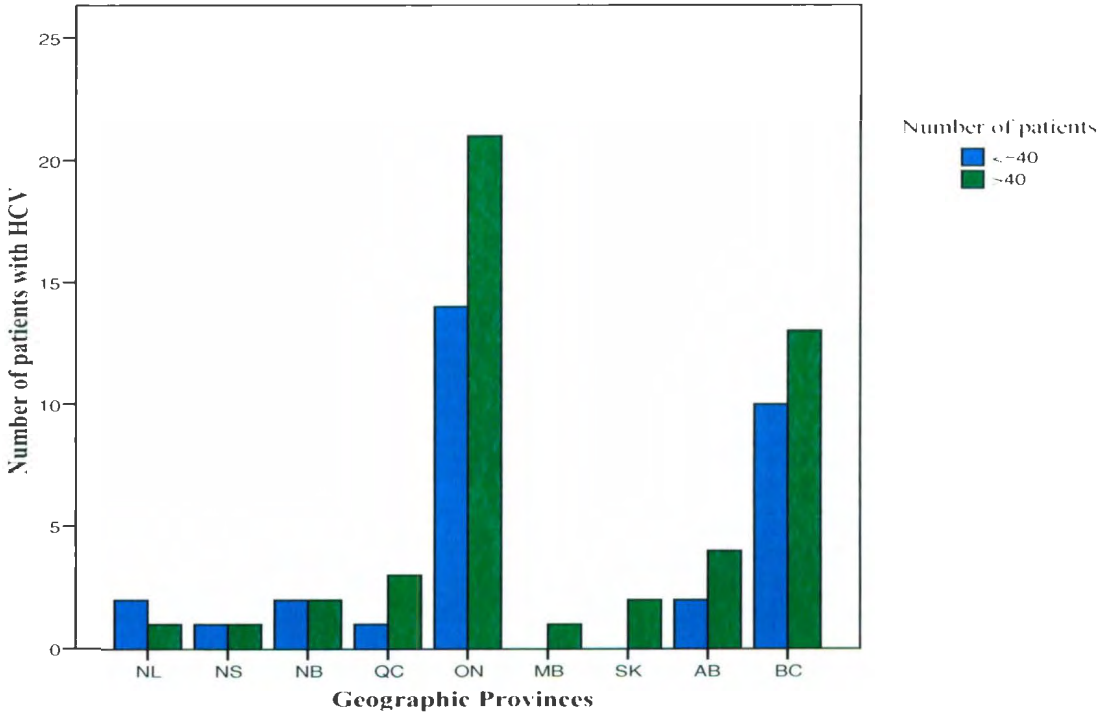

Figure 7: Number of patients with known HCV under the care of CSPs by province

Between 2003-2005 there is a gradual increasing trend in the number of patients seen by CSPs (refer Table 8). In 2003, 51.1% of CSPs saw over 20 patients, which increased to 57.3% in 2004, and finally to 59.4% in 2005.

Table 8: Approximate percentage of new patients seen by CSPs from 2003-2005

	Year		
Number of new patients	**2003**	**2004**	**2005**
<10	23.3%	16.9%	15.4%
10-19	25.6%	25.8%	25.3%
20-30	12.2%	15.7%	16.5%
>40	38.9%	41.6%	42.9%

The approximate percentage of new patients who miss their initial out-patient appointment was indicated to be between 10-24%, by 44% of the CSP respondents (refer to Figure 8).

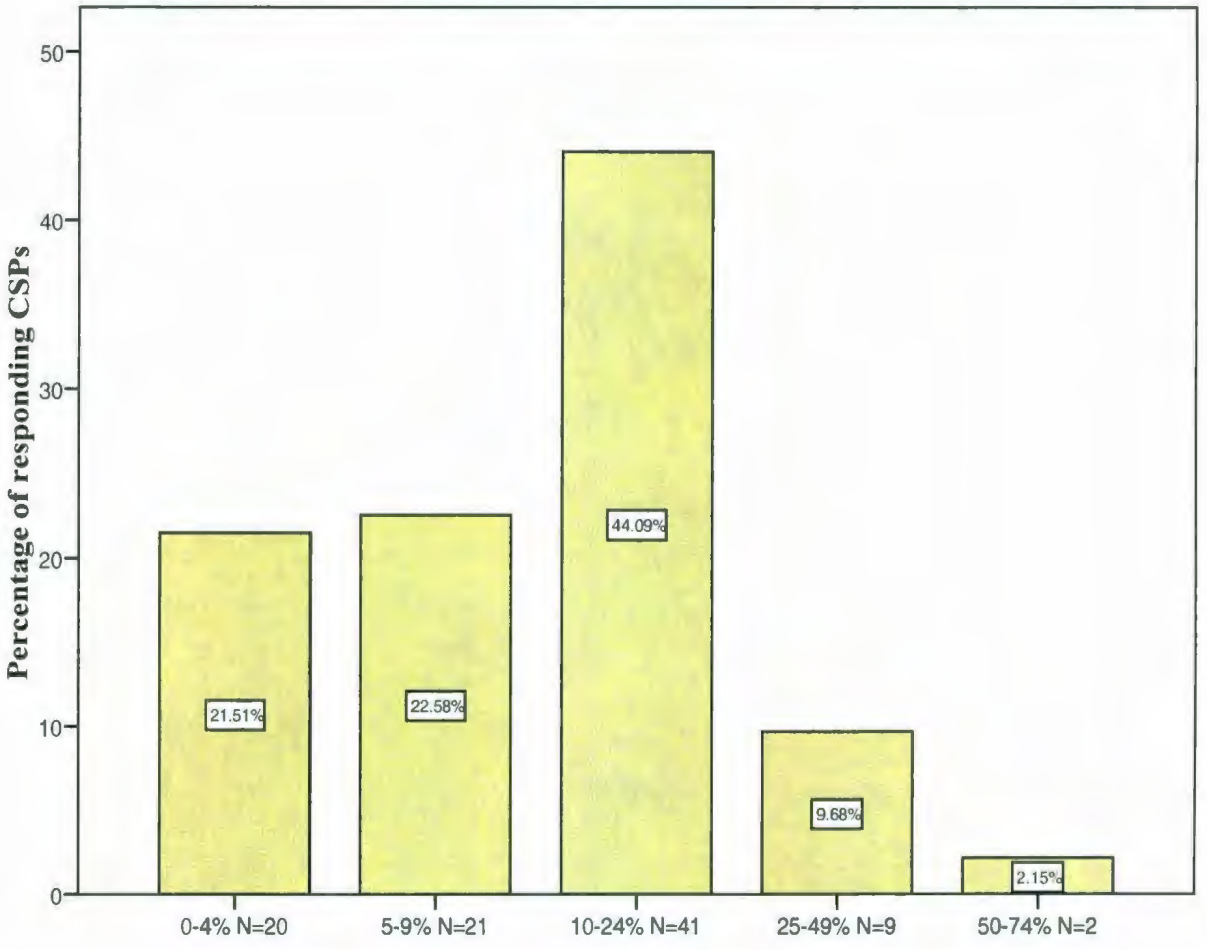

Figure 8: Approximate percentage of new patients who miss their initial appointment

Figure 9 reveals that the majority of CSPs spend between 5-24% of their time managing patients with HCV.

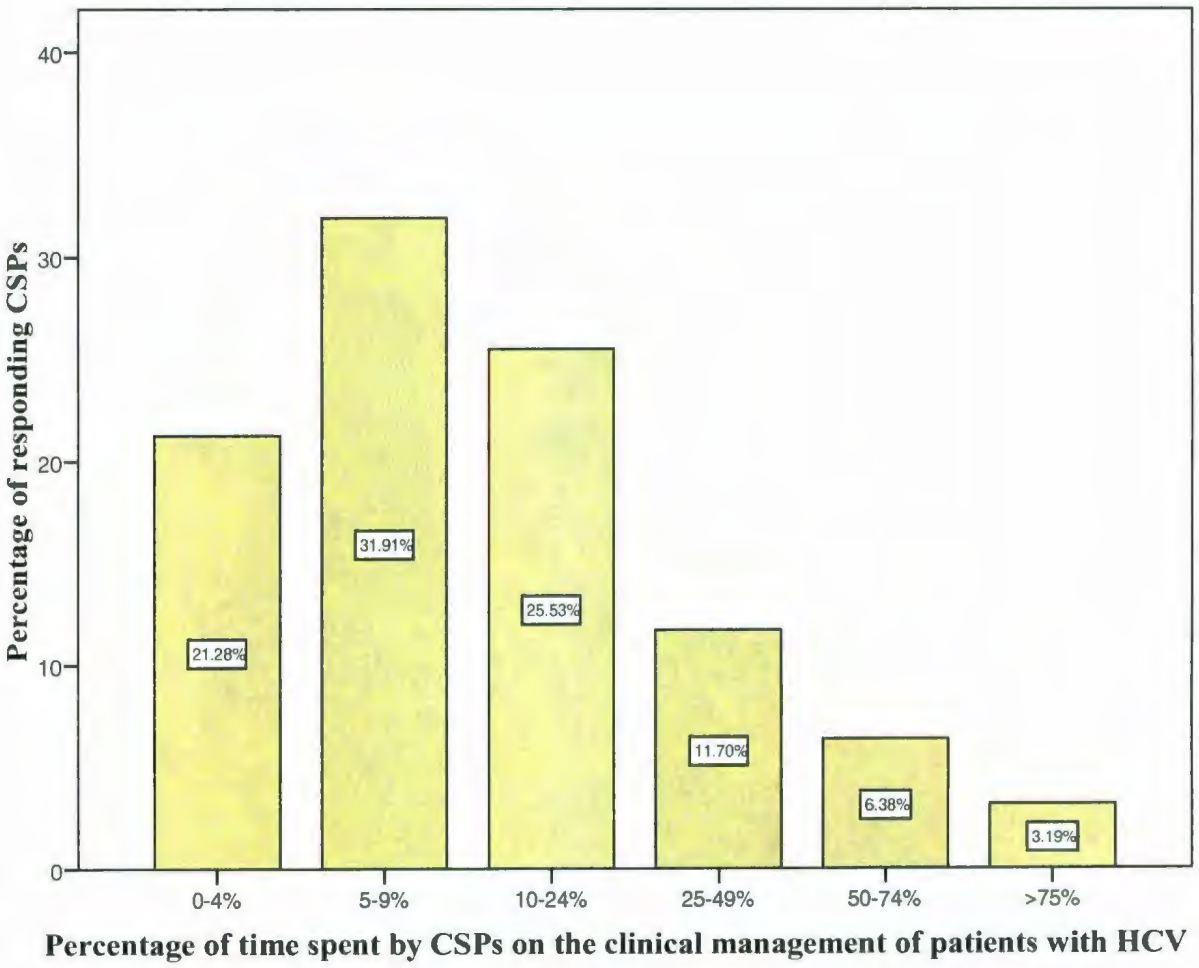

Figure 9: Percentage of time spent by CSPs on the clinical management of patients with HCV

4.5.1 Identification and Referral of HCV Patients Under the Care of CSPs

At the time of referral, half of the responding CSPs indicated that the diagnosis of HCV infection was already made over 75% of the time (refer to Figure 10).

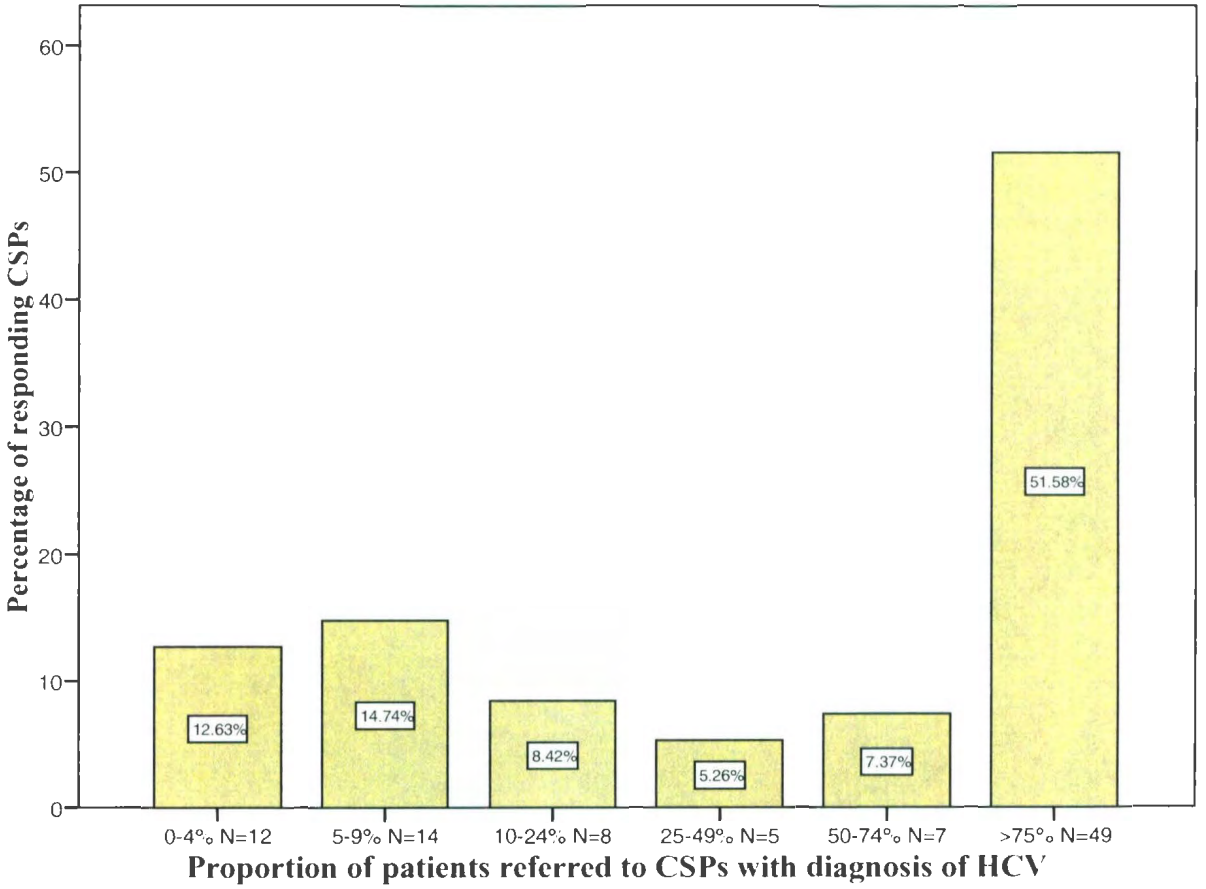

Figure 10: Proportion of patients referred to CSPs already diagnosed with HCV

Of patients referred with an established diagnosis, 60% of CSPs indicated that the majority of referrals came from primary care the majority of the time (80%). Gastroenterology and prison health care were the two other major clinical specialties in which patients were referred to CSPs already diagnosed; 11% of responding CSPs

indicated that they received patients already diagnosed over 10% of the time from prison health care, and 10% of responding CSPs indicated that they receive patients already diagnosed from gastroenterology over 10% of the time. Of those referrals where the CSP established the diagnosis of HCV, 63% of CSPs indicated that the majority of patients came from primary care over 80% of the time. Thus, the main source of referral to CSPs where the diagnosis was made before referral and where the CSP made the diagnosis is the same. Both referrals come from a primary care source. Therefore, patients being referred to CSPs from primary care have a 50% likelihood of already being diagnosed with HCV.

The majority of responding CSPs (80%) indicated that they refer patients to colleagues for further opinion or management. The main reasons for referral are as follows (refer to Table 9):

Table 9: Reasons for CSPs to refer HCV patients to colleagues (N=77)

Reasons for referral	Percentage of CSPs referring to colleagues
For treatment	5%
For follow-up	3%
For complex clinical issue relating to HCV	60%
For joint management (e.g. with psychiatry)	44%
For transplantation	83%
Patient wants a second opinion	33%

The main reasons that CSPs refer their HCV patients to colleagues are for transplantation, complex issues related to HCV and for joint management. In addition, CSPs respondents noted that they also refer patients to their colleagues for endoscopy, clinical trials and re-treatment.

4.5.2 Diagnostic Tests and Services Available for the Management of HCV Patients

The majority of the responding CSPs had access to diagnostic tests external to their practice or hospital (refer to Table 10). In contrast, more DIPs had access to such tests in-house than externally (see Table 5).

The availability of counselling and support services to CSPs for the treatment of HCV patients is shown in Figure 11. Access to an HCV specialist for post-test counselling and support was available to 46% of responding CSPs. In addition, 20% of CSPs had access to general counselling services, 12% had an HCV nurse, 3% had a nurse who was sponsored by a pharmaceutical company to counsel and support patients, and 16% had no access to any counselling services.

Table 10: Diagnostic tests available to CSPs

	Percentage of CSPs* with access to diagnostic services	
Service	***In-house***	**External**
Qualitative PCR	40%	65%
Viral load measurement	27%	76%
HCV genotyping	26%	77%
Specialist liver histopathology	50%	56%

*Totals can exceed 100% as more than one response

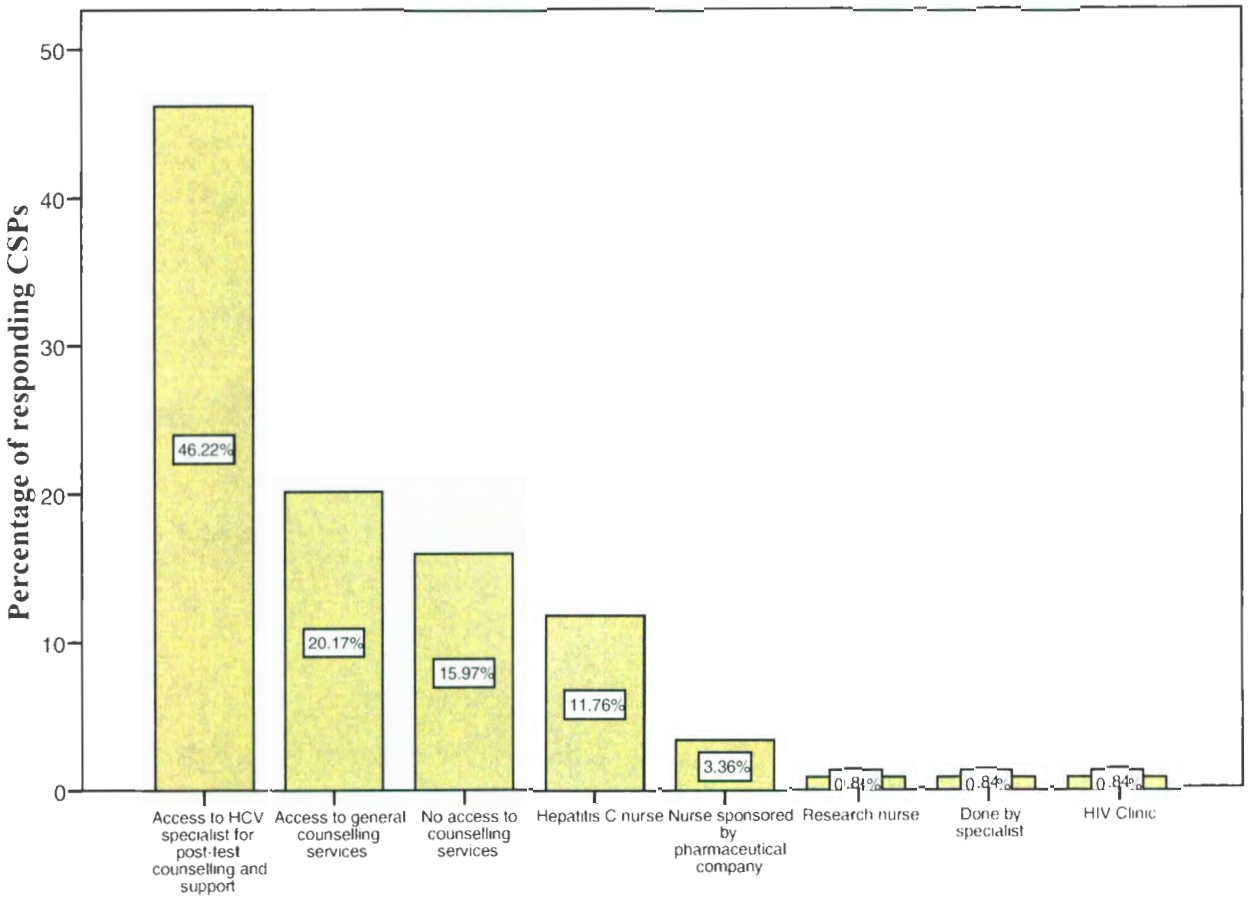

Figure 11: Counselling and support available to CSPs in their practice/hospital for HCV patients

4.5.3 Drug Treatment of HCV Patients

The majority of responding CSPs indicated that between 25-74% of new patients in their clinical practice were eligible for treatment in 2005 (refer to Figure 12).

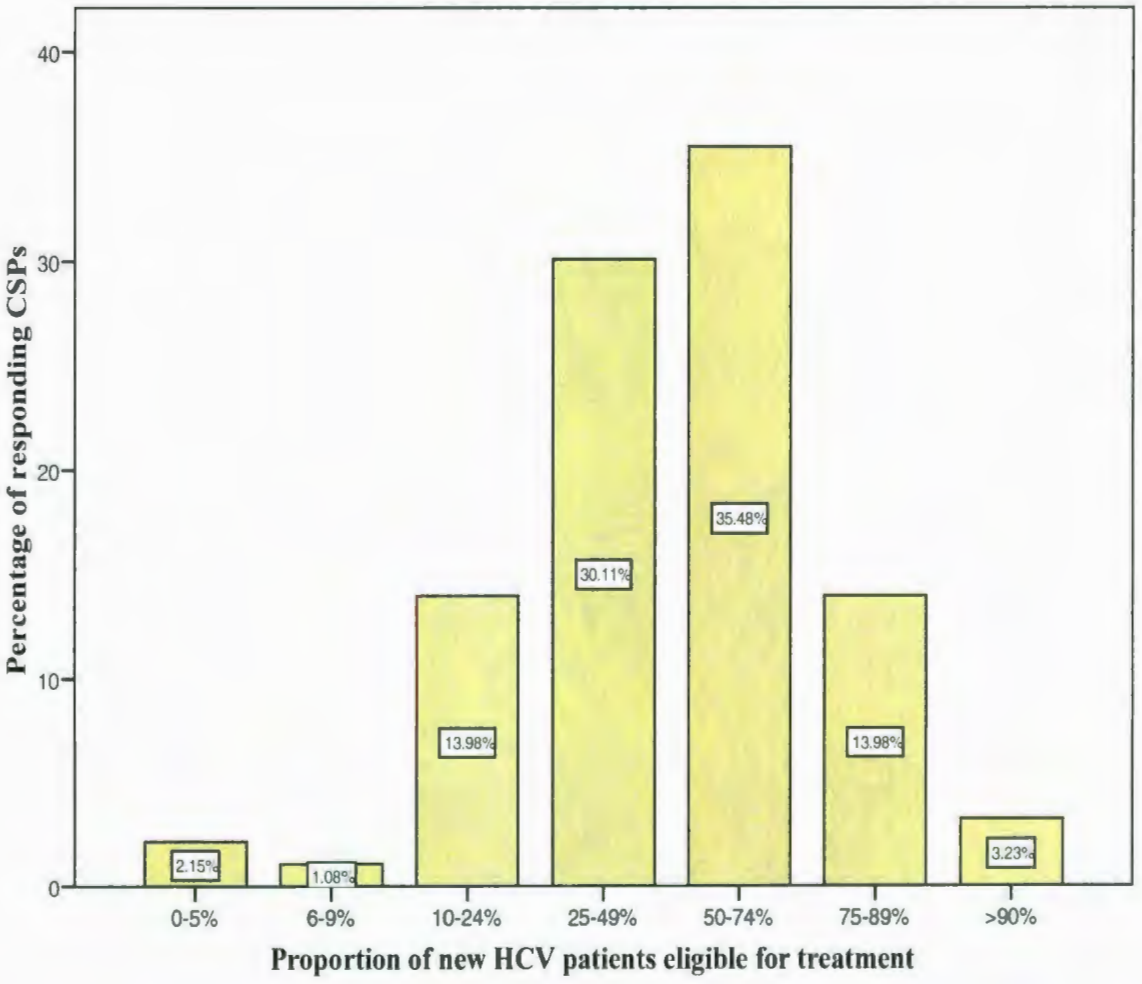

Figure 12: Proportion of new patients with HCV eligible for treatment in 2005 - based on reports from 93 CSPs.

Participants were asked to state the proportion of their HCV patients eligible for treatment who actually received treatment in 2005 (Figure 13). Over half of the CSPs (57%) indicated that at least 50% of their eligible patients received treatment. Thirty-three percent reported that over 75% of eligible patients were treated and 12% reported that over 90% of eligible patients received treatment. Figure 14 displays the percentage of patients who received treatment in the context of clinical trials in 2005. The majority of patients were not treated in the context of clinical trials with 58% of the responding CSPs indicating that only between 0-5% of their patients received treatment in the form of a clinical trial.

Table 11 shows the factors used to determine eligibility for treatment of patients with HCV. Over 90% of responding CSPs used severity of fibrosis and co-morbidities as criteria to determine eligibility. Other major factors considered are age (87%) and severity of hepatitis (86%). In addition, some respondents also indicated that they consider the following when determining treatment eligibility: insurance coverage, HCV RNA levels, prior treatment, psychosocial issues and compliance.

Virtually all of the responding CSPs definitely offered treatment to patients with moderate or severe hepatitis, extrahepatic manifestations, and Child-Pugh A (refer to Table 11). However, CSPs were less likely to treat patients with Child-Pugh C (19%) or if patients are awaiting transplantation (37%). The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. The score of 'A' refers to well-compensated disease, 'B'- a significant functional compromise, and 'C' -decompensated disease.

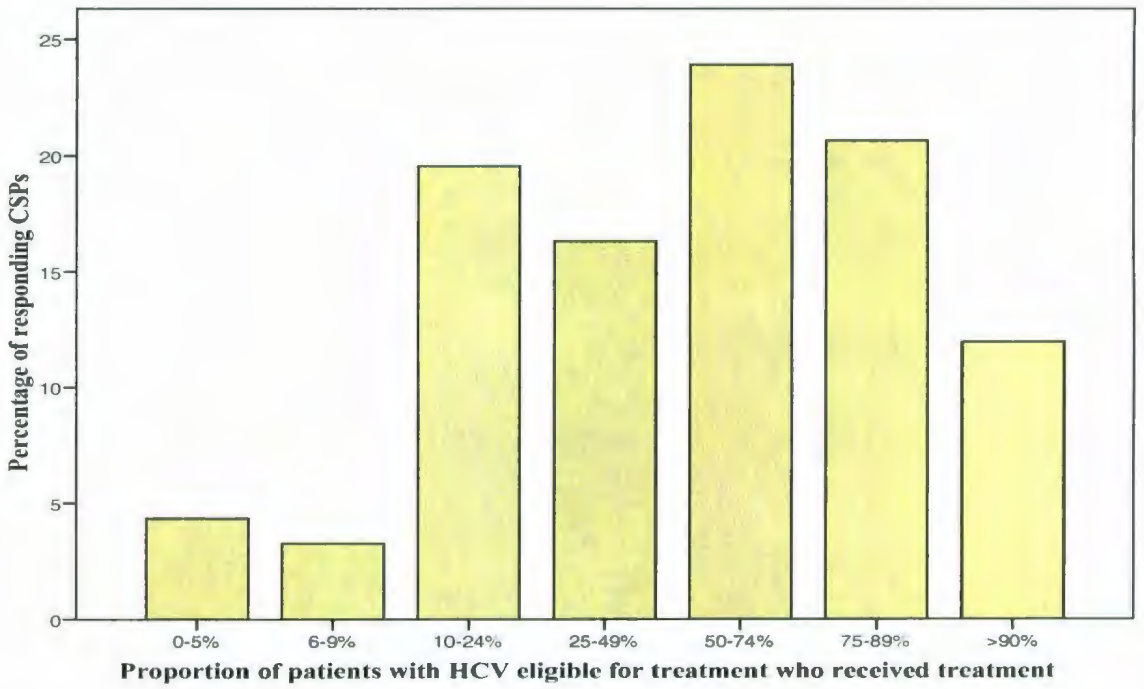

Figure 13: Proportion of HCV patients eligible for treatment who received treatment in 2005

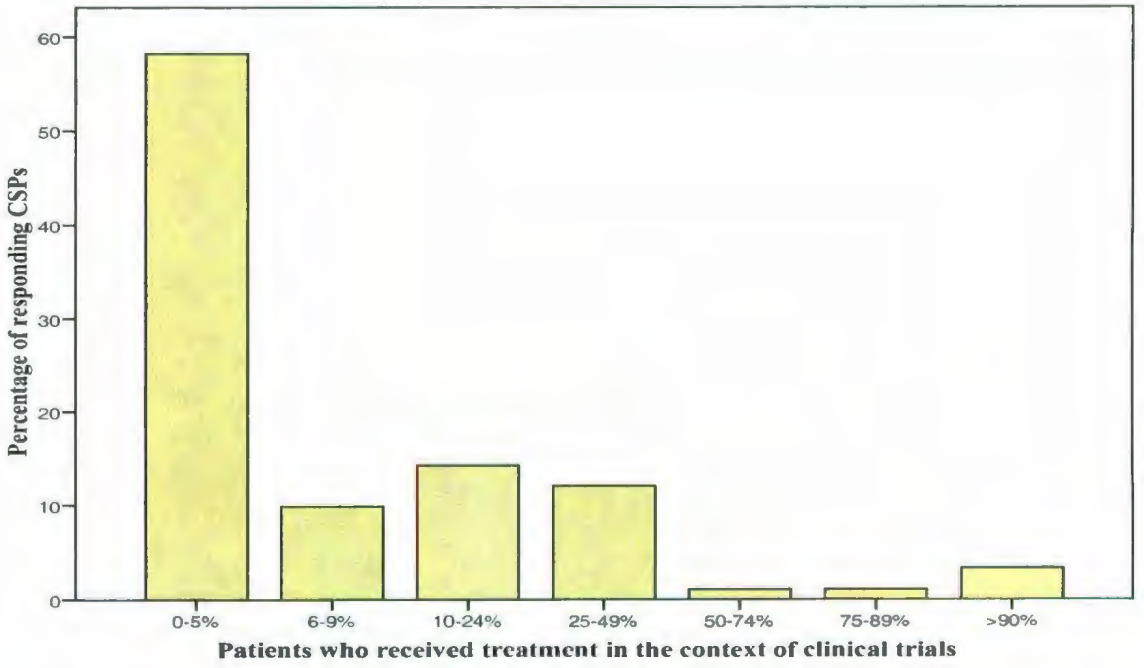

Figure 14: Patients who received treatment in the context of clinical trials in 2005

Table 11: Eligibility for anti-viral treatment of patients with HCV

Question	Choices	Percentage of CSPs saying yes
Which of the following criteria do you consider in determining eligibility for treatment?	Age **(N=92)**	87 %
	Sex **(N=91)**	9 %
	HCV genotype **(N=93)**	68 %
	Severity of hepatitis **(N=94)**	86 %
	Severity of fibrosis **(N=93)**	91 %
	History of substance use/abuse **(N=91)**	71 %
	Co-morbidities **(N=93)**	99 %
	Extrahepatic manifestations **(N=91)**	86 %
Would you likely offer treatment to patients with the following scenarios who had no other contraindications?	Mild hepatitis on biopsy **(N=89)**	73%
	Normal ALT **(N=88)**	60%
	With extrahepatic manifestations **(N=94)**	98%
	Moderate hepatitis **(N=94)**	96%
	Severe hepatitis **(N=94)**	97%
	Cirrhosis	
	Child-Pugh* A **(N=95)**	95%
	Child-Pugh B **(N=92)**	65%
	Child-Pugh C **(N=92)**	19%
	Patient awaiting transplantation **(N=92)**	37%

N= Number of respondents
***Child-Pugh score is used to assess the prognosis of chronic liver disease**

Responding CSPs indicated that the main reasons for patient ineligibility for treatment were ongoing illicit drug misuse, ongoing alcohol misuse, and psychiatric disorder. The main reasons that CSPs indicated for patient refusal of treatment were concern over drug reactions and inconvenience due to work pressures (refer to Table 12).

Table 12: Reasons for patient ineligibility and refusal of treatment (N=95)

Question	Choices	Percentage of CSPs saying yes
What are the main reasons for patients' refusal of treatment?	Refusal to modify chaotic lifestyle	46%
	Lack of belief in treatment effectiveness	27%
	Concern over adverse drug reactions	84%
	Inconvenient to start treatment due to work pressures	70%
	Lack of concern over future	13%
	Cost	50%
	Desire for pregnancy within 18 months	20%

The scenarios described in Table 13 were difficult to answer for many of the respondents, as there was not enough detail provided for each individual case. Moreover, 8% of respondents indicated that they would only provide treatment for certain scenarios if there was also co-care with a psychiatrist.

The majority of responding CSPs (94%) indicated that they would provide treatment to an ex-injection drug user who is stable on substitution therapy. Respondents were then asked to indicate how long the patient would have to be stable on substitution. Most CSPs (91%) indicated the patient would have to be on substitution treatment for more than 6 months, 4% of CSPs indicated the patients should be on substitution treatment for 3 months, and 4 % of CSPs indicated that there was no limit to the length of time.

Table 13: Treatment scenarios of people with moderate/severe chronic HCV

Question	Scenarios	Percentage of CSPs saying yes
Which of the following patients with moderate/severe chronic HCV are likely to receive treatment in your clinical practice?	Continuing injection drug user who regularly uses needle exchange	21% **(N=91)**
	Ex-injecting drug user stable on substitution treatment	94% **(N=92)**
	Heavy alcohol consumer in regular employment	14% **(N=92)**
	17 year old person with haemophilia: Would you do a liver biopsy?	25% **(N=85)**
	38 year old person with haemophilia without biopsy	91% **(N=85)**
	Person currently in treatment for psychiatric problems	61% **(N=86)**
	Person with history of attempted suicide	49% **(N=84)**
	Whilst using drugs of addiction	43% **(N=90)**
	In context of previous non drug related psychiatric problems	52% **(N=84)**
	Person with current diagnosis of depression related to HCV infection	78% **(N=92)**
	Person with current diagnosis of depression	58% **(N=91)**
	Person with past history of depression	97% **(N=92)**
	Person with poorly controlled diabetes	40% **(N=94)**
	Person with angina	34% **(N=93)**

Only 21% of CSPs would provide treatment to a continuing injection drug user who regularly uses a needle exchange program. The CSP specialty most likely to treat a current IDU were infectious disease specialists, of whom 40% reported that they would. This was followed by 24% of hepatologists and 12% of gastroenterologists. In reality, the scenarios in Table 13 are often more complex than what is described. Therefore, a yes or no answer cannot always be given to the underlying situation.

Effectively, all of the responding CSPs (99%) used pegylated interferon and ribavirin to treat patients with HCV. 67% of CSPs indicated that they do not use printed guidelines for dose reduction and stopping treatment. Of the CSPs who stated that they do follow guidelines (33%), 73% of responding CSPs follow the drug company standards and 18% follow the Canadian Association for the Study of the Liver guidelines.

A pre-treatment liver biopsy was performed on HCV patients less than 50% of the time by just over half of responding CSPs (56%). Only 22% of responding CSPs stated that they perform a pre-treatment liver biopsy over 75% of the time.

Just over half of responding CSPs (55%) reported that between 10-24% of patients stop treatment prematurely (both patients and professional initiated). The majority of the responding CSPs provided the following reasons for stopping treatment prematurely (refer to Table 14). The majority of responding CSPs (74%) selected no response to treatment as the number one reason for stopping treatment prematurely, followed by 61% indicating that side effects (patient initiated) was the second reason.

Table 14: Reasons for stopping treatment prematurely

Question	Reasons ranked 1-4
What are the reasons for stopping treatment prematurely?	1) No response to treatment 2) Side effects (patient initiated) 3) Side effects (professional initiated) 4) Loss to follow up

4.5.4 Patient Management

Co-ordinated management strategies for the treatment of patients with HCV were reported by CSPs (refer to Table 15). The most common formal collaboration between CSPs and other services was the link formed between the CSP and primary care, which was indicated by 30% of responding CSPs. This was followed by 22% of responding CSP indicating that they had a link with a nurse practitioner and drug and alcohol addictions services. In addition, of the 7% of responding CSPs who stated that they have other links to coordinated management, 50% indicated that they have a HCV nurse, while other CSPs indicated that they had links with HIV co-care and a social worker, both 17% respectively. Only 2% of CSP respondents from Table 15 described their coordinated management strategy used for providing care to their HCV patients. The answers provided indicated that of the CSPs, 32% have a multidisciplinary clinic, 28% have close communication with the referring physician and nurse practitioner, 16% have their patients managed by an HCV nurse, 12% are coordinated with the prison system, 8% have a nurse sponsored by a pharmaceutical company who managed their patients, and 4% are in close communication with a methadone clinic.

Table 15: Coordinated management of HCV patients

Question	Choices	Percentage of CSPs saying yes
Do you have a coordinated management strategy for patients with HCV linking secondary/tertiary care to:	Nurse practitioner	22% **(N=87)**
	Primary care	30% **(N=86)**
	Prison healthcare	15% **(N=85)**
	Drugs and alcohol services	22% **(N=85)**
	Homeless	4% **(N=85)**

The majority of responding CSPs (61%) had a multidisciplinary team coordinating the management of HCV. The composition of the team varied but most commonly included at least a consultant from the lead clinical specialty, and specialist nurse. Other teams were more complex and also had gastroenterologists, infectious diseases specialists and hepatologists (refer to Table 16). Of the 23% of CSPs who indicated that there were other members of the multidisciplinary team not provided in the selection choices, 50% stated that they also coordinate care with a psychologist, 21% have access to a social worker, 14% have access to a psychiatrist, and a hematologists and specialist dentist was indicated by 7% of responding CSPs respectively.

Table 16: Membership of multidisciplinary team to coordinate management of HCV patients (N=57)

Membership of multidisciplinary team	Percentage of CSPs saying yes
Gastroenterologist	56%
Internist	2%
Family Physician	16%
Hepatologist	40%
Specialist nurse	97%
Histopathologist	30%
Radiologist	18%
Infectious disease clinician	49%
Community drug and alcohol addictions counsellor representative	12%
Care professional from homeless agency	2%
Genito urinary medicine clinician	2%
Community intravenous drug users care professional	2%
Patient representative	2%
Community dentist	2%

4.5.5 Barriers to Providing a High Quality Service for Patients with HCV

91% of CSPs reported barriers in the management of patients with HCV. The main factors are shown in Table 17. Funding, patient non-attendance and staffing capacity were the most common.

Table 17: Barriers to providing a high quality service

Reason	Agree/strongly agree %	Unsure	Disagree/Strongly disagree %
Clinic waiting time for initial referral	43	5	52
Biopsy waiting times	15	3	83
Staffing capacity	46	3	51
Staffing skill mix	17	10	73
Funding for treatment	69	8	24
Patient refusal	58	16	26
Patient non-attendance	67	17	16
Patient identification	34	32	34

Table 18 displays the answers provided by CSPs who reported other barriers to care for patients with HCV. The main barriers indicated were lack of support and resources, such as access to HCV nurse specialists and funding from government and pharmacare, followed by education of other health care workers and referral at the family physician level.

Table 18: Additional comments regarding barriers in the management of patients with Hep C

Barriers	Percent of CSPs indicating barrier
Lack of support: funding(government/pharmacare); resources (Hep C nurse)	35%
Education of other health care workers and referral at family physician level	17%
Cost of treatment	14%
Time-consuming process	10%
Lack of coordinated multidisciplinary team	7%
Ineligible because of lifestyle issues (alcohol, drug use)	7%
Prison system not involved in coordination of HCV therapy	3%
Not enough physicians treating HCV patients	3%
Psychosocial issues (financial, employment, side-effects from treatment)	3%

Additional comments made by CSPs with regards to aspects of care for patients with HCV are summarised as follows. One CSP indicated that it is common practice for them to test for HCV RNA PCR at week four to detect if there was a rapid virological response to therapy. This is in addition to the customary HCV RNA PCR test at week 12. Other barriers to care involved treatment delay and long waiting lists. It was mentioned

that a large number of patients are referred to academic centres and not to their local physicians, thus creating a lengthier process for patients to initiate therapy. It was also indicated that the efficiency of the clinic was due to a dedicated care team and the presence of a nurse practitioner in the organisation and follow-up of treatment.

4.6 Geographical Distribution of Services

The distributions of English speaking physicians in the specialties of gastroenterology, hepatology and infectious diseases who are listed in the CMD are shown in Figure 15. The provinces with the smallest number of HCV health care providers are Prince Edward Island (n=1), Newfoundland (n 7) and New Brunswick (n=7). In contrast, the provinces with the largest number HCV health care providers are Ontario (n= 255), Alberta (97), and British Columbia (n=78). Figure 16 displays the distribution of HCV health care providers who responded to the survey. Canada's population by province is shown in Figure 17, which reveals that the distribution of specialists who are HCV healthcare providers follows a similar distribution to the population of each individual province. The only province that does not follow this pattern is Alberta, which shows that there are more HCV specialists in Alberta even though it has a smaller population than British Columbia.

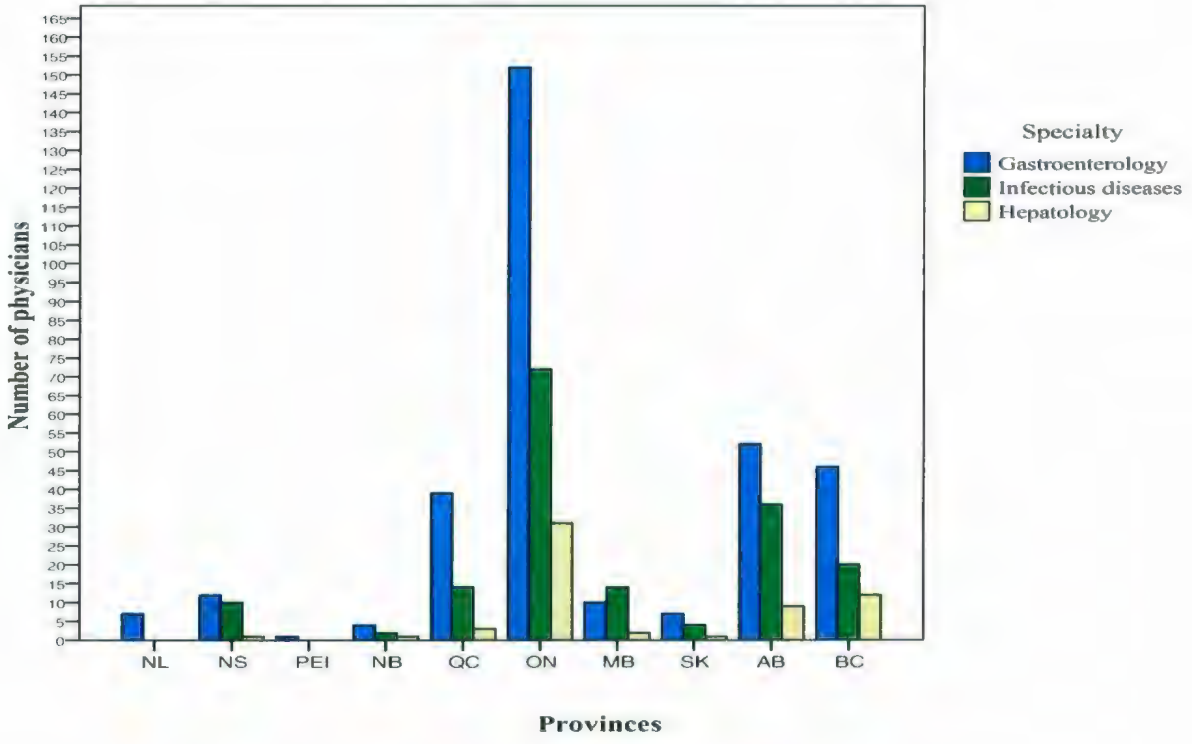

Figure 15: Distribution of English speaking HCV health care physicians by province

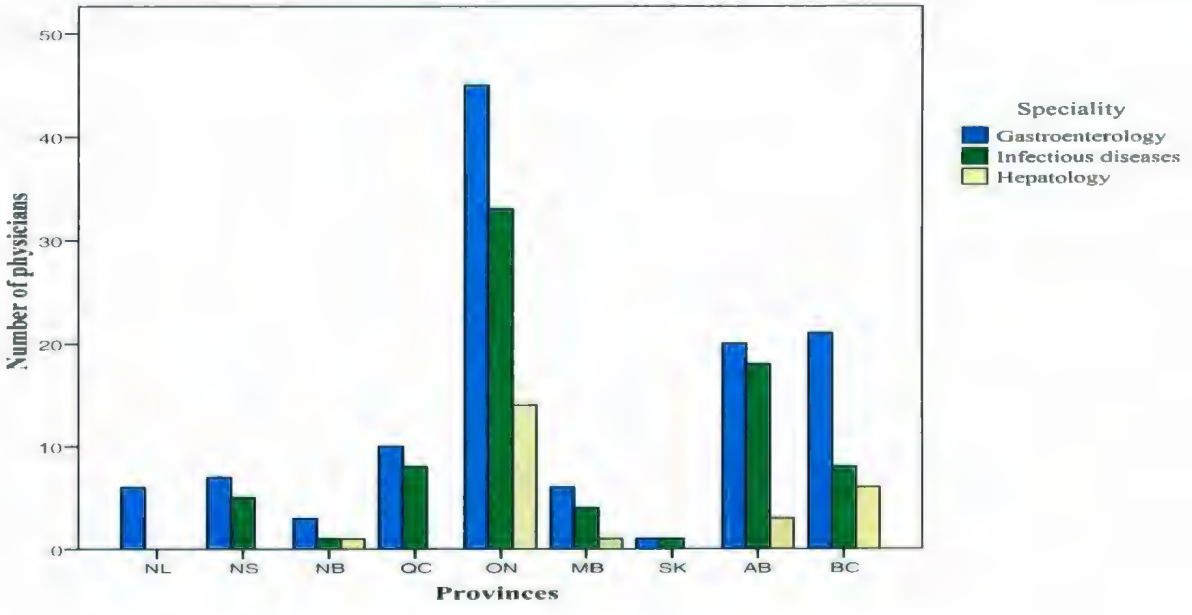

Figure 16: Distribution of English speaking HCV health care physicians who responded to the survey by province

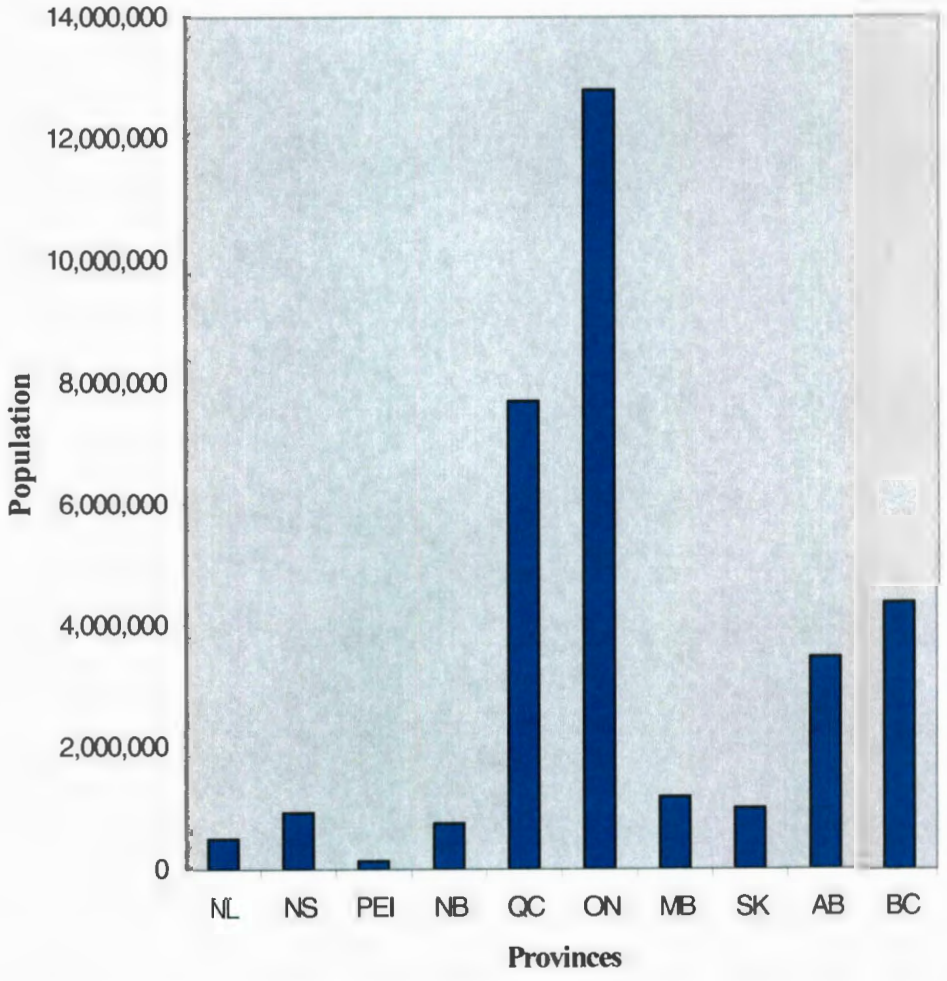

Figure 17: Canada's population estimates, July 2007 [172]

The majority of responding HCV healthcare providers from New Brunswick (100%), Saskatchewan, (100%), and Newfoundland (83%) indicated that they were CSPs. Respondents from Ontario and British Columbia reported that 43% were CSPs and 74% were CSPs respectively. The provinces that reported the smallest number of CSPs were Manitoba (9%), Alberta (22%), Nova Scotia (25%), and Quebec (28%) (refer to Figure 18).

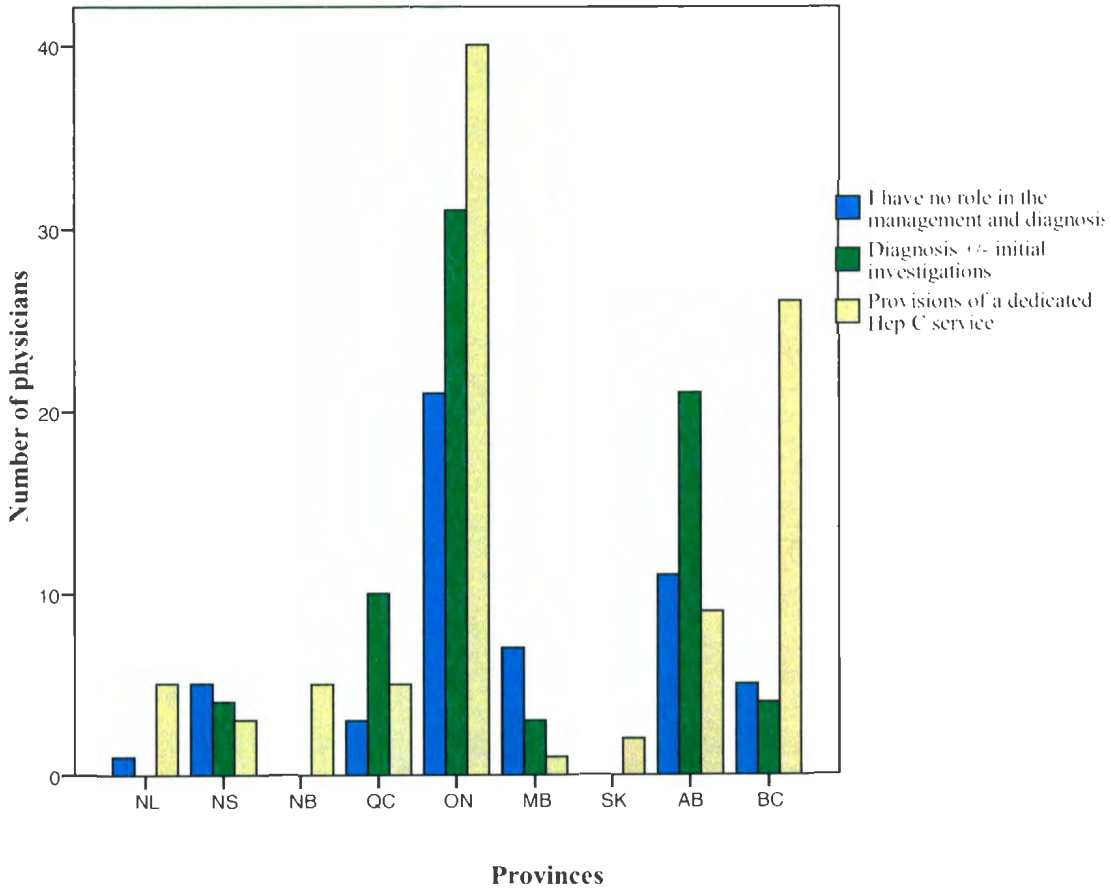

Figure 18: Distribution of roles in management of HCV patients by province

Figure 19 illustrates the distribution of HCV management roles across Canada. The survey results revealed that Western Canada has the greatest proportion of CSPs (74%), followed by Atlantic Canada (57%), Central Canada (41%) and the Prairies (22%).

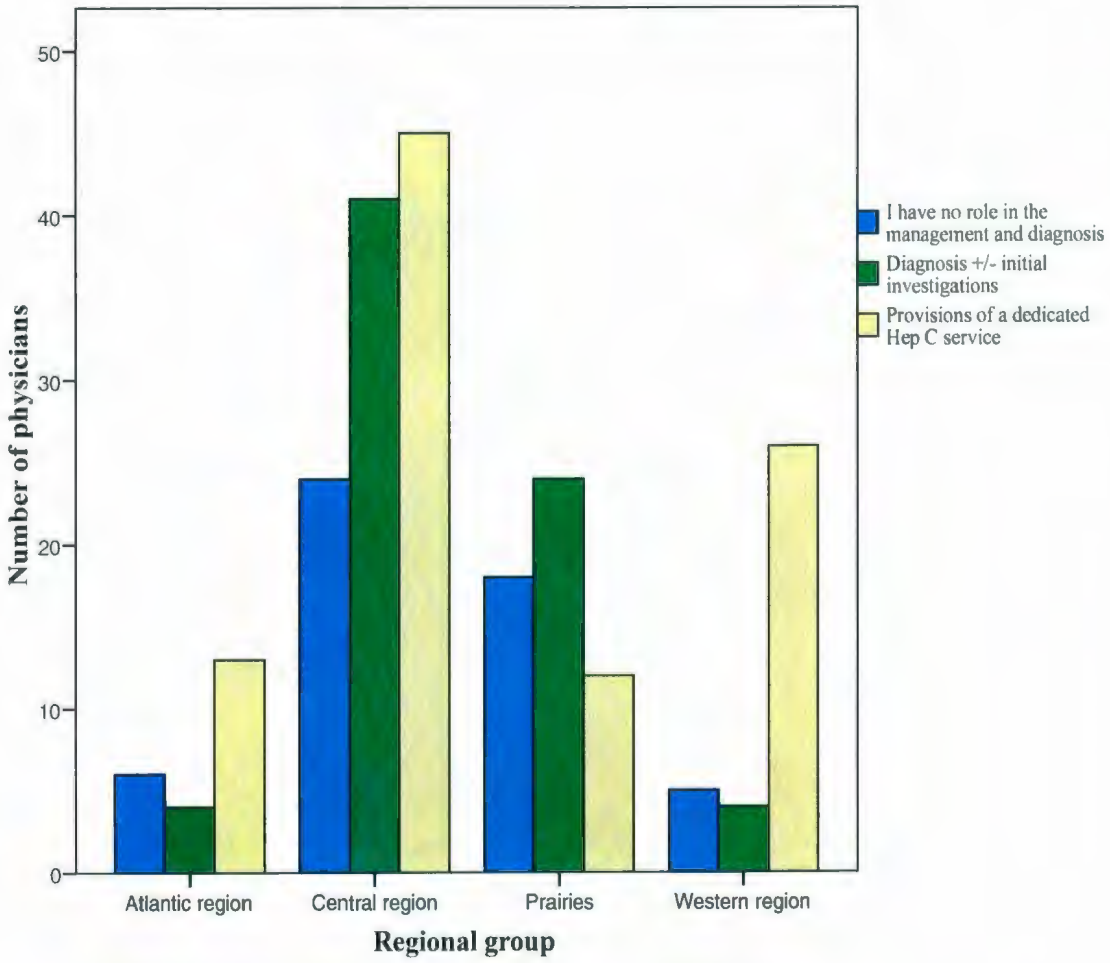

Figure 19: Distribution of roles in management of HCV patients by region
Atlantic Region=NL, NS, NB, PEI
Central Region=QC, ON
Prairies=MB, SK, AB
Western region= BC

The Prairies was the region that had the most CSPs (75%) who indicated that they saw over 40 patients in 2005. This was followed by 54% of CSPs in Western Canada, followed by 34% in Central Canada and 16% in Atlantic Canada (refer to Figure 20).

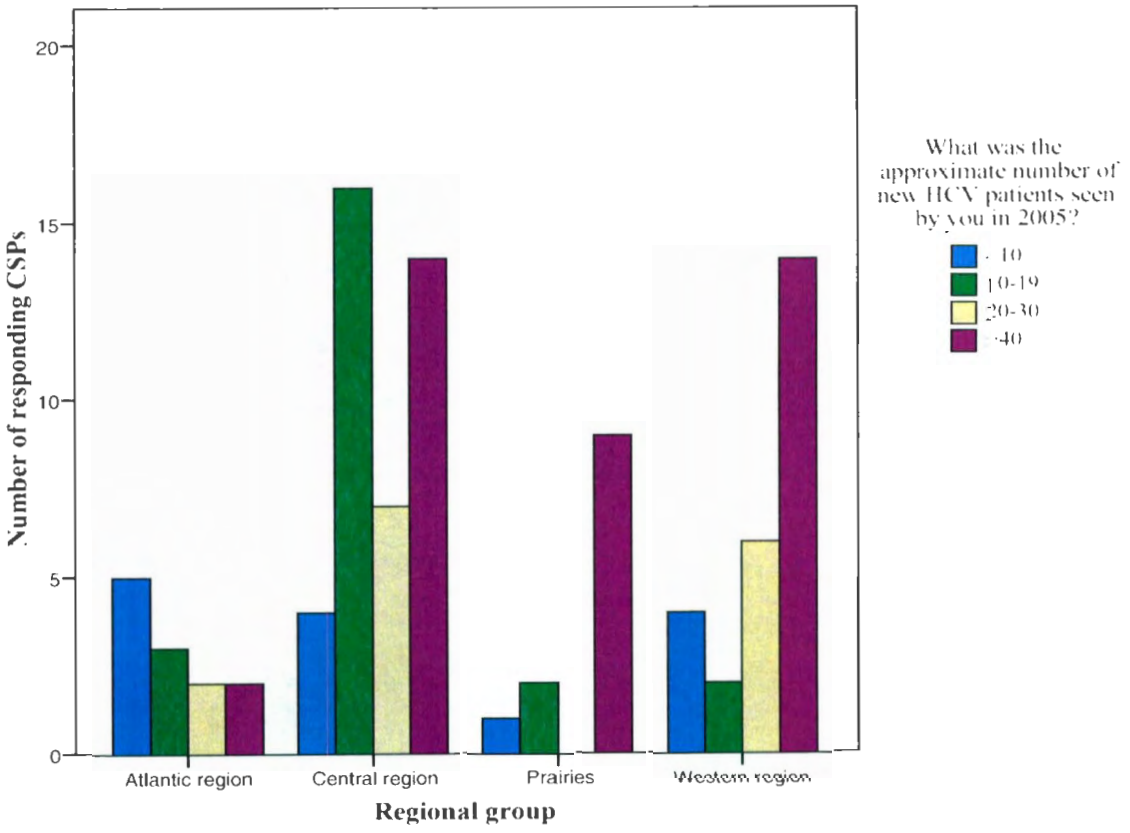

Figure 20: Number of new HCV patients seen by CSPs by region in 2005

The region that has the most CSPs working in a multidisciplinary team setting is the Prairies (92%). Western Canada has the second highest amount (73%), followed by Atlantic Canada (50%), and Central Canada (48%) (refer to Figure 21).

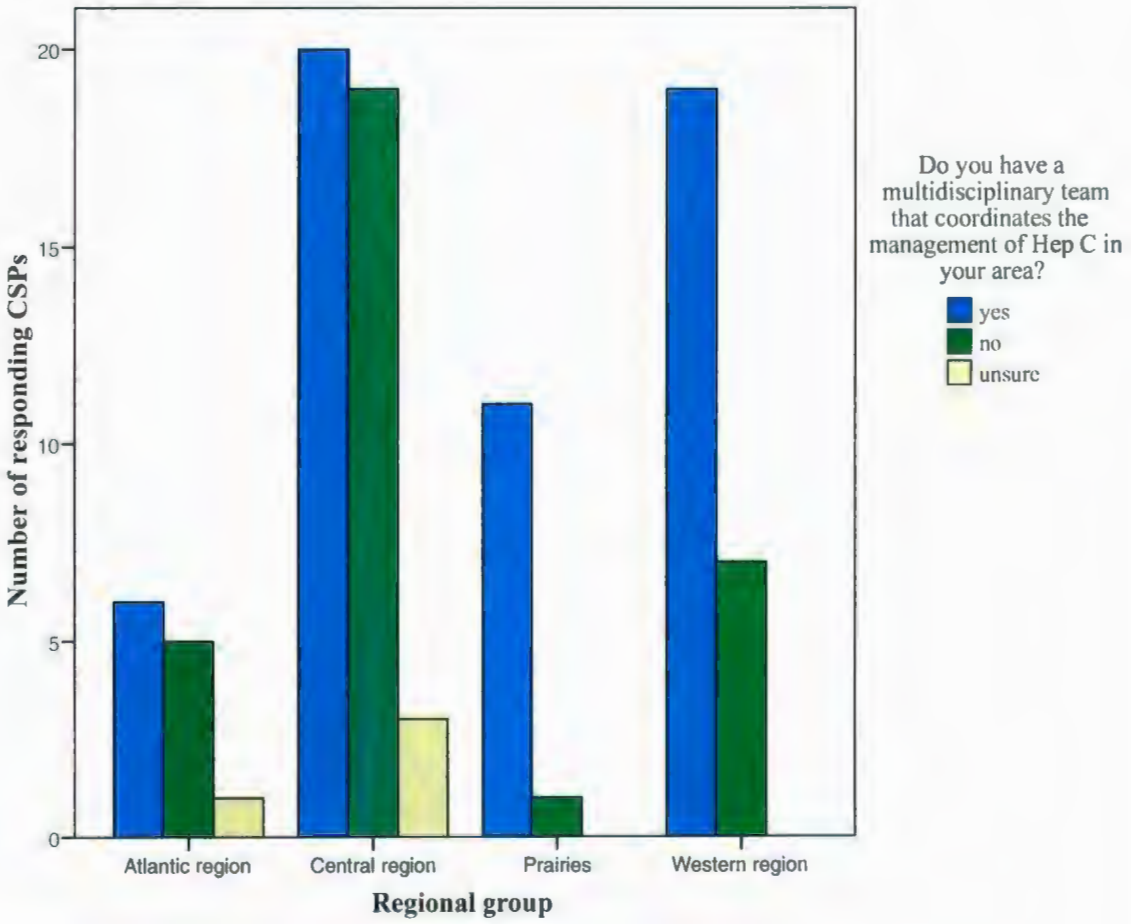

Figure 21: Distribution of multidisciplinary HCV care team by region

The province that had the highest percentage of CSPs most likely to treat a current IDU who uses a needle exchange on a regular basis was Alberta, with 50% of responding CSPs stating that they would provide treatment to a patient in this scenario (refer to Figure 22). This was followed by 33% of CSPs in Nova Scotia, 28% in Ontario, 20% in Quebec, and 12% in British Columbia.

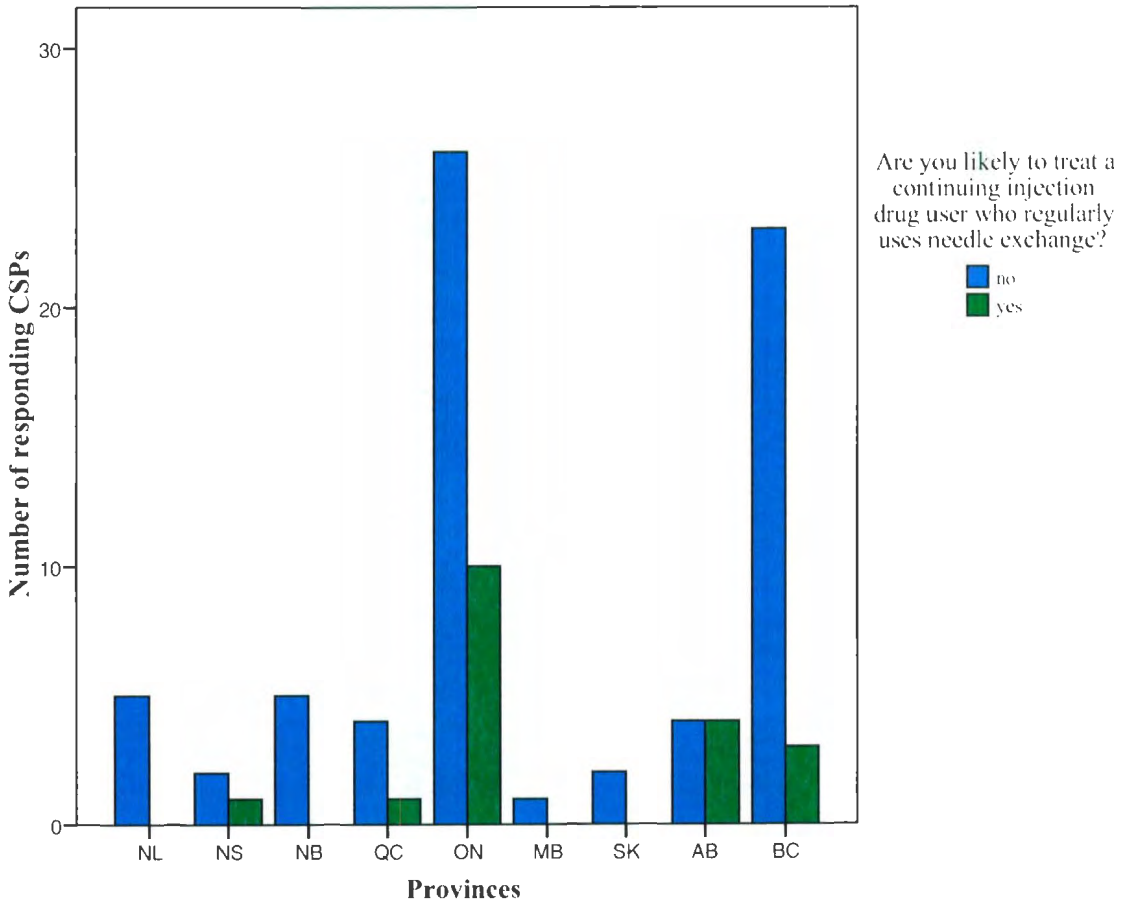

Figure 22: Distribution by province of CSPs most likely to treat a current IDU who regularly uses a needle exchange

CHAPTER 5: DISCUSSION

5.1 Introduction

This survey involved a national representative sample of physicians who manage patients with HCV. A completed questionnaire was received from 222 of the eligible 528 physicians surveyed, resulting in a response rate of 42%. This was higher than the response rate of 33% obtained in an American study on primary care physician's knowledge and practice patterns concerning HCV [152].

The study revealed variations in structure and configuration at all stages of the patient care pathway, such as size of practice community, number of patients, and type of care service provided.

5.2 Roles in the Management of HCV Patients

Variation was observed in the physician specialties (hepatology, gastroenterology and infectious diseases) that provided a coordinated service to HCV patients. Even though there were fewer physicians in the field of hepatology, 85% of hepatologists who responded to the survey designated themselves as a CSP. In contrast, only 45% of gastroenterologists and 28% of infectious disease specialists reported that they were a CSP.

Physicians who indicated that they provide a diagnostic investigative service stated that their patients are managed by hepatologists 50% of the time, followed by gastroenterologists 20% of the time. DIPs tended to look after very few HCV patients.

For instance, 72% of DIPs diagnosed less than 10 patients, and more than 90% of DIPs referred their HCV patients to a specialist HCV service.

5.3 Comprehensive Service Providers and HCV Patient Care

The distribution of HCV health care providers throughout Canada corresponded to the population distribution of each province. For instance, Ontario has the highest population with more than 12 million people [172] and also has the greatest number of HCV health care providers (infectious disease specialists, hepatologists, gastroenterologists) (n=255) listed in the CMD [2]. In contrast, PEI has the smallest population in Canada with 139,000 people, and only one HCV health care provider was identified in the CMD [2].

5.3.1 Provision of HCV care by Comprehensive Service Providers

CSPs tended to practice in large mixed-urban/urban communities with populations ranging between 100,000 to over 500,000 people. Despite the fact that there are fewer English speaking hepatologists practicing in Canada (n 60), compared to gastroenterologists (n=330) and infectious disease specialists (n=172), this survey found that the majority of HCV patients are cared for by hepatologists. It was found that a large number of gastroenterologists (n=119) were only caring for an average of 134 HCV patients. This is quite a difference compared to the 78 infectious disease specialists (who cared for an average of 259 patient and the 25 hepatologists (who cared for an average of 900 patients). This distribution of patients cared for by HCV care providers is likely due to the fact that the majority of HCV patients are referred to hepatology because

hepatologists generally have the most experience in the care and treatment of HCV patients.

5.3.2 Management of HCV Patients

Very few CSPs (46%) had full access to a specialist for post-test counselling and support. However, 66% of CSPs had either access to a specialist for post-test counselling and/or access to general counselling services. It should be noted that 15% of CSPs made a comment that a HCV nurse, either sponsored by a pharmaceutical company or hired by the clinic, conducted counselling and support. This demonstrates that some clinics have a trained nurse working directly with them to assess and monitor HCV patients, whereas others do not.

Despite the fact that 61% of responding CSPs reported that they work with a multidisciplinary team, only 2% of CSPs acknowledged that they have a coordinated management strategy involving connections to areas such as primary care, drug and alcohol services and nurse practitioners. Furthermore, only 13 of the CSPs who had coordinated management strategies indicated that they had links with prison health care, and only 3 CSPs had links to homeless agencies. Due to the complexity of the health and psychosocial issues of HCV patients, it is vital for HCV physicians to have a coordinated team approach with other areas, such as social services and drug and alcohol counselling, in order to provide comprehensive care to their patients. It is necessary for HCV health care providers to assess the population need in their area, which will primarily be driven by the local IDU prevalence (including people with HCV in the prison system).

5.3.3 Drug Treatment and Barriers

This survey found that very few HCV-infected patients under the care of CSPs are receiving anti-viral therapy. For instance, 43% of CSPs indicated that less than 50% of their patients eligible for treatment actually received treatment. In Canada, health-care costs associated with HCV are estimated at $500 million/year, and are expected to increase to over $1 billion a year this decade [173]. In order for these projections to be changed, a systematic program for the treatment of HCV infection must be put in place.

Barriers to care were identified, which revealed difficulties experienced by HCV health care providers in coping with the present burden of patients in the healthcare system. The variation observed from this survey could create an inequity in the provision of care for people living with HCV. Thus, this survey provides a base for future planning of services and health care pathways that can address the current inequalities.

The majority of CSPs (over 65%) identified funding for treatment and patient non-attendance as the two main barriers to care. As the number of patients with advanced liver disease due to HCV increases, these barriers will become even more apparent with major repercussions for health care providers in terms of recruiting, training and funding specialized staff.

5.3.4 Distribution of Comprehensive Service Providers by Province and Region

The distribution of CSPs across Canada varies, and may help identify an inequity in HCV care provision. For example, the majority of HCV providers in Saskatchewan, New Brunswick, and Newfoundland identified themselves as CSPs, whereas other provinces such as Alberta, Nova Scotia and Quebec stated that less than 30% of their

HCV providers were CSPs. Overall, when CSPs are examined by region it was revealed that Western Canada has the highest percentage of CSPs (74%) and the Prairies have the lowest percentage of CSPs (22%).

An interesting observation is that even though the Prairies have the least amount of CSPs per region, they have the highest number of HCV providers working in a multidisciplinary setting (92%). This may be the reason why the Prairies had the highest percentage of CSPs (75%) who saw over 40 patients in 2005.

5.3.5 Provision of Treatment to Current Injection Drug Users

Over 70% of new cases of HCV infection per year involve IDUs [5]. Currently, there is no consensus on how to offer them medical care. It is important to note that the majority of CSPs who responded to this survey indicated that they would not provide treatment to a current injection drug user who uses a needle exchange on a regular basis. CSPs within AB (50%) and NS (33%) were most likely to provide treatment to current IDUs. This is despite the fact that there is growing evidence that IDUs have had simliar compliance and treatment response rates when compared to non-IDUs [84, 86, 87, 90-92]. Moreover, it is suggested that adherence to antiviral therapy will be increased if patients are enrolled in multidisciplinary programs where there is collaboration between areas such as addictions counselling and a hepatologist in order to allow for thorough patient follow-up by the comprehensive care team [86]. The future burden of HCV is quite alarming and in order for patients to receive the care that they need, a more effective way to plan health care strategies and resource allocation is required.

5.4 Limitations of the Study

There were a number of limitations to this study. Even though the response rate was higher than other studies, such as the American study on primary care physician's knowledge and practice patterns concerning HCV (which had a response rate of 33% [152]), it was still fairly low at only 42%. Moreover, the data obtained from the surveys was self-report and made up of the respondents' estimates of the HCV-management conditions in their practice and their own behaviours, which are likely to be imprecise. Furthermore, it is possible that physicians overestimated their performance due to social desirability bias. Social desirability bias occurs when there is a predisposition to fill out a questionnaire when responses reflect the respondent in a favourable light, according to perceived social norms and values.

It is also possible that physicians who responded to the survey had more favourable HCV-related practice patterns. Consequently, HCV-management practices could be worse than what was documented. Thus, the validity of self-report needs consideration in interpreting the findings.

A major limitation was the fact that the survey was only sent out to English speaking HCV health care providers. This notably reduced the number of eligible participants from 721 to 562 and therefore did not provide a complete examination of HCV health care services and pathways throughout Canada (and Quebec in particular). Furthermore, the Territories (Nunavut, Yukon, North West Territories) were excluded from the study, limiting the examination of geographical variation..

In addition, health care providers that do not return the survey may create selection bias called non-response bias. Non-response bias is the effect of a set of

respondents who refuse or choose not to participate in research, which can make it very difficult to assess the results properly. As well, the responses received from the survey might have differed from the actual practice.

The Canadian Medical Directory [2] was the professional list used to sample participants. The list was fairly up-to-date (2006), but any inaccuracies may have led to some physicians not receiving the survey. Furthermore, physicians may have been defined inaccurately or identified under multiple subspecialties within CMD, and therefore some physicians that treat HCV patients might not have been surveyed if they were not categorized properly. It would have been helpful to have surveyed a random sample of family physicians because they play a key role in the diagnosis and identification of HCV patients. However, this was beyond the scope of the project due to time and budget constraints.

The survey tool itself was a limitation because some questions were too vague to allow respondents to provide a clear answer. Consequently, the collection tool may have been ambiguous at times and therefore unable to assess the issues being examined in a concise format.

CHAPTER 6: CONCLUSIONS AND IMPLICATIONS

6.1 Introduction

This survey evaluated how individuals with HCV are identified, referred, diagnosed, and treated within Canada. Respondents revealed that there is variation across Canada as to how patients are referred at the DIP and CSP level, as well as the type of care patients receive, whether it is in a multidisciplinary or academic setting. The main barriers to care were funding for treatment and patient non-attendance. Nevertheless, based on the multidisciplinary team settings and comprehensives services revealed by survey respondents, opportunities to model forms of healthcare strategies were reported to be quite successful. Moreover, urgent investment by government is needed to improve the identification, funding, and management of people with HCV in order to help decrease the chances of HCV-related deaths and the burden of the disease in the future.

6.2 How can services identified by this study be improved to meet the needs of HCV patients?

The distribution of CSPs by province corresponded to the population distribution across Canada. This reveals that there is a trend associated with the population of each province and the number of HCV health care providers that they have, with more HCV health care providers working in provinces with higher populations of people. Despite this fact, only 65% of the estimated cases of HCV in Canada have been identified [4]; regardless of the number of physcians available to provide HCV treatment, there needs to be a more effective method of providing HCV care. This has an opportunity to occur

through the management of regional HCV networks and support by a national information system which will allow more patients with HCV to receive comprehensive treatment.

Furthermore, this study clearly identifies a need for improved treatment access of people who inject drugs (the primary cause of HCV transmission). There needs to be a call for more walk-in clinics for HCV carriers with addictions, such as the one created in Oakland, California in 1998 [80]. This clinic was created to reduce specific barriers to providing HCV treatment and improve diagnosis of HCV in less-stable drug users. The focus of the clinic is on peer support and provides educational sessions about HCV and the entire diagnosis process [80]. The clinic has a care team consisting of an infectious disease specialist, a nurse, a psychiatric specialist and an administrator who provides educational services [80]. Therefore, all the needs of the patients can be met effectively.

In Canada, there is a similar clinic able to provide the type of care outlined in the Oakland, California model. In Vancouver, British Columbia the Pender Community Health Centre is a multidisciplinary program where the initial medical evaluation is assessed by family physicians and addiction specialists in deliberation with the infectious diseases consultants [174]. If a decision has been made to proceed with treatment, nursing staff then administer weekly IFN injections under direct observation. They monitor adherence, and report any adverse effects or other events to the physicians. In addition, trained counselling staff are available on-site to provide support. HCV support groups, monitored by an addictions counsellor, also meet once a week to discuss treatment progress, side-effects and challenges [174]. The Pender Community Health Centre should be used as a model for HCV care in other cities across the country in order

to provide interprofessional care that will allow HCV patients to receive treatment in a supportive environment.

The move towards a well-developed coordinated pathway of patient care would allow for more effective communication between the health and social disciplines. This would enable patients to have the support they need (i.e. housing, transportation, addictions counselling) while being monitored on HCV treatment. The majority of patients with HCV also have other medical conditions and consequently issues such as addictions must also be addressed. This would give patients the support that they need in order to make it through the entire course of antiviral therapy. A treatment team model would ideally include frequent psychiatric symptom monitoring and provision of care by primary care physicians, hepatologists, nurse practitioners, mental health professionals and substance abuse professionals [34]. This form of a coordinated care clinic would meet the needs of the patient while also allowing for continuity of care amongst the health disciplines. This would ideally increase the number of patients undergoing a successful regimen of antiviral therapy, and thus decrease the medical and economic burden of HCV in Canada.

REFERENCES

1. Wang, P., et al., *Indications for interferon/ribavirin therapy in hepatitis C patients: findings from a survey of Canadian hepatologists.* Canadian Journal of Gastroenterology, 2003. **17**(3): p. 183-186.
2. *MDSelect: Canadian Medical Directory.* [cited; Available from: http://www.mdselect.com/.
3. Di Bisceglie, A.M., *Hepatitis C.* Lancet, 1998. **351**(9099): p. 351-5.
4. Sherman, M., et al., *Management of chronic hepatitis C: Consensus guidelines.* Can J Gastroenterol, 2007. **21**: p. 25C-34C.
5. Remis, R.S., et al., *Estimating the number of blood transfusion recipients infected by hepatitis C virus in Canada, 1960-1985 and 1990-1992*, Health Canada, Editor. 1998.
6. Mathei, C., F. Buntinx, and P. van Damme, *Seroprevalence of hepatitis C markers among intravenous drug users in western European countries: a systematic review.* J Viral Hepat, 2002. **9**(3): p. 157-73.
7. Crofts, N., et al., *Epidemiology of hepatitis C virus infection among injecting drug users in Australia.* J Epidemiol Community Health, 1997. **51**(6): p. 692-7.
8. Kenny-Walsh, E., *Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group.* N Engl J Med, 1999. **340**(16): p. 1228-33.
9. Singh, S., et al., *The impact of hepatitis C in general practice.* Br J Gen Pract, 2000. **50**(456): p. 532, 535-6.
10. Major, M.E. and S.M. Feinstone, *The molecular virology of hepatitis C.* Hepatology, 1997. **25**(6): p. 1527-38.
11. Gutfreund, K.S. and V.G. Bain, *Chronic viral hepatitis C: management update.* Cmaj, 2000. **162**(6): p. 827-33.
12. Bartenschlager, R. and V. Lohmann, *Replication of hepatitis C virus.* Journal of General Virology, 2000. **81**: p. 1631-1648.
13. Farci, P., *Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome [Science 1989;244:359-362].* J Hepatol, 2002. **36**(5): p. 582-5.
14. Domingo, E., et al., *Quasispecies structure and persistence of RNA viruses.* Emerg Infect Dis, 1998. **4**(4): p. 521-7.
15. Kim, A.I. and S. Saab, *Treatment of hepatitis C.* Am J Med, 2005. **118**(8): p. 808-15.
16. Alter, M.J., *Hepatitis C virus infection in the United States.* J Hepatol, 1999. **31 Suppl 1**: p. 88-91.
17. Garfein, R.S., et al., *Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses.* Am J Public Health, 1996. **86**(5): p. 655-61.
18. Alter, M.J. and L.A. Moyer, *The importance of preventing hepatitis C virus infection among injection drug users in the United States.* J Acquir Immune Defic Syndr Hum Retrovirol, 1998. **18 Suppl 1**: p. S6-10.

19. Thomas, D.L., et al., *Viral hepatitis in health care personnel at The Johns Hopkins Hospital. The seroprevalence of and risk factors for hepatitis B virus and hepatitis C virus infection.* Arch Intern Med, 1993. **153**(14): p. 1705-12.
20. Zickmund, S., et al., *"They treated me like a leper". Stigmatization and the quality of life of patients with hepatitis C.* J Gen Intern Med, 2003. **18**(10): p. 835-44.
21. Herek, G.M. and E.K. Glunt, *An epidemic of stigma. Public reactions to AIDS.* Am Psychol, 1988. **43**(11): p. 886-91.
22. Sacks, V., *Women and AIDS: an analysis of media misrepresentations.* Soc Sci Med, 1996. **42**(1): p. 59-73.
23. Ouzan, D., et al., *[Screening and hepatitis C management survey in general medicine in the Alpes-Maritimes and east Var area].* Gastroenterol Clin Biol, 2003. **27**(1): p. 90-3.
24. Zou, S., M.L. Tepper, and A. Giulivi, *Viral Hepatitis and Emerging Bloodborne Pathogens in Canada*, Public Health Agency of Canada, Editor. 2001.
25. Pawlotsky, J.M., *Therapy of hepatitis C: from empiricism to eradication.* Hepatology, 2006. **43**(2 Suppl 1): p. S207-20.
26. Hoofnagle, J.H., et al., *Treatment of chronic non-A,non-B hepatitis with recombinant human alpha interferon. A preliminary report.* N Engl J Med, 1986. **315**(25): p. 1575-8.
27. Platanias, L.C., *Mechanisms of type-I- and type-II-interferon-mediated signalling.* Nat Rev Immunol, 2005. **5**(5): p. 375-86.
28. Lau, D.T., et al., *10-Year follow-up after interferon-alpha therapy for chronic hepatitis C.* Hepatology, 1998. **28**(4): p. 1121-7.
29. Bekisz, J., et al., *Human interferons alpha, beta and omega.* Growth Factors, 2004. **22**(4): p. 243-51.
30. Sen, G.C., *Viruses and interferons.* Annu Rev Microbiol, 2001. **55**: p. 255-81.
31. Di Bisceglie, A.M. and J.H. Hoofnagle, *Optimal therapy of hepatitis C.* Hepatology, 2002. **36**(5 Suppl 1): p. S121-7.
32. Reichard, O., et al., *Ribavirin treatment for chronic hepatitis C.* Lancet, 1991. **337**(8749): p. 1058-61.
33. Feld, J.J. and J.H. Hoofnagle, *Mechanism of action of interferon and ribavirin in treatment of hepatitis C.* Nature, 2005. **436**(7053): p. 967-72.
34. Loftis, J.M., A.M. Matthews, and P. Hauser, *Psychiatric and substance use disorders in individuals with hepatitis C: epidemiology and management.* Drugs, 2006. **66**(2): p. 155-74.
35. Dixit, N.M., et al., *Modelling how ribavirin improves interferon response rates in hepatitis C virus infection.* Nature, 2004. **432**(7019): p. 922-4.
36. Hoofnagle, J.H., et al., *Prolonged therapy of chronic hepatitis C with ribavirin.* J Viral Hepat, 1996. **3**(5): p. 247-52.
37. Di Bisceglie, A.M., et al., *Ribavirin as therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial.* Ann Intern Med, 1995. **123**(12): p. 897-903.
38. McHutchison, J.G. and T. Poynard, *Combination therapy with interferon plus ribavirin for the initial treatment of chronic hepatitis C.* Semin Liver Dis, 1999. **19 Suppl 1**: p. 57-65.

39. *EASL International Consensus Conference on hepatitis C. Paris, 26-27 February 1999. Consensus statement.* J Hepatol, 1999. **31 Suppl 1**: p. 3-8.
40. Glue, P., et al., *Pegylated interferon-alpha2b: pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Hepatitis C Intervention Therapy Group.* Clin Pharmacol Ther, 2000. **68**(5): p. 556-67.
41. Zeuzem, S., et al., *Peginterferon alfa-2a in patients with chronic hepatitis C.* N Engl J Med, 2000. **343**(23): p. 1666-72.
42. Lindsay, K.L., et al., *A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C.* Hepatology, 2001. **34**(2): p. 395-403.
43. Fried, M.W., et al., *Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection.* N Engl J Med, 2002. **347**(13): p. 975-82.
44. Manns, M.P., et al., *Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial.* Lancet, 2001. **358**(9286): p. 958-65.
45. Strader, D.B., *Understudied populations with hepatitis C.* Hepatology, 2002. **36**(5 Suppl 1): p. S226-36.
46. Pawlotsky, J.M. and J.G. McHutchison, *Hepatitis C. Development of new drugs and clinical trials: promises and pitfalls. Summary of an AASLD hepatitis single topic conference, Chicago, IL, February 27-March 1, 2003.* Hepatology, 2004. **39**(2): p. 554-67.
47. Reesink, H.W., et al., *Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase Ib, placebo-controlled, randomized study.* Gastroenterology, 2006. **131**(4): p. 997-1002.
48. Richman, D.D., *The impact of drug resistance on the effectiveness of chemotherapy for chronic hepatitis B.* Hepatology, 2000. **32**(4 Pt 1): p. 866-7.
49. McHutchison, J.G., et al., *Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C.* Gastroenterology, 2002. **123**(4): p. 1061-9.
50. Mihm, U., et al., *Review article: predicting response in hepatitis C virus therapy.* Aliment Pharmacol Ther, 2006. **23**(8): p. 1043-54.
51. Heathcote, J. and J. Main, *Treatment of hepatitis C.* J Viral Hepat, 2005. **12**(3): p. 223-35.
52. Weigand, K., W. Stremmel, and J. Encke, *Treatment of hepatitis C virus infection.* World J Gastroenterol, 2007. **13**(13): p. 1897-905.
53. Fried, M.W., *Side effects of therapy of hepatitis C and their management.* Hepatology, 2002. **36**(5 Suppl 1): p. S237-44.
54. McHutchison, J.G., et al., *Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group.* N Engl J Med, 1998. **339**(21): p. 1485-92.
55. Musselman, D.L., et al., *Paroxetine for the prevention of depression induced by high-dose interferon alfa.* N Engl J Med, 2001. **344**(13): p. 961-6.
56. Dienstag, J.L. and J.G. McHutchison, *American Gastroenterological Association technical review on the management of hepatitis C.* Gastroenterology, 2006. **130**(1): p. 231-64; quiz 214-7.

57. Dan, A.A., et al., *Anger experiences among hepatitis C patients: relationship to depressive symptoms and health-related quality of life.* Psychosomatics, 2007. **48**(3): p. 223-9.
58. D'Souza, R. and G.R. Foster, *Diagnosis and treatment of hepatitis C.* J R Soc Med, 2004. **97**(5): p. 223-5.
59. Strader, D.B., et al., *Diagnosis, management, and treatment of hepatitis C.* Hepatology, 2004. **39**(4): p. 1147-71.
60. *National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002.* Hepatology, 2002. **36**(5 Suppl 1): p. S3-20.
61. Poynard, T., et al., *Is an "a la carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group.* Hepatology, 2000. **31**(1): p. 211-8.
62. Wright, T.L., *Treatment of patients with hepatitis C and cirrhosis.* Hepatology, 2002. **36**(5 Suppl 1): p. S185-94.
63. Shiffman, M.L., *Retreatment of patients with chronic hepatitis C.* Hepatology, 2002. **36**(5 Suppl 1): p. S128-34.
64. McHutchison, J.G., et al., *The impact of interferon plus ribavirin on response to therapy in black patients with chronic hepatitis C. The International Hepatitis Interventional Therapy Group.* Gastroenterology, 2000. **119**(5): p. 1317-23.
65. Public Health Agency of Canada. *Management of Viral Hepatitis: Recommended Guidelines for Physicians.* 2003 [cited; Available from: http://www.phac-aspc.gc.ca/hepc/pubs/mvh-pchv00/virus_e.html.
66. Hoofnagle, J.H., *Course and outcome of hepatitis C.* Hepatology, 2002. **36**(5 Suppl 1): p. S21-9.
67. Puoti, M., et al., *Hepatitis C virus RNA and antibody response in the clinical course of acute hepatitis C virus infection.* Hepatology, 1992. **16**(4): p. 877-81.
68. Pawlotsky, J.M., *Use and interpretation of virological tests for hepatitis C.* Hepatology, 2002. **36**(5 Suppl 1): p. S65-73.
69. Simmonds, P., *Viral heterogeneity of the hepatitis C virus.* J Hepatol, 1999. **31 Suppl 1**: p. 54-60.
70. Mangia, A., et al., *Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3.* N Engl J Med, 2005. **352**(25): p. 2609-17.
71. Micallef, J.M., J.M. Kaldor, and G.J. Dore, *Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies.* J Viral Hepat, 2006. **13**(1): p. 34-41.
72. Santantonio, T., et al., *Efficacy of a 24-week course of PEG-interferon alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance.* J Hepatol, 2005. **42**(3): p. 329-33.
73. Maio, G., et al., *Hepatitis C virus infection and alanine transaminase levels in the general population: a survey in a southern Italian town.* J Hepatol, 2000. **33**(1): p. 116-20.
74. Comandini, U.V., et al., *Sporadic hepatitis C virus infection: a case-control study of transmission routes in a selected hospital sample of the general population in Italy.* Scand J Infect Dis, 1998. **30**(1): p. 11-5.

75. Patrick, D.M., et al., *Public health and hepatitis C.* Can J Public Health, 2000. **91 Suppl 1**: p. S18-21, S19-23.
76. Hagan, H., et al., *Eligibility for treatment of hepatitis C virus infection among young injection drug users in 3 US cities.* Clin Infect Dis, 2006. **42**(5): p. 669-72.
77. Edlin, B.R., et al., *Is it justifiable to withhold treatment for hepatitis C from illicit-drug users?* N Engl J Med, 2001. **345**(3): p. 211-5.
78. Dore, G.J., *Enhancing hepatitis C treatment uptake and outcomes for injection drug users.* Hepatology, 2007. **45**(1): p. 3-5.
79. *National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 1997--March 24-26, 1997*
1997 [cited October 2nd 2007]; Available from: http://consensus.nih.gov/1997/1997HepatitisC105html.htm.
80. Sylvestre, D.L., et al., *Co-occurring Hepatitis C, substance use, and psychiatric illness: treatment issues and developing integrated models of care.* J Urban Health, 2004. **81**(4): p. 719-34.
81. Osher, F.C., et al., *Substance abuse and the transmission of hepatitis C among persons with severe mental illness.* Psychiatr Serv, 2003. **54**(6): p. 842-7.
82. Zdilar, D., et al., *Hepatitis C, interferon alfa, and depression.* Hepatology, 2000. **31**(6): p. 1207-11.
83. Klinkenberg, W.D., et al., *Prevalence of human immunodeficiency virus, hepatitis B, and hepatitis C among homeless persons with co-occurring severe mental illness and substance use disorders.* Compr Psychiatry, 2003. **44**(4): p. 293-302.
84. Backmund, M., et al., *Treatment of hepatitis C infection in injection drug users.* Hepatology, 2001. **34**(1): p. 188-93.
85. Grebely, J., et al., *Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users.* J Gastroenterol Hepatol, 2007. **22**(9): p. 1519-25.
86. Robaeys, G., et al., *Similar compliance and effect of treatment in chronic hepatitis C resulting from intravenous drug use in comparison with other infection causes.* Eur J Gastroenterol Hepatol, 2006. **18**(2): p. 159-66.
87. Jeffrey, G.P., et al., *Hepatitis C virus eradication in intravenous drug users maintained with subcutaneous naltrexone implants.* Hepatology, 2007. **45**(1): p. 111-7.
88. Kontorinis, N., et al., *Outcome, tolerability and compliance of compassionate use interferon and ribavirin for hepatitis C infection in a shared care hospital clinic.* Intern Med J, 2003. **33**(11): p. 500-4.
89. Sylvestre, D. *Hepatitis C in Drug Users: What to Do?* 2007 [cited 7/25/2007]; Available from: http://www.hcvadvocate.org/hcsp/articles/IDU.html.
90. Cournot, M., et al., *Management of hepatitis C in active drugs users: experience of an addiction care hepatology unit.* Gastroenterol Clin Biol, 2004. **28**(6-7 Pt 1): p. 533-9.
91. Van Thiel, D.H., A. Anantharaju, and S. Creech, *Response to treatment of hepatitis C in individuals with a recent history of intravenous drug abuse.* Am J Gastroenterol, 2003. **98**(10): p. 2281-8.

92. Sylvestre, D.L., et al., *The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone.* J Subst Abuse Treat, 2005. **29**(3): p. 159-65.
93. Rawson, R., et al., *Addiction pharmacotherapy 2000: new options, new challenges.* J of Psychoactive Drugs, 2003. **32**: p. 371-377.
94. Anand, B.S., et al., *Alcohol use and treatment of hepatitis C virus: results of a national multicenter study.* Gastroenterology, 2006. **130**(6): p. 1607-16.
95. Kresina, T.F., et al., *Addressing the need for treatment paradigms for drug-abusing patients with multiple morbidities.* Clin Infect Dis, 2004. **38 Suppl 5**: p. S398-401.
96. Dalgard, O., et al., *Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up.* Eur Addict Res, 2002. **8**(1): p. 45-9.
97. Backmund, M., K. Meyer, and B.R. Edlin, *Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users.* Clin Infect Dis, 2004. **39**(10): p. 1540-3.
98. Falck-Ytter, Y., et al., *Surprisingly small effect of antiviral treatment in patients with hepatitis C.* Ann Intern Med, 2002. **136**(4): p. 288-92.
99. Thomas, D.L., et al., *The natural history of hepatitis C virus infection: host, viral, and environmental factors.* Jama, 2000. **284**(4): p. 450-6.
100. Strathdee, S.A., et al., *Barriers to use of free antiretroviral therapy in injection drug users.* Jama, 1998. **280**(6): p. 547-9.
101. Celentano, D.D., et al., *Self-reported antiretroviral therapy in injection drug users.* Jama, 1998. **280**(6): p. 544-6.
102. Strathdee, S.A., et al., *Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users.* Clin Infect Dis, 2005. **40 Suppl 5**: p. S304-12.
103. Salomon, N., et al., *Implementation of universal directly observed therapy at a New York City hospital and evaluation of an out-patient directly observed therapy program.* Int J Tuberc Lung Dis, 1997. **1**(5): p. 397-404.
104. Broers, B., A. Morabia, and B. Hirschel, *A cohort study of drug users' compliance with zidovudine treatment.* Arch Intern Med, 1994. **154**(10): p. 1121-7.
105. Gourevitch, M.N., et al., *Successful adherence to observed prophylaxis and treatment of tuberculosis among drug users in a methadone program.* J Addict Dis, 1996. **15**(1): p. 93-104.
106. Ewart, A., et al., *Providing treatment for hepatitis C in an Australian district centre.* Postgrad Med J, 2004. **80**(941): p. 180-2.
107. Mehta, S.H., et al., *A framework for understanding factors that affect access and utilization of treatment for hepatitis C virus infection among HCV-mono-infected and HIV/HCV-co-infected injection drug users.* Aids, 2005. **19 Suppl 3**: p. S179-89.
108. Grebely, J., et al., *Hepatitis C virus reinfection in injection drug users.* Hepatology, 2006. **44**(5): p. 1139-45.
109. Stephenson, J., *Former addicts face barriers to treatment for HCV.* Jama, 2001. **285**(8): p. 1003-5.

110. Doab, A., C. Treloar, and G.J. Dore, *Knowledge and attitudes about treatment for hepatitis C virus infection and barriers to treatment among current injection drug users in Australia.* Clin Infect Dis, 2005. **40 Suppl 5**: p. S313-20.
111. Schaefer, M., A. Heinz, and M. Backmund, *Treatment of chronic hepatitis C in patients with drug dependence: time to change the rules?* Addiction, 2004. **99**(9): p. 1167-75.
112. Dieperink, E., et al., *A prospective study of neuropsychiatric symptoms associated with interferon-alpha-2b and ribavirin therapy for patients with chronic hepatitis C.* Psychosomatics, 2003. **44**(2): p. 104-12.
113. Davis, G.L. and J.R. Rodrigue, *Treatment of chronic hepatitis C in active drug users.* N Engl J Med, 2001. **345**(3): p. 215-7.
114. Van Thiel, D.H., et al., *Interferon-alpha can be used successfully in patients with hepatitis C virus-positive chronic hepatitis who have a psychiatric illness.* Eur J Gastroenterol Hepatol, 1995. **7**(2): p. 165-8.
115. Kraus, M.R., et al., *Prophylactic SSRI during interferon alpha re-therapy in patients with chronic hepatitis C and a history of interferon-induced depression.* J Viral Hepat, 2005. **12**(1): p. 96-100.
116. Schaefer, M., et al., *Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C.* J Hepatol, 2005. **42**(6): p. 793-8.
117. Cawthorne, C.H., et al., *Limited success of HCV antiviral therapy in United States veterans.* Am J Gastroenterol, 2002. **97**(1): p. 149-55.
118. Soriano, V., et al., *New paradigms in the management of HIV and hepatitis C virus coinfection.* Curr Opin Infect Dis, 2005. **18**(6): p. 550-60.
119. Brau, N., *Update on chronic hepatitis C in HIV/HCV-coinfected patients: viral interactions and therapy.* Aids, 2003. **17**(16): p. 2279-90.
120. Amin, J., et al., *HIV and hepatitis C coinfection within the CAESAR study.* HIV Med, 2004. **5**(3): p. 174-9.
121. Hughes, C.A. and S.D. Shafran, *Treatment of hepatitis C in HIV-coinfected patients.* Ann Pharmacother, 2006. **40**(3): p. 479-89; quiz 582-3.
122. Soriano, V., et al., *Care of patients with hepatitis C and HIV co-infection.* Aids, 2004. **18**(1): p. 1-12.
123. Vento, S., et al., *Rapid decline of CD4+ cells after IFN alpha treatment in HIV-1 infection.* Lancet, 1993. **341**(8850): p. 958-9.
124. Powderly, W.G., *Antiretroviral therapy in patients with hepatitis and HIV: weighing risks and benefits.* Clin Infect Dis, 2004. **38 Suppl 2**: p. S109-13.
125. Mauss, S. and J.K. Rockstroh, *HCV/HIV-coinfection--is there a state of the art after APRICOT and RIBAVIC?* J Antimicrob Chemother, 2005. **56**(4): p. 615-8.
126. *Rationale and recommendations for a Canadian hepatitis C strategy.* 2004 [cited; Available from: http://www.canhepc.net/pdf/canhepc_strategy_mar12.pdf.
127. Zou, S., M. Tepper, and A. Giulivi, *Current status of hepatitis C in Canada.* Can J Public Health, 2000. **91 Suppl 1**: p. S10-5, S10-6.
128. Haydon, E., B. Fischer, and M. Krajden, *Fact Sheet: Hepatitis C Virus (HCV) infection and illicit drug use.* 2005, Canadian Centre on Substance Abuse.

129. Zou, S., M.L. Tepper, and A. Giulivi, *Hepatitis C in Canada*, Public Health Agency of Canada, Editor. 2001.
130. Health Canada, *Get the facts: Mid-term evaluation report*. 2003.
131. Zou, S., L. Forrester, and A. Giulivi, *Hepatitis C Update*. Canadian Journal of Public Health, 2003. **94**(2): p. 127-129.
132. Health Canada, *The hepatitis C prevention, support and research program: Health Canada initiatives on hepatitis C*. Canadian Journal of Public Health, 2000. **91**: p. S27-S29.
133. Witkos, M., et al., *Predictors of antiviral therapy in a post transfusion cohort of hepatitis C patients*. 2005.
134. Bacon, B.R., *Managing hepatitis C*. Am J Manag Care, 2004. **10**(2 Suppl): p. S30-40.
135. Chong, C.A., et al., *Health-state utilities and quality of life in hepatitis C patients*. Am J Gastroenterol, 2003. **98**(3): p. 630-8.
136. Forton, D.M., et al., *Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease*. Hepatology, 2002. **35**(2): p. 433-9.
137. Balfour, L., et al., *Depression and cigarette smoking independently relate to reduced health-related quality of life among Canadians living with hepatitis C*. Can J Gastroenterol, 2006. **20**(2): p. 81-6.
138. Renault, P.F., et al., *Psychiatric complications of long-term interferon alfa therapy*. Arch Intern Med, 1987. **147**(9): p. 1577-80.
139. Treadwell, J.R., D. Kearney, and M. Davila, *Health profile preferences of hepatitis C patients*. Dig Dis Sci, 2000. **45**(2): p. 345-50.
140. Patil, R., et al., *Physicians' preference values for hepatitis C health states and antiviral therapy: a survey*. BMC Gastroenterol, 2001. **1**: p. 6.
141. Public Health Agency of Canada. *What Determines Health?* 2003 [cited; Available from: http://www.phac-aspc.gc.ca/ph-sp/phdd/determinants/index.html.
142. Zacks, S., et al., *Social stigmatization and hepatitis C virus infection*. J Clin Gastroenterol, 2006. **40**(3): p. 220-4.
143. Day, C., J. Ross, and K. Dolan, *Hepatitis C-related discrimination among heroin users in Sydney: drug user or hepatitis C discrimination?* Drug Alcohol Rev, 2003. **22**(3): p. 317-21.
144. D'Souza, R.F., et al., *Knowledge of chronic hepatitis C among East London primary care physicians following the Department of Health's educational campaign*. Qjm, 2004. **97**(6): p. 331-6.
145. *National Hepatitis C Strategy 1999-2000 to 2003-2004*, Commonwealth Department of Health and Aged Care Australia, Editor. 2000.
146. Peksen, Y., et al., *Primary care physicians' approach to diagnosis and treatment of hepatitis B and hepatitis C patients*. BMC Gastroenterol, 2004. **4**: p. 3.
147. Fraser, J., C. Alexander, and K. Fisher, *Hepatitis C education needs of rural general practitioners working in northern New South Wales*. Aust J Rural Health, 2004. **12**(4): p. 152-6.
148. Cozzolongo, R., et al., *Approach of primary care physicians to hepatitis C: an educational survey from a Southern Italian area*. J Infect, 2005. **51**(5): p. 396-400.

149. Shehab, T.M., S.S. Sonnad, and A.S. Lok, *Management of hepatitis C patients by primary care physicians in the USA: results of a national survey.* J Viral Hepat, 2001. **8**(5): p. 377-83.
150. Clark, E.C., et al., *Hepatitis C identification and management by family physicians.* Fam Med, 2005. **37**(9): p. 644-9.
151. Coppola, A.G., et al., *Hepatitis C knowledge among primary care residents: is our teaching adequate for the times?* Am J Gastroenterol, 2004. **99**(9): p. 1720-5.
152. Shehab, T.M., et al., *Current practice patterns of primary care physicians in the management of patients with hepatitis C.* Hepatology, 1999. **30**(3): p. 794-800.
153. Shatin, D., et al., *Population-based hepatitis C surveillance and treatment in a national managed care organization.* Am J Manag Care, 2004. **10**(4): p. 250-6.
154. Gupta, L., S. Shah, and J.E. Ward, *Educational and health service needs of Australian general practitioners in managing hepatitis C.* J Gastroenterol Hepatol, 2006. **21**(4): p. 694-9.
155. Dev, A. and W. Sievert, *A survey of Australian general practice management of hepatitis C-infected patients from non-English-speaking backgrounds.* J Gastroenterol Hepatol, 2002. **17**(3): p. 295-300.
156. Conte, D., et al., *Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women.* Hepatology, 2000. **31**(3): p. 751-5.
157. Graves, L., J. Cox, and M. Steben, *Physicians and HCV perceptions*, in *Navigating Life with Hepatitis C Atlantic Conference 2006.* 2005: Halifax, Nova Scotia.
158. Litwin, A.H., et al., *Hepatitis C management by addiction medicine physicians: Results from a national survey.* J Subst Abuse Treat, 2007. **33**(1): p. 99-105.
159. Parkes, J., et al., *Variation in Hepatitis C services may lead to inequity of health-care provision: a survey of the organisation and delivery of services in the United Kingdom.* BMC Public Health, 2006. **6**(3).
160. Everhart, J., M. Stolar, and J.H. Hoofnagle, *Management of hepatitis C: A national survey of gastroenterologists and hepatologists.* Hepatology, 1997. **26**(3): p. 78S-82S.
161. Irving, W.L., et al., *Clinical pathways for patients with newly diagnosed hepatitis C - what actually happens.* J Viral Hepat, 2006. **13**(4): p. 264-71.
162. Mohsen, A.H., *The epidemiology of hepatitis C in a UK health regional population of 5.12 million.* Gut, 2001. **48**(5): p. 707-13.
163. Dusheiko, G., *HCV infection should be managed in specialist centres.* Gut, 2002. **51**(5): p. 625-6.
164. Brown, J.L., *HCV infection should be managed in specialist centres.* Gut, 2002. **51**(5): p. 626-7.
165. Asch, D.A., M.K. Jedrziewski, and N.A. Christakis, *Response rates to mail surveys published in medical journals.* J Clin Epidemiol, 1997. **50**(10): p. 1129-36.
166. Kaner, E.F., C.A. Haighton, and B.R. McAvoy, *'So much post, so busy with practice--so, no time!': a telephone survey of general practitioners' reasons for*

not participating in postal questionnaire surveys. Br J Gen Pract, 1998. **48**(428): p. 1067-9.
167. Barclay, S., et al., *Not another questionnaire! Maximizing the response rate, predicting non-response and assessing non-response bias in postal questionnaire studies of GPs.* Fam Pract, 2002. **19**(1): p. 105-11.
168. Dillman, D., *Mail and Internet Surveys: the tailored design method.* 2nd ed. 2000, New York: John Wiley & Sons.
169. Field, T.S., et al., *Surveying physicians: do components of the "Total Design Approach" to optimizing survey response rates apply to physicians?* Med Care, 2002. **40**(7): p. 596-605.
170. Edwards, P., et al., *Increasing response rates to postal questionnaires: systematic review.* BMJ, 2002. **324**(7347): p. 1183-.
171. Natural Resources Canada. *The Atlas of Canada.* 2007 [cited; Available from: http://atlas.nrcan.gc.ca/sites/english/index.html.
172. Statistics Canada. *Canada's Population estimates.* 2007 [cited; Available from: http://www.statcan.ca/Daily/English/070927/d070927a.htm.
173. Fischer, B., et al., *Injection drug use and the hepatitis C virus: considerations for a targeted treatment approach--the case study of Canada.* J Urban Health, 2004. **81**(3): p. 428-47.
174. Conway, B., et al., *A systematic approach to the treatment of HIV and hepatitis C virus infection in the inner city: a Canadian perspective.* Clin Infect Dis, 2005. **41 Suppl 1**: p. S73-8.

APPENDICES

APPENDIX A : PRE-NOTIFICATION LETTER

Division of Community
Health & Humanities
Faculty of Medicine
Memorial University
300 Prince Philip Dr.
St. John's, NL A1B 3V6

Recipients Address

Dear Dr.

Within the next few days, you will receive a request to complete a questionnaire. I am mailing it to you in an effort to learn more about Hepatitis C virus (HCV) treatment in Canada.

The aim of the study is to investigate the identification, testing, referral, selection for treatment, and follow-up of HCV positive patients. Through the questionnaire I hope to identify regional variations in HCV practice, which has implications for improving HCV care and the quality of life for people living with HCV. Results derived from this study will be able to identify regional variations in HCV practice, which has implications for improving HCV care.

The information data that I will need will be treated as confidential and kept in the faculty at Memorial Universty in secure storage. Access to the questionnaires is restricted to my supervisor and myself. The survey will be anonymous and completion of the questionnaire is voluntary. If you decide that you no longer want to be involved in this study you are free to withdraw at any time. Returning the complete questionnaire indicates you have been informed and will be considered your consent to participate in the study. The Human Investigation Committee at Memorial University has approved the study.

I would greatly appreciate your taking the few minutes necessary to complete and return your questionnaire. Please feel free to contact me [(709) 749-9697 or angeliquemyles@gmail.com] or my supervisor, Dr. Peter Wang [(709) 777-8571 or pwang@mun.ca] as you wish

Thank you in advance for your help.

Sincerely,

Angelique Myles
Principal Investigator

APPENDIX B: COVER LETTER IN SURVEY PACKAGE

Division of Community
Health & Humanities
Faculty of Medicine
Memorial University
300 Prince Philip Dr.
St. John's, NL A1B 3V6

Recipients Address

Dear Dr.

My name is Angelique Myles and I am a Masters student in Community Health at Memorial University under the supervision of Dr. Peter Wang. I am writing to invite you to participate in research in the form of a questionnaire.

My Masters Project is entitled "An Examination of Regional Variation in Treating Hepatitis C Patients in Canada." Specifically, it is assessing how physicians are providing treatment to people living with Hepatitis C Virus (HCV). The aim of the study is to investigate the identification, testing, referral, selection for treatment, and follow-up of HCV positive patients. This information is of importance to you because it will establish baseline information to plan future services for people living with HCV. Through the questionnaire I hope to identify regional variations in HCV practice, which has implications for improving HCV care and the quality of life for people living with HCV.

The questionnaire should take about 5 minutes to complete. Enclosed is a pre-paid envelope for the return of the questionnaire. I would greatly appreciate it if you would complete the questionnaire within one week of receiving it. In order for information from the study to be truly representative, it is essential that each person in the sample return their questionnaire. I will be making a follow-up telephone call in two weeks time to remind you to complete the questionnaire if you have not already done so.

This is an anonymous survey and the information data that I will need will be treated as confidential and kept in the faculty at Memorial Universty in secure storage. Access to the questionnaires is restricted to my supervisor and myself. Completion of the questionnaire is voluntary. If you decide that you no longer want to be involved in this study you are free to withdraw at any time.

Completion of the questionnaire indicates you have been informed and will be considered your consent to participate in the study. Upon receipt, the questionnaire will be coded and your name and address will be kept separate from it. When you return the questionnaire, you do not give up your legal rights. Researchers or agencies involved in this research study still have their legal and professional responsibilities. If you would like to obtain a summary of the results of this research I would be happy to send you copy upon completion of the study

Please feel free to contact me [(709) 749-9697 or angeliquemyles@gmail.com] or my supervisor, Dr. Peter Wang [(709) 777-8571 or pwang@mun.ca] as you wish. In addition, please ask your secretary to e-mail me a convenient time at which I can call your office.

Sincerely,
Angelique Myles *Principal Investigator*

APPENDIX C: SURVEY-QUESTIONNAIRE

National Study of Hepatitis C Services

ID

Please complete the following details: Your replies will be treated in strict confidence
Your role in management of Hepatitis C

1. **What is your role in the management of Patients with Hepatitis C?**

   Circle answer that most applies to your practice.

   a) **I have no role in the management and diagnosis of patients with Hepatitis C.**

Please answer the following question and return questionnaire in envelope provided.

It would be very helpful to this national survey if you could state in the space below the name of the consultant who provides a specialist Hepatitis C service for your patient population.

Hospital _____

Thank you very much for your help.
Please return the questionnaire in the stamped addressed envelope provided.

   b) **Diagnosis +/- initial investigations, followed by referral to a dedicated Hepatitis C service*.**
   Please answer Q2-12 on pages 2-4 and return questionnaire in envelope provided.

   c) **Provision of a dedicated Hepatitis C service*.**
   Please proceed directly to Q13 on page 5.

* Includes diagnosis, investigation, treatment, & follow-up

Survey adapted from Parkes, J., et al., *Variation in Hepatitis C services may lead to inequity of health-care provision: a survey of the organisation and delivery of services in the United Kingdom.* BMC Public Health, 2006. **6**(3).

☛ If you selected (Q1b), please complete the following question.

2. Health Care Provider Demographics

Age	
<30	☐
30-39	☐
40-49	☐
50-59	☐
60 or older	☐

Years in practice	
< 5	☐
5-9	☐
10-19	☐
≥ 20	☐

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3. Sex male ☐ female☐

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4. Size of community where you practice

≤ 25,000	☐
> 25,000 but < 100,000	☐
100,000 to 500,000	☐
> 500,000	☐

---

5. Practice Type (check all that apply)

Solo practice	☐
Multiple-specialty group	☐
Academic	☐
Other	☐

Your Hospital

6. **Please specify the description that best fits the population served by your clinical practice/hospital.**

Urban (wholly)
Urban (predominantly)
Mixed urban (more urban than rural)
Mixed rural (more rural than urban)
Rural (predominantly)
Rural (wholly)
Other please specify

7. **What proportions of patients diagnosed with Hepatitis C in your practice/hospital are managed by the following?**

Hepatologist* %
Gastroenterologist %
Infectious disease specialist %
Internist %
Other - please specify_____

***(hepatologist = those doctors whose substantive work is in liver disease)**

8. **Approximately how many patients with Hepatitis C did you diagnose in 2005?**

<10
10-19
20-29
30-39
40-49
>50

9. **What percentage of these patients did you refer to a specialist Hepatitis C service?**

<10%
10-24%
25-49%
50-74%
75-90%
>90

Diagnosis

10. Do you have access to the following tests?

Service	In house (yes/no)	External (yes/no)	Number of tests requested by you on average per month
Qualitative PCR			
Viral load measurement			
HCV genotyping			
Specialist liver histopathology			

11. Do you *EVER* treat patients with Hepatitis C? Yes/No

12. It would be very helpful to this national survey if you could state in the space below the name of the consultant(s) who provide(s) a specialist Hepatitis C service for your patient population.

Hospital _____

Thank you very much for your help.
Please return the questionnaire in the stamped addressed envelope provided.

Your replies will be treated in strict confidence.

If you provide a dedicated Hepatitis C service (Q1c), please complete the following questions.

13. Health Care Provider Demographics

Age	
<30	☐
30-39	☐
40-49	☐
50-59	☐
60 or older	☐

Years in practice	
< 5	☐
5-9	☐
10-19	☐
> 20	☐

---

14. Sex male ☐ female ☐

---

15. Size of community where you practice

≤ 25,000	☐
> 25,000 but < 100,000	☐
100,000 to 500,000	☐
> 500,000	☐

---

16. Practice Type (check all that apply)

Solo practice	☐
Multiple-specialty group	☐
Academic	☐
Other	☐

Your Hospital

17. Please specify the description that best fits the population served by your clinical practice/hospital.

Urban (wholly)
Urban (predominantly)
Mixed urban (more urban than rural)
Mixed rural (more rural than urban)
Rural (predominantly)
Rural (wholly)
Other please specify_____

Prevalence of Hepatitis C in your practice

18. What is the total number of patients with known hepatitis C currently under your care?

19. What was the approximate number of new HCV patients seen by you in each of the following years?

	2003	2004	2005
<10			
10-19			
20-30			
>40			

20. What is the approximate percentage of new patients who default from their initial out-patient appointment?

0-4%
5-9%
10-24%
25-49%
50-74%
>75%

21. What percentage of your time is spent on the clinical management of patients with Hepatitis C?

0-4%
5-9%
10-24%
25-49%
50-74%
>75%

Referrals

Source of referrals

The following questions apply both to those patients referred to you in 2005 with a problem subsequently diagnosed as Hepatitis C AND also those referred to you with an established diagnosis of hepatitis C.

22. What proportion of patients referred to you came with a diagnosis of Hepatitis C?

0-4%
5-9%
10-24%
25-49%
50-74%
>75%
Unsure

23. Where the *initial* diagnosis of hepatitis C was made before referral, please give the approximate percentage of referrals from each of these sources.

Primary care %
Prison healthcare %
Drug and Alcohol service %
Hepatology %
Gastroenterology %
Infectious diseases %
Internist %
Other please specify_____

24. In those patients in whom YOU make the diagnosis of Hepatitis C, please indicate the source of referral with approximate proportions.

Primary care %
Prison healthcare %
Drug and Alcohol service %
Gastroenterology %
Infectious diseases %
Internist %
Hepatology %
Unsure
Other - please specify_____

Management of patients with Hepatitis C

25. Do you ever refer patients with Hepatitis C to colleagues for further opinion or management?

Yes/No
If Yes

26. In what circumstances do you refer to colleagues?

For treatment

For follow up
For complex clinical issues relating to Hepatitis C
For joint management e.g. with psychiatry
For transplantation
Patient wants a second opinion

Other - please specify_____

Diagnosis

27. Do you have the following investigative tests available?

Service	In house (yes/no)	External (yes/no)	Number of tests per month
Qualitative PCR			
Viral load measurement			
HCV genotyping			
Specialist liver histopathology			

Counselling

28. What counselling and support services are available in your practice/hospital for patients with Hepatitis C?

Access to HCV specialist (any profession/grade) for post-test counselling and support
Access to general counselling services
No access to counselling services
Other - please specify_____

Treatment

Initiating treatment

29. Which of the following criteria do you consider in determining eligibility for treatment?

Age	Yes/No
Sex	Yes/No
HCV Genotype	Yes/No
Severity of hepatitis	Yes/No
Severity of fibrosis	Yes/No
History of substance use/abuse	Yes/No
Co-morbidities	Yes/No
Extrahepatic manifestations	Yes/No

Other - please specify_____

30. Would you be likely to offer treatment to a patient with the following scenarios who had no additional contraindications:

Mild hepatitis on biopsy	Yes/No
Normal ALT	Yes/No
With extrahepatic manifestations	Yes/No
Moderate hepatitis	Yes/No
Severe hepatitis	Yes/No
Cirrhosis	
Child - Pugh A	Yes/No
Child - Pugh B	Yes/No
Child - Pugh C	Yes/No
Patient awaiting transplantation	Yes/No

31. Which of the following patients with moderate/severe Chronic Hepatitis C are likely to receive treatment in your clinical practice? Please tick all that apply.

Continuing injecting drug user who regularly uses needle exchange	Yes/No
Ex-injecting drug user stable on substitution therapy (If yes, for how long must they have been stable on substitution?)	Yes/No
Heavy alcohol consumer in regular employment	Yes/No
17 year old person with haemophilia would you do a liver biopsy?	Yes/No
38 year old person with haemophilia without biopsy	Yes/No
Person currently in treatment for psychiatric problems	Yes/No
Persons with past history of suicide	Yes/No
whilst using drugs of addiction	Yes/No
in context of previous non drug related psychiatric problems	Yes/No
Person with current diagnosis of depression related to HCV infection	Yes/No
Person with current diagnosis of depression	Yes/No
Person with past history of depression	Yes/No
Person with poorly controlled diabetes	Yes/No
Person with angina	Yes/No

32. What proportion of new patients with Hepatitis C seen in your clinical practice in 2005 were *ELIGIBLE* for treatment?

0-5%
6-9%
10-24%
25-49%
50-74%
75 -89%
>90%

33. What were the main reasons for patients' ineligibility? Please rank 1-6 in descending order of importance.

Psychiatric disorder
Cardiovascular disease
Ongoing illicit drug misuse
Ongoing alcohol misuse
Other medical co-morbidities
HIV co-infection
Other (Please specify)_____

34. What proportion of your patients with Hepatitis C eligible for treatment received treatment in 2005?

0-5%
6-9%
10-24%
25-49%
50-74%
75 -89%
>90%

35. How many of these have been treated in the context of clinical trials in 2005?

0-5%
6-9%
10-24%
25-49%
50-74%
75 -89%
>90%

36. What antiviral drug regimes do you currently use to treat patients with Hepatitis C? Please tick all that apply.

Interferon alpha alone
Interferon alpha and ribavirin
Pegylated interferon alone
Pegylated interferon and ribavarin
Amantadine

Other - please specify_____

Stopping treatment

37. Which of the following criteria do you use to end treatment? Please tick all appropriate boxes.

Therapy regime	**HCV PCR +**		**Persistently raised ALT**		**Lack of ≥ 2 log reduction in viral load**	
	3 months	6 months	3 months	6 months	3 months	6months
IFN alone						
IFN/R						
Peg IFN						
Peg IFN/R						

38. Do you have printed guidelines for dose reduction and stopping therapy?

Yes/No

If yes, we would be grateful for a copy to be enclosed with your returned questionnaire.

39. In what percentage of patients do you perform a pre treatment liver biopsy?

0-5%
6-9%
10-24%
25-49%
50-74%
75-89%
>90%

Refusal of treatment

40. What reasons do eligible patients who refuse treatment give? Please tick all that apply.

Refusal to modify chaotic lifestyle
Lack of belief in treatment effectiveness
Concern over adverse drug reactions
Inconvenient to start treatment due to work pressures
Lack of concern over future
Cost
Desire for pregnancy within 18 months
Other - please specify_____

41. What percentage of patients stop treatment prematurely (both patient and professional initiated)?

0-5%
6-9%
10-24%
25-49%
50-74%
75 -89%
~90%

42. What are the reasons for stopping treatment prematurely? Please rank 1-5 in descending order of importance.

No response to treatment
Side effects (patient initiated)
Side effects (professional initiated)
Loss to follow up
Other - please specify_____

Service configuration

Liaison

43. Do you have a coordinated management strategy for patients with HCV linking secondary/tertiary care to:

Family Nurse Practitioner reservations	Yes/No
Primary care	Yes/No
Prison healthcare	Yes/No
Drugs and alcohol services	Yes/No
Homeless	Yes/No
Other - please specify_____	

If Yes to any of the above

44. Please state briefly a summary of the strategy or attach documentation if available.

45. Do you have a multidisciplinary team that coordinates the management of Hepatitis C in your area?

Yes/No/Unsure

If Yes:

Please indicate the membership of the group. Tick all that apply.

Gastroenterologist
Internist
Family Physician
Hepatologist
Specialist nurse
Histopathologist
Radiologist
Infectious disease clinician
Community Drug and Alcohol Team representative
Care professional from homeless agency
Genito urinary medicine clinician
Community Intravenous drug users care professional
Patient representative
Community dentist
Other - please specify_____

Barriers and blockage in the management of patients with Hepatitis C

46. Are there any identified barriers in the management of patients with Hepatitis C?

Yes/No

If Yes:

47. Please indicate your response to each of the given statements describing possible barriers to care for patients with Hepatitis C.

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
Clinic waiting time for initial referral					
Biopsy waiting times					
Staffing capacity					
Staffing skillmix					
Funding for treatment					
Patient refusal					
Patient non attendance					
Patient identification					
Other - please specify					

Please write any additional comments regarding barriers in the management of patients with Hepatitis C below.

48. Please give the approximate numbers of your patients with Hepatitis C who are currently

Awaiting out patient appointment
Awaiting investigations
Awaiting funding decisions
Awaiting treatment
Other points in the health/social care systems where patients are waiting
(please specify)_____

49. If you would like to make any further comments on aspects of care for patients with Hepatitis C, please use the space below.

Thank you very much indeed for taking the time to fill this questionnaire. It will make a substantial contribution to the completeness of the national needs assessment of Hepatitis C in Canada and provide information with which to plan future services.

Please return the questionnaire in the stamped addressed envelope provided.

Your replies will be treated in strict confidence.

APPENDIX D: THANK YOU CARD

APPENDIX E: TELEPHONE SCRIPT

Hello can I speak to Dr. xxx?

Hi Dr. xxx, my name is Angelique Myles and I am a Masters student at Memorial University. I am calling to inform you that last week a questionnaire about Hepatitis C treatment was mailed to you.

If you have already completed and returned the questionnaire to me, please accept my sincere thanks. If you have not, please continue filling out the questionnaire and returning it. I am especially grateful for your help because I believe that your response will be useful to understanding potential barriers to referral and treatment of Hepatitis C patients.

If you did not receive a questionnaire, or if it was misplaced, please let me know and I will send you another copy in the mail today.

Thank you for your time and patience.

APPENDIX F: ETHICS APPROVAL

January 17, 2007

Reference #06.189

Ms. Angelique Myles
C/o Dr. P. Wang
Division of Community Health & Humanities
Memorial University of Newfoundland

Dear Ms. Myles:

This will acknowledge your correspondence dated, January 12, 2007, wherein you nd provide a revised telephone script for your research study entitled **"An examination of regional variation in treating hepatitis C patients in Canada".**

The Co-Chairs of the HIC reviewed your correspondence, approved the revised telephone transcript and, granted ***full approval*** of your research study. This will be reported to the full Human Investigation Committee, for their information at the meeting scheduled for February 1, 2007.

Full approval has been granted for one year. You will be contacted to complete the annual form update approximately 8 weeks before the approval will lapse on **January 17, 2008**. It is your responsibility to ensure that the renewal form is forwarded to the HIC office not less than 30 days prior to the renewal date for review and approval to continue the study. The annual renewal form can be downloaded from the HIC website http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc.

Modifications of the protocol/consent are not permitted without prior approval from the Human Investigation Committee. Implementing changes in the protocol/consent without HIC approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HIC website) and submitted to the HIC for review.

For a hospital-based study, it is **your responsibility to seek the necessary approval from the Health Care Corporation of St. John's and/or other hospital boards as appropriate**.

This Research Ethics Board (the HIC) has reviewed and approved the application and consent form for the study which is to be conducted by you as the qualified investigator named above at the specified study site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Human Investigation Committee currently operates according to the Tri-Council Policy Statement and applicable laws and regulations. The membership of this research ethics board complies with the membership requirements for research ethics boards defined in Division 5 of the Food and Drug Regulations.

Notwithstanding the approval of the HIC, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

John D. Harnett, MD, FRCPC
Co-Chair
Human Investigation Committee

Richard S. Neuman, PhD
Co-Chair
Human Investigation Committee

JDH;RSN\jed

C Dr. C. Loomis, Vice-President (Research), MUN
Mr. W. Miller, Director of Planning & Research, Eastern Health