HEPATITIS C VIRUS INFECTION IN INJECTION DRUG USERS

by

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B.Sc., The University of British Columbia, 2002

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

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES

(Pharmacology and Therapeutics)

THE UNIVERSITY OF BRITISH COLUMBIA

May 2007

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ABSTRACT

Injection drug users (IDUs) represent the core of the hepatitis C virus (HCV) epidemic, but little is known about the natural history and treatment of HCV in IDUs. This thesis characterizes spontaneous clearance of HCV, investigates HCV re-infection following clearance and evaluates novel models for improving uptake and treatment responses among IDUs.

To better understand characteristics associated with HCV clearance in IDUs, data from a community-based cohort study were linked with longitudinal laboratory databases to compare individuals with HCV clearance to those with HCV persistence to evaluate factors associated with clearance of HCV infection. Aboriginal ethnicity and female gender were associated with increased rates of HCV clearance, while HIV co-infection and illicit drug use were associated with increased HCV persistence.

To further investigate the impact of illicit drug use on HCV persistence, we compared the rate of re-infection in individuals with HCV clearance to the rate of infection observed in previously uninfected individuals to evaluate whether previous clearance of HCV infection is protective against re-infection. Those with viral clearance were about 4 times less likely to become re-infected than those infected for the first time, suggesting that individuals with HCV clearance have a lower risk of acquiring HCV than individuals who have never been infected, despite ongoing exposure to HCV.

Lastly, we sought to evaluate novel models for improving uptake of and response rates to the treatment of HCV among current and former IDUs. First, we demonstrated that within a prospective, multidisciplinary, directly observed therapy program for the treatment of HCV infection of IDUs, overall response rates parallel results from large, randomized controlled trials, despite ongoing illicit drug use during treatment. Second, we demonstrated a high uptake of and response to therapy among IDUs infected with HCV attending a weekly support group. Taken together, these data demonstrate that IDUs can be safely and successfully treated for HCV infection within a multidisciplinary program integrating HCV, addiction and primary care.
Given the considerable burden of HCV infection in IDUs, this data contributes significantly to the field by providing a greater understanding of the natural history and treatment of HCV in this setting.
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<td>hepatitis C virus</td>
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<td>IDUs</td>
<td>injection drug users</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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<td>ALT</td>
<td>alanine aminotransferase</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>CD4</td>
<td>cluster of differentiation 4 (cell receptor)</td>
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<tr>
<td>CD8</td>
<td>cluster of differentiation 8 (cell receptor)</td>
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<td>NK</td>
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<td>SVR</td>
<td>sustained virologic response</td>
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<td>polyethylene glycol</td>
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<td>EVR</td>
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<td>end of treatment response</td>
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<td>RVR</td>
<td>rapid virologic response</td>
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<td>directly observed therapy</td>
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<td>IFN</td>
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<td>enzyme immunoassay</td>
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<td>χ²</td>
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<td>OR</td>
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<td>CI</td>
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<td>RBV</td>
<td>ribavirin</td>
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<td>ULN</td>
<td>upper limit of normal</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>IQR</td>
<td>interquartile range</td>
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<td>HCC</td>
<td>hepatocellular carcinoma</td>
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LIST OF PUBLICATIONS AND ABSTRACTS

Material from this dissertation has been published in:


Material from this dissertation has been presented in oral format at the following international meetings:


Material from this dissertation has been presented in poster format at the following international meetings:


Material from this dissertation has also been presented orally for the Graduate Student Seminars Series in the Department of Anesthesiology, Pharmacology and Therapeutics at UBC
ACKNOWLEDGEMENTS

My time as a graduate student has been enjoyable and has taught me lessons that will prove valuable in my endeavors as an investigator. Foremost, my deepest thanks go to Dr. Brian Conway, who embodies everything one could ask for in a scientist, supervisor and friend. Through his guidance, I have developed a stronger focus and achieved considerable development as an individual and a scientist. He has provided me with opportunities that very few graduate students experience, which have significantly developed my understanding and capacity for research. I owe him a great sense of gratitude for the knowledge and experiences he has shared with me and for his confidence in my abilities, his trust in my leadership, his encouragement and his never-ending patience. With this, I owe you a great deal of gratitude and thanks. Thank you.

Second, I must thank my good friend and colleague, Mr. Jesse Raffa. Without you, much of this work could not have been possible. Your continuous statistical expertise and patience has enhanced my knowledge, helping me to become a better researcher. I appreciate everything you have done for me and I look forward to our continued work together in the field.

Also, I must thank Dr. Mark Tyndall, Dr. Mel Krajden and Dr. Ismail Laher. As committee members, you have gone above and beyond your duties. First, I must thank Dr. Tyndall and Dr. Krajden for their continuous guidance, patience and continuous encouragement in the conduct of my research. You have consistently dedicated a considerable amount of time to my development as a researcher, acting as co-supervisors rather than committee members. I appreciate your efforts in this regard and none of this work would have been possible without your support. I must also thank Dr. Ismail Laher for providing his pharmacology expertise and his guidance in developing my future research plans. Your involvement has been greatly appreciated.

Over the past several years, I have also had the opportunity to learn and work with an exceptional group of trainees, physicians, nurses, counselors and administrative staff at the Pender Community Health Centre (PCHC). I would like to thank Harout Tossonian and Krista Genoway for your hard work and dedication. Also, I must thank Dr. Stanley deVlaming. As physician leader at the PCHC, you have provided me with limitless resources and support in my
aspirations to expand HCV treatment in the Downtown Eastside of Vancouver. I also owe a deep
gratitude towards Dr. Fiona Duncan, Dr. Mark Viljoen and Dr. Milan Khara for all of your
efforts in the development of the HCV treatment program at PCHC. Without your considerable
dedication towards improving the lives of those living with HCV, we would not have achieved
such success. I respect you as colleagues and friends and look forward to continuing this
relationship in the future. In addition, I must thank the nurses at PCHC, Lian McKenzie, Jennifer
Quesnelle and Natasha Suvorova, without whom there would be no program for the treatment of
HCV infection. You are truly valued in the work that you do. I must also thank one special
nurse, Lesley Gallagher. Since the beginning of my studies, you have constantly been there for
support, as a co-worker and friend. I have always appreciated your input and have immensely
enjoyed working with you. Your dedication towards patients living with HCV does not go
unnoticed and you have played a key role in the success of our research program. For this I thank
you. Lastly, I must thank Doug Elliott, our HCV counselor. Your assistance with the
development of the HCV program at Pender has translated into considerable success, as
measured by our explosive growth over the past year. I appreciate your help and you have
become a good friend. To the rest of the physicians, nurses, counselors and administrative staff
at PCHC, thank you for your support.

I perhaps owe the greatest gratitude to my mother, father and sister, who throughout my life have
continuously forced me to push the envelope towards reaching my goals, explore new
opportunities and achieve the unattainable. Your guidance has been essential in my inherent
drive and my development as an individual. I must also thank my uncle, Andrew Grebely, for
providing my with countless opportunities that contributed to my development as an individual
and spending the time with an inquisitive young mind with a million questions that needed
answers. To my most amazing family and friends, thank you for your encouragement, advice,
love and support. Thank you for understanding when I couldn’t be there and thank you for being
there when I needed you.

Finally, I would like to acknowledge the Natural Canadian Research Training Program in
Hepatitis C for salary and training support and Schering Canada, Hoffmann-La Roche Ltd., the
BC Medical Services Foundation and Vancouver Coastal Health for their financial assistance.
CO-AUTHORSHIP STATEMENT

Chapter 2: Factors Associated With Spontaneous Clearance of HCV Among Illicit Drug Users

Mark W. Tyndall was responsible for the development and recruitment of the cohort described in this paper and reviewing the final draft. Calvin Lai performed necessary data linkages and database management tasks. Jason Grebely developed the experimental approach together with the Brian Conway, Mel Krajden and Mark W. Tyndall. Jason Grebely conducted the analysis of research in collaboration with Jesse D. Raffa, who performed the detailed statistical analysis. Jason Grebely wrote the initial draft of this chapter and attended to the revisions required for final publication. Brian Conway and Mark W. Tyndall supervised the research and assisted with revisions of the final draft.

Chapter 3: Hepatitis C Virus Re-infection in Injection Drug Users

Mark W. Tyndall was responsible for the development and recruitment of the cohort described in this paper and reviewing the final draft. Calvin Lai performed necessary data linkages and database management tasks. Jason Grebely developed the experimental approach together with the Brian Conway, Mel Krajden and Mark W. Tyndall. Jason Grebely conducted the analysis of research in collaboration with Jesse D. Raffa, who performed the detailed statistical analysis. Jason Grebely wrote the initial draft of this chapter and attended to the revisions required for final publication. Brian Conway and Mark W. Tyndall supervised the research and assisted with revisions of the final draft.

Chapter 4: Directly Observed Therapy for the Treatment of Hepatitis C Virus Infection in Current and Former Injection Drug Users

Jason Grebely developed the experimental approach and the study protocol together with the Brian Conway. Milan Khara, Fiona Duncan, Mark Viljoen, Chris Fraser, Annabel Mead, Mark McLean, Stanley deVlaming and Brian Conway were the physicians involved in patient
recruitment, the provision of HCV treatment and assisted with the design of the proposed study. Jason Grebely also performed all the data analysis in consultation with Jesse D. Raffa. Jason Grebely wrote the initial draft of this chapter and attended to the revisions required for final publication. Brian Conway supervised the research and assisted with revisions of the final draft. Caite Meagher assisted with data collection for the study. Brian Conway also supervised the research.

Chapter 5: Treatment Uptake and Outcomes Among Current and Former Injection Drug Users Receiving Directly Observed Therapy Within a Multidisciplinary Group Model for the Treatment of Hepatitis C Virus Infection

Jason Grebely and Doug Elliott were involved in the development of the weekly support group described in this paper. Jason Grebely developed the questionnaires and study protocol under the supervision of Brian Conway. Jason Grebely also developed the experimental approach together with the Brian Conway. Milan Khara, Fiona Duncan, Mark Viljoen, Stanley deVlaming and Brian Conway were the physicians involved in patient recruitment, the provision of HCV treatment and assisted with the design of the proposed study. Jason Grebely performed all the data analysis in consultation with Jesse D. Raffa. Jason Grebely wrote the initial draft of this paper and attended to the revisions required for final publication. Brian Conway supervised the research and assisted with revisions of the final draft. Krista A. Genoway assisted in data collection and analysis of this study. Brian Conway also supervised the research.
CHAPTER I

Introduction to Hepatitis C Virus Infection in Injection Drug Users

1.1 Injection Drug Users: The Overlooked Epicentre of the HCV Epidemic

Hippocrates first described viral hepatitis in the fifth century BC as an epidemic of jaundice. Epidemics of jaundice were particularly common during vaccination campaigns and wars occurring in the 19th and 20th centuries and are likely attributed to outbreaks of viral hepatitis. The first documentation of viral hepatitis transmitted by direct inoculation of blood or blood products was described by Lurman in Bremen, Germany, in 1883 during a smallpox immunization campaign (1). Various other outbreaks of hepatitis were subsequently described in a variety of risk groups (2, 3). However, the lack of appropriate diagnostic assays precluded the identification of the responsible agent(s). In the 1930s and 1940s, epidemiologic studies provided evidence to suggest that hepatitis was caused by at least two different etiologic agents. In 1947, MacCallum and Bauer (4) proposed a nomenclature for two of these agents; hepatitis A, an agent predominant in children transmitted primarily by an oral-fecal route, and hepatitis B, which was common in adults and transmitted by percutaneous exposure to blood products. As diagnostic assays became available to distinguish hepatitis A and hepatitis B, it became clear that there existed distinct etiologic agents responsible for a form of non-A, non-B hepatitis. Studies of patients infected with non-A, non-B hepatitis (5) led to the identification of hepatitis C virus (HCV) infection in 1989 (6) and hepatitis E virus in 1990 (7).

HCV has spread extensively throughout the world as a result of its efficient parenteral transmission via transfusion of contaminated blood products, medical procedures and injection drug use. In developed nations, the availability of sensitive assays for the detection of HCV, universal blood donor screening and the development of health policies for the sterile administration of therapeutic injections led to a virtual elimination of iatrogenic transmission of HCV. However, HCV transmission remains rampant among individuals engaged in injection drug use as a result of the sharing of injection equipment. It is now evident in this setting that injection drug users (IDUs) represent the majority of infected cases of HCV and are the major source of new infections. Among long-term injectors, 90% of IDUs are infected with HCV and
are at considerable risk of developing serious liver complications, including cirrhosis, end stage liver disease, hepatocellular carcinoma and death. Any effort to reduce the global burden of HCV infection must include research into the natural history and treatment of HCV infection in IDUs, the overlooked core of the HCV epidemic.

1.2 Epidemiology of HCV Infection

Since its discovery in 1989, HCV has been recognized as a major cause of chronic liver disease. The most recent estimates from the World Health Organization suggest that the global prevalence of HCV is ~2.0%, representing 125-170 million infected individuals worldwide (8). In Canada, it is estimated that 300,000 individuals (0.8%) are infected with HCV, with 5,000-7,000 new infections occurring each year (9). However, these figures likely underestimate the true burden of HCV, given that homeless and incarcerated populations, in which infection is most prevalent, are not included in these estimates.

Risk factors most commonly attributed to HCV transmission include blood transfusion from unscreened donors, injection drug use, unsafe therapeutic injections, and other health-care related procedures (10). Although sexual and maternal-fetal transmission of HCV has been observed, this occurs relatively infrequently. In developing nations, the widespread administration of unsafe therapeutic injections and transfusions from unscreened donors represent major modes of HCV acquisition (10).

IDUs represent the core of the HCV epidemic in many developed nations, with the majority of new and existing infections occurring in this group. In Canada, the United States, Europe and Australia, IDUs account for 50-70% of existing infections (11-16) and the proportion of new infections attributed to injection drug use is steadily increasing. Data from Canada and Australia suggest that 65-93% of incident HCV infection is associated with injection drug use (17, 18).

HCV infection is thought to occur rapidly after the initiation of injection drug use. In one study, the prevalence of HCV infection was 78% among individuals with at least 1 year of injection drug use experience (19). As the duration of injection drug use increases, so does the likelihood
of acquiring HCV infection. In the same study, 94% of individuals with >10 years of injection drug use tested positive for HCV infection. This association between the increased risk HCV acquisition as a result of longer injection drug use duration has also been observed in other populations of IDUs (20-23). Among long-term IDUs with an injection history of more than 6 years, the prevalence of HCV remains high, with 64-94% of IDUs testing positive for HCV (19, 24). Similar results have been reported from high-risk cohorts of IDUs in Canada. Among 2,000 such individuals recruited into the VIDUS (Vancouver Injection Drug Users Study) and SEOSI (Scientific Evaluation of the Supervised Injection Site) cohorts, the HCV prevalence was 82-88% (13, 25). Recent data from Vancouver and San Francisco suggest that the spread of infection is still rampant, given that HCV incidence rates ranging from 30-52% have been observed among high-risk, young IDUs (26, 27). If any effort is to be made to alter the current epidemiology of HCV and curtail the epidemic in this population, it is imperative that programs are designed to address HCV infection in this group, with the goal of preventing long-term liver related morbidity and mortality associated with HCV and the transmission of infection.

1.3 Natural History of HCV infection

1.3.1 Introduction
Hepatitis C infection is caused by a small, single-stranded positive sense RNA virus (28, 29). HCV primarily infects and replicates in hepatocytes in the liver. However, evidence exists for extrahepatic reservoirs of infection including peripheral blood lymphocytes (29), epithelial cells in the gut (30) and the central nervous system (31). In the liver, HCV replicates at a high rate, generating average serum HCV RNA levels of 1 to 2 million genome equivalents per millilitre (32). Replication occurs via the HCV RNA-dependent RNA polymerase, which is highly error prone and lacks proofreading capacity, resulting in the development of random mutations into the viral genome (29). This can lead to the establishment of a population of closely related, yet heterogeneous sequences of HCV within an individual, the viral quasispecies. This high error rate of RNA-dependent RNA replication and interactions between the virus and host over time have led to considerable global diversity in the genetic composition of HCV. Overall, 6 genotypes of HCV exist, which vary in nucleotide sequence by 30 to 50% (33). The distribution of HCV genotypes often vary by either geographic region or the risk behaviour for acquisition (34). Of the six identified genotypes, HCV genotypes 1, 2 and 3 are the most common in North America, with 65-75% of subjects in the United States and Canada infected with genotype 1 (35-
Data suggests that the prevalence of HCV genotype 3a is much higher in IDUs than in other risk groups, although this may vary with geographic region (38-44). HCV genotype appears to have no effect on the pathogenesis and natural history of HCV.

1.3.2 Acute HCV Infection

Initial infection with HCV is characterized by the rapid appearance of HCV viremia in the blood (within 2-14 days of exposure), increases in liver-associated serum enzymes (i.e. alanine aminotransferase, ALT) and the gradual appearance of HCV-specific antibodies (within 20-150 days of exposure) (27, 45-47). Infection with HCV is often asymptomatic, with only 15-30% of individuals developing an acute hepatitis syndrome, which is generally mild, occurs within 5-12 weeks of exposure and lasts 2-12 weeks (48, 49). Acute infection with HCV generally lasts 6 months and is characterized by a low likelihood of spontaneous clearance, defined by the resolution of infection. However, in the majority of acutely infected subjects (55-85%) viremia persists beyond 6 months, leading to the development of chronic HCV infection (Figure 1.1).

![Figure 1.1 Natural history of HCV infection.](image)

Two patterns of HCV viremia during the acute phase of HCV have been described among humans (50, 51) and chimpanzees (52, 53) (Figure 1.2). The first pattern involves a significant drop in viremia after it reaches peak levels and is associated with successful spontaneous clearance of HCV. Although a transient rebound in viremia may occur after an initial peak, in this setting, HCV RNA is cleared from the blood of these individuals during the first 6 months of infection. The other pattern of viremia occurs among individuals who do not achieve viral clearance and develop persistent viremia. In some individuals, HCV RNA may be continuously detected in the plasma during the entire phase of acute infection, resulting in chronic infection.
Alternatively, some individuals may temporarily control viral replication, but then subsequently lose control, leading to viral rebound and the development of persistent infection. In the setting of acute HCV infection, successful spontaneous clearance will occur in ~15-45% of subjects.

Figure 1.2 Proposed model of immune response to HCV infection. A. HCV clearance. B. HCV persistence (50, 51).

1.3.3 Spontaneous Clearance of HCV
Clearance of HCV is dependent on the route of transmission and other host and pathogen-related characteristics. Host factors associated with HCV clearance include the initial immune response to HCV (54-61), the age at time of HCV infection (62, 63), alcohol (64), sex (63, 65-69) and race (70, 71). In addition, pathogen-associated factors such as the diversity of HCV viral quasispecies (72), the HCV viral load (63) and co-infection with HIV (63, 70, 73) have been associated with the host’s ability to resolve HCV infection. However, the ability to develop a complete understanding of virologic clearance in the setting of acute infection is limited by the small numbers of reported cases, the frequent asymptomatic nature of acute infection and the fact that infection often goes undetected.

1.3.3.1 Host Factors Associated with HCV Clearance
The most important factor in the spontaneous clearance of HCV is the breadth and vigour of initial immune response to HCV (74, 75). Chimpanzees (75-77) and humans (54-61) who mount an early, multi-specific CD4+ and CD8+ T-cell response to HCV proteins can achieve virologic clearance. Moreover, the inability to maintain sustained activation of CD4+ and CD48+ T-cell responses in both humans (55, 61) and chimpanzees (75, 77) with acute HCV infection leads to a
loss of spontaneous control and the development of persistent infection. These data speak to a co-ordinated role for both CD4+ and CD8+ T cells in the control of initial infection with HCV.

In addition to immunity, several other host factors are important in determining clearance of HCV. Increased alcohol consumption has been observed to reduce clearance of infection, however, the mechanism behind this observation is not clear (64). The impact of age at infection on HCV clearance is apparent from the observation that HCV clearance rates in transfusion associated-hepatitis that largely included individuals >50 years of age are ~15% (5, 78) compared to ~45% among infected infants and young women (62, 65, 79, 80). In one study of hemophiliacs without HIV infection, individuals infected before the age of 2 years had a much higher rate of HCV clearance (40%) as compared to those infected after the age of 15 years (15%). This is consistent with several other studies demonstrating that a younger age at infection is associated with increased rates of HCV clearance (79, 81). Gender may also be important in determining clearance of HCV. In a systematic review of thirty-one longitudinal studies evaluating the correlates of spontaneous HCV clearance, gender was the only significant predictor of clearance with males being two-times less likely to clear HCV spontaneously (19%) when compared to females (40%) (69). With respect to ethnicity, it has been demonstrated that African Americans may have decreased rates of HCV clearance when compared to Caucasians (70, 71). Conversely, there are data from Canada and the United States demonstrating higher rates of spontaneous clearance among Aboriginal people when compared to Caucasians (82-84). Although the relationship between age, gender and clearance of HCV is well defined, further studies are needed to investigate the role of ethnicity in this context.

The association of gender and race with spontaneous HCV clearance suggests that host genetic factors encoding immunity to HCV may play an important role in viral control of HCV infection. It has been demonstrated that genetic polymorphisms encoding proteins involved in the innate and adaptive immune response to HCV may be associated with clearance (85-91). Inhibitory NK cells and the innate immune response may be important in clearance (91). It has been demonstrated that the activity of certain genes encoding interactions between HLA class I molecules and NK cells may play an important role in the effectiveness of this process (91). Given the importance of the inflammatory response in the eradication of HCV infection, data suggest that certain genetic polymorphisms of proteins involved in inflammatory and cellular immune responses to HCV (such as IL-10, IL-19, IL-20 and TNF-alpha) are associated with
reduced viral clearance (85, 90, 92). Immunologic studies in Aboriginals suggest a lower genetic tendency to produce IL-10 than Caucasians and a reduced susceptibility to HCV protein induced IL-10 immune responses, implicating a role for the immune system in this enhanced protection (93). Additionally, polymorphisms in genes encoding enzymes with antiviral activity against HCV may have an impact of the host to naturally resolve HCV infection (94). There are also data to suggest that polymorphisms in genes encoding HLA class I and II molecules, which interact with CD4 and CD8 T cells and stimulate an efficient adaptive immune response against HCV, are associated with clearance of HCV infection (86, 87, 89, 95, 96). A number of these studies have demonstrated that the expression of genetic polymorphisms of many of these proteins differs among various ethnicities and may partially explain differences in clearance among different ethnicities (85, 87, 90). However, further research is needed in order to better understand the associations between host genetics, the immune system and HCV clearance.

1.3.3.2 Pathogen Factors Associated with HCV Clearance

In addition to host-related characteristics, pathogen-associated factors such as the diversity of viral quasispecies (72), HCV viral load (71, 97) and co-infection with HIV (63, 70, 73) have been associated with clearance of HCV infection. Given the infidelity of the RNA-dependent RNA polymerase, mutations are frequently incorporated into the replicating HCV RNA genome. This leads to the generation of a diverse population of closely related viral variants known as the quasispecies, which may allow the virus to circumvent the immune response to HCV. In humans, the development of a diverse viral quasispecies during acute HCV infection has been associated with mutations in various HCV proteins and an impaired ability to spontaneously resolve HCV infection (72). The fact that lower levels of HCV RNA are associated with increased clearance may relate to some reduction in quasispecies generation (71, 97). There have been several studies which have demonstrated that HIV infection is associated with a two-fold decrease in clearance of HCV infection (63, 70). However, the absence of systematic testing in these populations and the asymptomatic nature of HCV infection often has made it difficult to detect the order of HIV and HCV infections and determine whether HIV decreases HCV clearance or increases HCV persistence, through either a recrudescence of existing low-level viremia or an increased susceptibility towards re-infection. Further studies are needed to fully elucidate the impact of HIV infection on persistence of HCV.
It is clear that a delicate balance between host, viral and environmental factors, determines spontaneous clearance of HCV infection. Host immunity and CD4+ and CD8+ T-cell responses against HCV probably determine the ability of the host to resolve infection. However, this is countered by the considerable diversity of HCV and its ability to evade the host immune response during initial infection. This is complicated by a number of external factors that can tip the balance in favour of the virus or the host.

1.3.3.3 Spontaneous Clearance of HCV in IDUs – A Special Case?

It is important to note that although these studies of virologic clearance have significantly improved our understanding of the natural history of HCV infection, the majority of them have been performed in groups other than IDUs. These include community-based studies of young women and children infected with HCV following exposure to contaminated blood products (65, 79, 80), blood donors (98) or persons with post-transfusion hepatitis (99). Such individuals are at an increased risk of engaging in alcohol and injection drug use, both of which may increase the persistence of HCV infection. Additionally, the use of illicit drugs has a significant impact on the immune system (100) and may impair the ability of the host to spontaneously clear HCV infection. As such, it is important to understand the factors associated with clearance among IDUs and current knowledge in this field is limited at best.

This being said, viral clearance rates among cohorts of injection drug users range from 11% to 42%, depending on the population studied (63, 70, 71, 101). Currently, the majority of what is known of the natural history of HCV infection among IDUs comes from a large longitudinal study in Baltimore developed to investigate the natural history of HIV infection in this population (19, 70, 71). In one study from this cohort, 43 individuals developing acute HCV infection were assessed for viremia and factors associated with viral clearance. Viral clearance was observed in 19% (6/34) of individuals, with white ethnicity (vs. black), icteric presentation and lower peak viral titre associated with viral clearance (71). In follow-up to this study, the investigators evaluated HCV clearance among a larger subset of 919 subjects with chronic HCV infection (70). Overall, only 11% of subjects had spontaneous clearance of HCV, with clearance occurring more frequently in non-blacks and individuals without HIV co-infection. However, in these studies, ~90% of subjects were black and ~80% were male, both of which are associated with reduced clearance of HCV, making it difficult to generalize the interpretations of these data to other settings with higher proportions of other ethnicities and females. One study from
Australia evaluating HCV clearance among 57 young IDUs with acute HCV infection in a predominantly Caucasian population (63%) demonstrated a clearance rate of 42%. However, given the small sample size in this study, no factors associated with HCV clearance could be identified (101). Further data from a cohort of 418 HCV seropositive IDUs in New York demonstrated that 25% achieved HCV clearance (63). Factors associated with clearance of HCV included female gender and the absence of both HIV co-infection and injection drug use behaviours. As such, given the small number of studies investigating the natural history of HCV infection and the small sample sizes in those studies with data available, there are considerable gaps in our knowledge in this area.

The association of injection drug use and decreased clearance of HCV is interesting and warrants further research, given that re-infection with HCV as a result of ongoing injection drug use may increase HCV persistence. Moreover, further work is required to understand the impact of HIV infection on persistence of HCV in IDUs, given that the order of HIV and HCV infections are often not known and it is not certain whether HIV is impacting clearance or persistence of HCV. Lastly, the impact of other ethnicities on HCV clearance remains to be determined. It is apparent that further work investigating factors associated with clearance of HCV among IDUs will be essential in understanding the pathogenesis of HCV in the population which is most affected by this condition.

1.3.3.4 HCV re-infection in IDUs
Following spontaneous clearance of HCV infection, it is not clear whether previous clearance provides protection against re-infection among IDUs with ongoing injection drug use. Re-infection can occur and has been demonstrated in a variety of settings. Viremia reappeared in 5 thalassemic children that were re-challenged after spontaneous HCV clearance (102) and HCV patients who receive a liver transplant from an HCV+ donor have shown super-infection with a new genotype (103). Re-infection has also been observed among IDUs who were subsequently re-exposed to the virus (104-106).

However, in chimpanzees re-infected with HCV, there is often rapid control of viral replication, short-lived viremia and universal spontaneous resolution of secondary infection (107). Although re-infection can occur in chimpanzees re-challenged with HCV after its clearance (77, 108-110), there is a relative resistance to subsequent HCV infection likely related to immune protection
All infected chimpanzees that have been studied to date demonstrate an attenuated course of infection, with lower HCV levels and no evidence of liver disease (77, 109-111). This is consistent with protective immunity. Also, rapid control of re-infection was associated with HCV-specific T-cell responses (77, 109). When CD4+ T-cells were depleted in vivo before re-infection, chronic HCV infection ensued (75). Similarly, the depletion of CD8+ T-cells led to prolonged HCV viremia, which was only controlled once CD8+ T cells reappeared in the liver (77).

However, there are limited data about whether protective immunity to HCV exists in humans. One study of acute HCV infection and re-infection demonstrated that HCV viremia in the setting of HCV re-infection was at a lower level, generally transient and shorter duration than compared to initial infection (56). In one epidemiological study of IDUs, the incidence of HCV infection over 6-24 months was 12% in 98 subjects who were known to be HCV antibody positive but aviremic, as compared to 21% in 164 subjects never infected with this virus (73). This suggests that IDUs with previous clearance of HCV had a lower risk of developing de novo infection as compared to individuals with no evidence of previous infection. Moreover, individuals that had spontaneously cleared HCV infection and subsequently acquired HIV infection during the follow-up period lost this apparent immune protection, implicating a role for CD4+ T-cells in HCV-specific immunity. Although these studies suggest that HCV-specific protective immunity may occur in some individuals with resolution of HCV, further studies are required to confirm these findings. Additionally, it will be important to understand whether the protective immunity that is observed in the setting of natural HCV clearance also applies to treatment-induced clearance of viremia. If protection against HCV re-infection does occur, this could have important implications for the treatment of HCV in IDUs and development of vaccines for individuals at highest risk, with the goal of preventing the long-term liver-related morbidity and mortality associated with HCV infection.

1.3.4 When Spontaneous Clearance Does Not Occur - Chronic HCV Infection

The clinical course of chronic HCV infection generally unfolds over several decades and the majority of individuals do not manifest symptoms that can be clearly linked to the infection (Figure 1.3). Chronic HCV infection is defined by the persistence of HCV RNA ≥6 months beyond initial exposure. Subsequent to infection with HCV, the serum HCV RNA will often reach a stable level between 4 and 6 log_{10} which will remain relatively constant for decades,
while the serum alanine aminotransferase (ALT) levels often fluctuate (112-114). The most important sequelae of chronic HCV infection are progressive liver fibrosis, leading to cirrhosis, end-stage liver disease and HCC (hepatocellular carcinoma).

Figure 1.3 Natural history of chronic HCV infection (115).

1.3.4.1 Progression of Fibrosis

Despite the fact that there may be very few clinical symptoms and signs of liver progression before the development of end-stage liver disease, histopathologic evidence of progression can be identified earlier. The gold standard for the assessment of the extent of liver disease is the liver biopsy (116, 117), which provides important information on inflammation and fibrosis occurring in the liver. During persistent HCV infection, there is a chronic inflammatory response which is associated with the development of fibrosis (118, 119). Fibrosis will often progress into cirrhosis, eventually leading to end-stage liver disease or HCC (120). However, disease progression is affected by a number of factors and not all chronically infected patients follow this sequence of events, and those who do progress do so over 20 to 40 years or even longer.
1.3.4.2 Hepatic Consequences of Liver Disease

The percentage of chronically infected individuals developing cirrhosis during the first 10 to 20 years of infection ranges from 5% to 25% (121-126). However, very little information is available regarding progression beyond 30 years. Although follow-up studies of persons infected at the time of blood product transfusion demonstrated a high rate of cirrhosis two to three decades after exposure (17%-55%), these reports likely overestimated this risk due to a referral bias, given that these studies were performed in tertiary care clinics (119, 127-129). In one long-term study in which transfusion recipients with HCV infection were followed and matched with a group of uninfected transfusion recipients (99, 130), it was demonstrated that 15% of HCV-infected subjects had cirrhosis within 20 years, with infected individuals having increased rates of liver-associated mortality as compared to HCV-uninfected individuals (4.1% vs. 1.3%, P=0.05). However, lower rates of cirrhosis have been observed in community-based studies. In one cohort of 1667 HCV-infected IDUs infected for an estimated mean of 14 years and followed for a mean of 8.8 years, a random sample of 210 HCV-infected subjects had liver biopsies performed and only 10% demonstrated serious liver disease (Ishak modified fibrosis scores of 3-6) (70). Similarly, in two other community-based studies of females infected by contaminated Rh immune globulin, the incidence of cirrhosis was <5% after 15 to 20 years of follow-up (65, 80). This is consistent with low rates of cirrhosis (<5%) observed 20 years after infection during or shortly after birth (79, 131). Of those developing cirrhosis, it is estimated that end-stage liver disease and hepatocellular carcinoma occur at rates of 2% to 4% and 1% to 7% per year, respectively (132-134).

1.3.4.3 Factors Associated with Liver Disease Progression

Factors associated with increased progression of HCV-related liver disease include older age at infection (70, 135, 136), male sex (136), HIV co-infection (137-147), non-alcoholic steatohepatitis (148, 149) and heavy alcohol intake (150-154). Perhaps the most important predictor of fibrosis progression is the age at which infection occurs (70, 135, 136). Low rates of progression to cirrhosis have been observed in young women infected via Rh immune globulin (65), young injection drug users (70) and persons infected during childhood (79, 155-157). This is in contrast with other studies containing a wider range of age groups demonstrating that higher cirrhosis rates are observed in older individuals, even after adjusting for the duration of infection (136). In a large systematic review of 57 studies, the rate of cirrhosis progression after 20 years of chronic HCV infection was 22% among tertiary care liver clinic cohorts, 24% in studies of
post-transfusion hepatitis, 7% in community-based studies and 4% in studies of blood donors (158). Importantly, age at infection was significantly associated with increased liver disease progression, in addition to male gender and heavy alcohol intake. Alcohol intake is perhaps the most important environmental factor affecting liver fibrosis (150-154) and interacts in a synergistic fashion with HCV, with one study demonstrating that heavy alcohol intake (>50-125 g/day) leads to approximately a 100-fold increased risk of cirrhosis (152). Similarly, co-infection with HIV leads to rapid progression of liver disease (137-147). In one study comparing fibrosis progression rates in 122 HIV/HCV co-infected subjects with 122 HCV infected controls, the time to progression of cirrhosis was significantly higher among HIV/HCV co-infected subjects, especially in the setting of increased alcohol consumption (137).

Overall, the progression of chronic HCV is highly variable and is dependent on a number of host and environmental related factors. However, the availability of an effective regimen for the treatment of HCV provides an important means of altering the natural history of HCV, thereby reducing the impact of liver disease and its complications.

1.4 Therapy for HCV Infection

1.4.1 Introduction

Advances in the treatment of HCV infection have led to the development of treatment regimens that can result in a cure in at least half of treated patients. The sustained virologic response (SVR) is the best indicator to date of treatment response, defined as the absence of viremia 24 weeks after the end of therapy. In most cases with SVR, viral eradication from the serum and the intrahepatic reservoirs remains durable over the long-term, given that 95-98% of these individuals will remain aviremic following SVR (159, 160), consistent with a virologic cure (161). The long-term outcome of an SVR include the normalization of ALT liver enzymes (162), improvement in hepatic necroinflammation and fibrosis stage (162), improvement in health related quality of life (163), a decreased chance of developing hepatocellular carcinoma (164) and improved survival (165).
1.4.2 Interferon-α and Ribavirin

1.4.2.1 Interferon-α

In 1986, the causative agent responsible for the development of “non-A, non-B” hepatitis had not yet been discovered. As such, nothing was known of the suspected viral characteristics that would assist in drug design and there was no way of evaluating antiviral activity. However, given its activity against a wide spectrum of hepatitis viruses (including hepatitis A, B and delta viruses), recombinant human interferon α was a natural choice as a possible agent for the treatment of non-A, non-B hepatitis. This led to a small pilot study which evaluated various doses of recombinant human interferon α (0.5 to 5 million units) for 48 weeks in 10 patients with non-A, non-B hepatitis (166). A significant decline in ALT was observed in 8 of 10 subjects and a significant improvement in hepatic histology was documented in the 3 subjects having undergone liver biopsies. Interestingly, a 10 year follow-up study of this cohort demonstrated that 5 of 10 patients had no detectable HCV RNA and had achieved an SVR after treatment (167). Although this response rate (50%) was higher than was seen in subsequent studies (12-16%), it could likely attributed be to the young age, mild to moderate degree of fibrosis and high proportion of subjects infected with HCV genotypes 2/3, all of which are factors associated with improved response to interferon α (168, 169).

This led to a number of randomized controlled trials investigating the optimal dosing and duration of interferon α for the treatment of chronic HCV infection (170, 171). Based on data from these studies and a meta-analysis of randomized trials of interferon α (171), the first NIH Consensus Development Conference on Management of Hepatitis C, held in 1997, recommended standard interferon α at a dose of 3 million units three times a week for 48 weeks to be the standard treatment for chronic hepatitis C (172). However, SVR rates of only 12% to 16% were observed with this schedule (170), outlining a clear need to develop other therapies which could improve treatment outcomes.

1.4.2.2 Ribavirin

Efforts to find other therapies to supplement interferon led to the testing of a number of investigational agents in humans, including the nucleoside analogue, ribavirin, known to have a broad spectrum of activity against many RNA and DNA viruses. The first clinical trial of ribavirin was performed in 1991 (173) and significant reductions in ALT liver enzymes were observed, suggesting a biochemical response during ribavirin treatment. Unfortunately,
subsequent studies demonstrated that although ribavirin improved ALT levels, there was little impact on viral replication (174-176). Although this tempered initial enthusiasm for this drug, Brillanti and colleagues had already initiated a study to investigate the efficacy of interferon α in combination with ribavirin (177). Overall, 40% of subjects receiving combination therapy with interferon α and ribavirin achieved an SVR, as compared to no subjects in the interferon α only arm. This landmark study had a major impact on the management of HCV infection.

1.4.2.3 Interferon-α and Ribavirin Combination Therapy

These findings prompted the launch of several randomized controlled trials to evaluate the efficacy of interferon α and ribavirin combination therapy (168, 169). Response rates of 38-43% were achieved among subjects receiving 48 weeks of combination therapy as compared to only 13-19% of subjects receiving monotherapy with interferon α (168, 169).

Although combination therapy with thrice-weekly standard interferon-α and daily ribavirin offered improved response rates over interferon α alone, the interferon component of the therapy remained problematic in many respects. Following subcutaneous injection, standard interferon-α is rapidly absorbed (absorption $t_{1/2}$ 2.3 hours), reaches peak plasma levels within 1-8 hours, is widely distributed throughout body fluids and tissues and rapidly metabolized and cleared by the kidney (178, 179). This leads to rapid elimination (elimination $t_{1/2}$ 3-8 hours) and undetectable concentrations in the serum within 24 hours of administration (178, 179). The pharmacokinetic properties of interferon α certainly suggested that the thrice-weekly dosing regimen was suboptimal, especially given that there are two consecutive days each week where patients have no detectable levels of the administered medication. Given that HCV has a high rate of replication (approximately $3.7 \times 10^{11}$ virions per day) (32), there is the potential for viral rebound and the development of viral mutations leading to drug resistance in the presence of suboptimal drug concentrations. With this in mind, pegylation technology was applied to improve the pharmacokinetics and pharmacodynamics of interferon α to avoid large fluctuations in serum concentrations and to improve the inconvenient dosing regimen.
1.4.3 Improving the Pharmacology of Interferon α and Ribavirin

1.4.3.1 Pharmacokinetics of Interferon α and Ribavirin

Pegylated interferon α (peginterferon α) was developed by the conjugation of a polyethylene glycol (PEG) molecule to standard interferon α. Polyethylene glycol (PEG) is linear, uncharged, hydrophilic polymer with low toxicity and is non-immunogenic (180). The conjugation of polyethylene glycol (PEG) to standard interferon α results in a molecule with improved pharmacologic activity and increased half-life. There are currently two forms of peginterferon currently approved for the treatment of HCV infection: peginterferon α2a (Pegasys, Hoffmann-La Roche) and peginterferon α2b (Peg-Intron, Schering-Plough). These two forms of pegylated interferon differ somewhat in their pharmacokinetic properties.

Peginterferon α2a is monopegylated and contains a 40 kDa branched PEG molecule, which can exist as four major positional isomers at the Lys\textsuperscript{31}, Lys\textsuperscript{121}, Lys\textsuperscript{131}, Lys\textsuperscript{134} positions of interferon α (181). In healthy volunteers, a single dose of 180 μg produces a mean maximum serum concentration (C\textsubscript{max}) of 14.2 μg/L, which is reached in a mean time (T\textsubscript{max}) of 78 hours (182). In patients with chronic HCV receiving multiple doses of peginterferon α2a (180 μg once-weekly), the C\textsubscript{max} and T\textsubscript{max} values are 25.6 μg/L and 45 hours, respectively (183). Peginterferon α2a demonstrates an increased absorption (50 hours vs. 2.3 hours) and elimination half-life (65 hours vs. 3-8 hours) as compared to standard interferon α2a (184). Five to eight weeks after the initiation of therapy, a steady state is achieved, and the ratio of serum peak to trough concentrations of peginterferon α2a is about 1.5 to 2.0, indicative of sustained serum drug concentrations during the 1 week dosing interval. The mean terminal half-life is 80 hours, which is 16 times that of conventional interferon α2a (5.1 hours). After the completion of a 48 week course of treatment with peginterferon α2a (180 μg once-weekly), it takes 4 to 6 weeks for serum concentrations to become undetectable (183). The bio-distribution is restricted, with the highest concentrations occurring in the liver (185). Clearance occurs via the kidney and the liver, although given the large size of peginterferon α2a, it is primarily cleared by the liver.

Peginterferon α2b is also monopegylated, but is covalently attached to a smaller, 12 kDa linear PEG molecule. Given the smaller size of the PEG chain, peginterferon α2b generally exists as one of 14 monopegylated positional isomers attached to nucleophilic amino acids of interferon including lysine, serine, tyrosine, histidine and N-terminal cysteine (186). Similar to peginterferon α2a, peginterferon α2b has an improved mean absorption (4.6 hours vs. 2.3 hours)
and elimination half-life (40 hours vs. 4 hours) when compared to standard interferon α2b following a subcutaneous dose (187). Additionally, at therapeutic doses, peginterferon α2b demonstrates 10-fold greater peak levels than interferon α2b (187). The time required to reach peak serum concentrations of peginterferon α2b ranges from 15 to 44 hours. These peak concentrations are generally sustained for up to 48 to 72 hours (187, 188). In patients with chronic HCV infection, the mean terminal half-life is 40 hours. Importantly, given that peginterferon α2b is widely distributed throughout the body fluids and tissues (volume of distribution 1.4 L/kg) and their volume of distribution is dependant on the individual’s body weight, weight-based dosing is recommended (189). Renal clearance accounts for 30% of peginterferon α2b, with the remainder degraded through interactions with cellular interferon receptors or via the liver.

Co-administration of peginterferon with ribavirin does not affect the pharmacokinetics of ribavirin. Similarly, there is no evidence to suggest that ribavirin influences the pharmacokinetics of pegylated interferon (188). In subjects treated with 600, 800 and 1000-1200 mg ribavirin daily (in combination with peginterferon α2b), the mean peak plasma ribavirin concentrations in week 1 were 741 ng/mL, 799 ng/mL and 1101 ng/mL, respectively. The T<sub>max</sub> occurred between 1 and 2 hours after dosing. Mean peak plasma ribavirin concentrations in week 4 were 1770 ng/mL, 2297 ng/mL and 2750 ng/mL for subjects treated with 600, 800 and 1000-1200 mg ribavirin daily (in combination with peginterferon α2b), respectively. Apparent ribavirin clearance appears to be consistent (23-26 L/h) across all dosing groups (188).

These data illustrate that the pegylation of both interferon α2a and α2b have considerably improved the pharmacokinetic profile of both molecules. Additionally, there seems to be no pharmacologic interaction between peginterferon and ribavirin that would require adjustment of dosing regimens. However, there are subtle differences in the pharmacokinetic and pharmacodynamic properties of each peginterferon molecule. Peginterferon α2b reaches peak concentrations more quickly when compared to peginterferon α2a, however, it is also cleared more rapidly and has a shorter absorption and elimination half-life. This results in more sustained serum concentrations of peginterferon α2a over the dosing period when compared to peginterferon α2b. Pharmacodynamic data suggest that pegylated interferon α2b has greater activity as measured by interferon response gene profiling (186), which is supported by the only in vivo randomized comparison of these two agents without the addition of ribavirin (190).
However, similar response rates have been observed in clinical trials of these agents, bringing into question the clinical significance of their differing pharmacokinetic and pharmacodynamic profiles.

1.4.3.2 Pharmacodynamics of Interferon α and Ribavirin

An appreciation of the pharmacodynamic effects of peginterferon and ribavirin requires an understanding of the HCV steady-state kinetics in chronically infected patients, which have been elucidated using mathematical models of viral decay during therapy with interferon α therapy (32). The liver of an individual infected with HCV is composed of infected and uninfected hepatocytes (Figure 1.4). Infected hepatocytes are the site of HCV replication and continuously produce virions, which pass into the peripheral circulation, to infect naïve hepatocytes. Cell death of both infected and uninfected hepatocytes also occurs via apoptosis. In the liver and the periphery, circulating virions are continuously degraded via unknown mechanisms in immunologically protected compartments. Thus, during chronic infection with HCV, the steady-state viral kinetics are characterized by: 1) an equilibrium between the death of infected hepatocytes and the infection of naïve hepatocytes, leading to a pool size of infected cells which remains constant; and 2) an equilibrium between the release of newly produced HCV viral particles into the peripheral circulation and their subsequent degradation, resulting in a HCV viral load which remains constant. With this in mind, the goal of therapy for HCV infection is to alter this equilibrium by promoting the clearance of HCV infected cells and reducing HCV virion release into the peripheral blood. Once all infected cells have been cleared from the body, virologic cure is achieved.
Figure 1.4 Steady-state HCV kinetics during chronic infection, based on mathematical modeling of viral decay during interferon alpha therapy (32).

Mathematical modelling of the first phase of viral decline during therapy for HCV suggests that interferon $\alpha$ elicits its antiviral effects by directly inhibiting HCV viral replication (32). However, the absence of a suitable cell model precluded the confirmation of this hypothesis. In 1999, the development of an \textit{in vitro} subgenomic HCV replicon cell model (191) represented a major advance in the field and subsequent studies using this \textit{in vitro} cell model demonstrated that interferon acted by directly inhibiting HCV replication (192-194). This led to further studies demonstrating a direct antiviral effect of interferon $\alpha$ on HCV replication in assays of virus productive cell cultures (29) and in primary cultures of normal human hepatocytes (195). However, the interferon-induced proteins and enzymatic pathways associated with the establishment of an antiviral state among infected and uninfected hepatocytes have not been completely elucidated (196). Interferon $\alpha$ is a cytokine which has extremely important functions in the innate antiviral immune response (196). The binding of interferon $\alpha$ to cell-surface receptors activates a signalling cascade involving Janus-activated kinases, signal transduction, activation of various transcription factors and the induction of multiple interferon stimulating genes (197). This complex signalling cascade results in the induction of host genes that encode...
double-stranded RNases, inhibitors of viral protein translation and proteins that destabilize viral messenger RNA. Interferon α also induces the expression of genes involved in the immune response, resulting in the activation of natural killer cells, maturation of dendritic cells, proliferation of memory T cells and prevention of T-cell apoptosis (198). Mathematical modelling suggests that the second phase of viral decline during therapy with interferon α is a result of the clearance of infected hepatocytes from the peripheral circulation (32). However, it is unclear whether the immunomodulatory effects of interferon α are associated with increased clearance of hepatocytes or whether interferon α acts solely as a direct inhibitor of viral replication. Thus, the direct antiviral effects of interferon α remain elusive.

The precise mechanisms of action of ribavirin during therapy for HCV infection are unclear. Ribavirin is a synthetic guanosine analogue, which is activated via intracellular phosphorylation to its active form, ribavirin triphosphate. However, interestingly, ribavirin only has a moderate and transient dose-dependent inhibitory effect on HCV replication in vivo (199). It has been demonstrated that the clinical effect of ribavirin acts to decrease relapse in subjects responding to combination therapy with ribavirin and interferon α (200), which may be associated with a shortened half-life of HCV infected cells in the presence of interferon α. However, a number of other mechanisms of action for ribavirin have been proposed. In vitro data suggests that ribavirin only has a minimal direct impact on HCV replication, by weakly inhibiting the HCV RNA-dependent RNA polymerase, which is required for the replication of HCV (201). Ribavirin also inhibits inosine monophosphate dehydrogenase (IMPDH), which may lead to the depletion of intracellular guanosine triphosphate (GTP), which is required for HCV viral RNA synthesis (202). Ribavirin may also have immune modulatory effects, shifting the balance between T-helper (Th1)/Th2 responses towards a Th1 response (203), which is important in the eradication of HCV in both humans and chimpanzees (204). Lastly, evidence from mathematical modelling of HCV viral kinetics during interferon α and ribavirin combination therapy suggests that ribavirin may render HCV virions less infectious (205). Thus, ribavirin may act to decrease the de novo susceptibility of uninfected hepatocytes, while interferon α inhibits virus production. Interestingly, it has also been demonstrated that ribavirin is a RNA mutagen and may increase the rate at which random nucleotide mutations are incorporated into the viral genome during HCV replication (206). This may lead to a concept known as “error catastrophe”, where there is a loss of viral fitness by the lethal accumulation of nucleotide mutations during HCV replication. However, no studies to date have demonstrated an increased mutagenesis of HCV during therapy.
with ribavirin (207, 208). These data suggest that ribavirin may act via a number of different mechanisms. Further research is required to fully understand the most important components attributable to the antiviral effect observed in the clinic.

1.4.4 Pegylated Interferon α and Ribavirin in Clinical Practice

Combination therapy with peginterferon and ribavirin is the cornerstone for the current treatment of chronic HCV infection (Figure 1.5). As previously mentioned, the most important therapeutic endpoint in subjects receiving combination therapy for chronic HCV infection is sustained virologic response (SVR), which is defined by the absence of detectable HCV RNA in the serum 6 months after the completion of therapy by an assay with a sensitivity of at least 100 copies per mL. In two large, randomized controlled trials, the rates of SVR after 48 weeks of treatment with peginterferon in combination with ribavirin were 54% and 56% as compared to 44% and 47% with standard interferon and ribavirin and only 29% with peginterferon alone (162, 209).

![Figure 1.5 Development of therapy for chronic hepatitis C virus infection (210).](image)

The SVR rates were much higher in individuals infected with HCV genotypes 2 or 3 and ranged from 76 to 84%, as compared to 42 to 52% in those infected with genotype 1 (162, 209). In a subsequent study evaluating various regimens of peginterferon and ribavirin it was demonstrated that individuals infected with HCV genotype 2 or 3 only require 24 weeks of treatment, given similar SVR rates in those receiving 24 (81-84%) or 48 weeks (79-80%) of treatment (211). In addition to genotype, factors associated with an SVR include lower baseline viral load, lower
body weight, younger age and milder hepatic fibrosis (162, 209, 211). Understanding these characteristics associated with improved response rates to therapy have been important in the clinical management of chronic HCV infection.

1.4.4.1 Predicting Response to Therapy

Virologic testing for HCV infection has also become an important tool for not only the diagnosis of infection and the assessment of response to treatment, but also for tailoring treatment for HCV based on the virologic response during therapy. HCV genotyping prior to the initiation of therapy provides an indication of the duration of therapy required, the dose of ribavirin and the virologic monitoring procedure (117). Based on the viral kinetics during therapy for HCV a number of virologic monitoring markers can be used to determine the response to treatment (Figure 1.6).

Given that 70 to 80% of subjects infected with HCV genotype 2 or 3 will respond to therapy, viral load monitoring is currently not indicated. However, in individuals infected with genotype 1, only 40-50% of subjects will respond to therapy and virologic assessments prior to and during therapy can provide important information as to whether an individual will respond to therapy. This allows the early discontinuation of treatment in those with a low chance of achieving an SVR, avoiding the toxicities and cost associated with the full duration of treatment. Viral quantification is performed at baseline and at week 12 in order to better understand the viral kinetics of response to therapy (Figure 1.6). Among treated patients, one subset are null-responders who do not achieve an early virologic response (EVR, undetectable or <2 log decrease in HCV viral load by week 12). Null-responders generally do not manifest further decreases in HCV viral load during continued therapy for 48 weeks and have almost no chance of achieving an SVR (212, 213). Treatment discontinuation is recommended in this group (117).

The second subset of patients are partial responders who achieve a ≥2 log decrease in HCV viral load by week 12, which however continues to be detectable by week 24. Partial responders also have a low likelihood of developing an SVR and treatment is generally discontinued (unless the goal of therapy is to slow the progression of disease in those with a poor prognosis) (213). The third subset of patients are termed relapsers, who achieve an end of treatment response (ETR, defined as undetectable HCV RNA at the cessation of therapy), but do not go on to achieve an SVR. This occurs in only ~15% of subjects that achieve an ETR. The final subset of patients are
those that are responders to therapy. Nearly always, this group achieves an EVR at 12 weeks and has a high likelihood of sustained response to therapy.

Figure 1.6 Virologic response to interferon-based therapy.

Emerging data suggest that among individuals with an EVR, there is a further group of “super responders” who achieve a rapid virologic response (RVR) or undetectable HCV RNA by week 4. It has been demonstrated that a rapid virologic response after 4 weeks of therapy is predictive of an SVR during therapy (214). Additionally, data are available to suggest that among individuals infected with genotypes 2 and 3, shorter treatment durations may be possible among subjects achieving an RVR by week 4 (215). Further prospective clinical trials evaluating this as a strategy for the treatment of HCV infection are required before this is routinely integrated into clinical practice. However, if the duration of treatment could be shortened in some individuals, it would have a considerable impact on the management of HCV infection, allowing for therapy to be truncated in individuals experiencing side effects to therapy.
1.4.4.2 Adverse Events

Adverse events affect virtually all patients who receive treatment. The most common side effects attributed to peginterferon include muscle aches and fatigue (162, 209, 211). Flu-like symptoms and cytopenias are also commonly observed. Interferon can also lead to neuropsychiatric side effects in those with and without pre-existing psychiatric disease, including depression, anxiety, irritability, sleep disturbance and difficulty concentrating (216-218). This can be managed with medications, such as selective serotonin re-uptake inhibitors (218, 219). Other common side include anorexia, nausea, skin rash, diarrhoea, arthralgias, headaches, dizziness, and paresthesias. With respect to ribavirin, the most commonly reported adverse event is hemolysis, which may lead to clinically significant anemia (162, 209, 211). Ribavirin is also teratogenic, requiring strict adherence to birth control for both men and women receiving this drug. It is not known whether ribavirin is contained in sperm and if it exerts teratogenic effects upon fertilization of the ova. However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners. The majority of adverse events occurring with these agents subside after the cessation of treatment and can be managed with appropriate clinical monitoring during therapy.

1.4.4.3 Current Treatment Guidelines

Given the available data, the current indications for the treatment of HCV are based on statements from a Consensus Development Conference Panel of the National Institutes of Health and the Canadian Consensus Conference (117, 220). Persons with chronic HCV who are willing to be treated and do not have any contraindications for therapy are candidates for treatment if they have detectable HCV RNA in serum and evidence of chronic hepatitis (identified by elevations in serum alanine aminotransferase levels or the presence of considerable necroinflammatory activity and fibrosis on biopsy). The currently recommended regimen for the treatment of HCV infection is weekly subcutaneous injections of peginterferon in combination with twice-daily oral doses of ribavirin (117, 220). The recommended dose of peginterferon a2a is 180 µg per week (209), and that of peginterferon a2b is 1.5 µg per kilogram of body weight per week (162). In Canadian guidelines, ribavirin dosing varies according to the regimen of peginterferon. Individuals infected with genotype 2 or 3 receiving peginterferon a2a should receive 800 mg of ribavirin, while individuals with HCV genotype 1 should receive weight-based dosing (1000 mg or 1200 mg). Individuals receiving peginterferon a2b should receive weight-based dosing of ribavirin (800-1200 mg), regardless of genotype. Therapy duration is
dependant on genotype, with individuals infected with HCV genotype 2 or 3 requiring 24 weeks of therapy as compared to 48 weeks in individuals infected with HCV genotype 1. With respect to injection drug use, statements from both consensus conferences suggest that injection drug use should not be considered a contraindication for therapy and that in all cases the decision to treat must be individualized (117, 220). This represents a significant advance in the provision of treatment for IDUs.

1.5 The Treatment of Hepatitis C Virus Infection in Injection Drug Users

1.5.1 Barriers in the Treatment of HCV in IDUs

The treatment of HCV-infected IDUs presents multiple challenges, such as co-morbid psychiatric disease, adherence to therapy, relapse of substance use, access to care and the potential for HCV re-infection (221). In 1997, guidelines recommended that IDUs not be offered HCV treatment until they had remained abstinent from all illicit drug use for > 6 months, raising some questions about fairness and discrimination (222). However, extensive evidence exists that, when specific needs-oriented programs are developed, IDUs can be successfully engaged in care (223-235). With respect to the treatment of HCV infection, it is important to recognize the barriers associated with treatment and develop individualized approaches for addressing these issues.

Psychiatric disease is highly prevalent among IDUs (236-238). It has been suggested that since peginterferon is associated with significant neuropsychiatric side effects, including depression and anxiety (216-218), its administration in IDUs may exacerbate pre-existing depressive disorders in this population (216). However, several studies have shown that patients with depression can be treated safely and successfully while on treatment with interferon (217, 218, 239). Strategies for managing depressive symptoms in patients receiving therapy for HCV infection may include the prophylactic administration of antidepressants and psychiatric counseling. In one small pilot study, the prophylactic administration of the antidepressant, citalopram, was shown to significantly reduce the number of discontinuations due to major depression among psychiatric risk patients receiving therapy for HCV infection (240).
IDUs may also exhibit poor adherence to scheduled appointments and medication regimens (228, 230, 231, 241-243). However, this is a problem common to many chronic medical conditions (244, 245). In IDUs, strategies shown to improve adherence include directly-observed therapy (DOT), cash incentives, and comprehensive case management (223, 242, 243, 246-254). Weekly IFN dosing now provides a means of improving HCV treatment adherence, and makes a DOT approach more practical (162). In the context of adherence and drug use, failure to achieve a high level of adherence necessary to achieve therapeutic success should be viewed as a flaw in the treatment program rather than a failure on the part of the patient.

Therapy for HCV infection may place some IDUs at a risk of relapsing to injection drug use. The side effects of peginterferon therapy (sleeplessness, sweating, nausea, vomiting, fever, headache and pain) mimic opioid withdrawal symptoms. It has also been postulated that prescribing an injectable medication in IDUs may be thought to stimulate drug craving (255, 256). However, no study to date has documented a causal relationship between peginterferon injections and relapse to illicit drug use (257). Moreover, increases in illicit drug use during treatment for HCV have not been observed (258-260). On-site counseling and peer-support groups may be important in managing this component of HCV treatment. However, there are limited data on strategies for the prevention of relapse to illicit drug use during therapy for HCV infection.

Access to care may be difficult for HCV-infected IDUs seeking treatment. Up until recently, given that injection drug use was a contraindication for the treatment of HCV, very few clinics offered treatment to those continuing to use illicit drugs. However, with the recent revision of consensus guidelines, there are a greater number of inner city clinics that are offering treatment for HCV infection. Using lessons learned from the field of HIV, it is clear that by using the infrastructure for addiction treatment, IDUs can be successfully engaged in care for HCV.

IDUs may also be at an increased risk of HCV re-infection and the perceived high risk of HCV re-infection is often cited as a reason to withhold treatment (255). Although re-infection has been described in several settings, it has been demonstrated in chimpanzees (108, 111) and in humans (73) that spontaneous clearance of HCV may be protective against re-infection in some individuals. Whether this protection extends to individuals with clearance as a result of treatment
remains to be determined. However, in 18 IDUs responding to HCV therapy, no more than 2 (and possibly none) were found to be re-infected over a mean 33.8 month follow-up period (261). However, further research is required to confirm these findings in the setting of both natural and treatment induced clearance of viremia. If such protection extends to those who have cleared their viremia following antiviral therapy, it could provide a stronger rationale for expanding treatment programs to IDUs who continue to be at risk for HCV re-exposure.

1.5.2 HCV Treatment Uptake and Willingness Among IDUs

Although most guidelines currently allow for the treatment of HCV infection in IDUs, support for this approach remains limited at best. In our centre, only 3.4% of 1,361 HCV-infected inner city residents evaluated in 2003-2004 reported having received treatment for HCV infection despite it being freely available to them (262). These results are similar to those reported in Australia, where only 4% of 2,500 current IDUs attending needle exchange programs in 2003 had been treated, with only 0.6% actually on treatment at the time of the survey (196). There are no data to suggest that higher treatment uptake should be expected in the United States and Europe.

However, there is now mounting evidence current and former IDUs are interested in receiving treatment for HCV infection. In a survey conducted in 216 treatment-naïve IDUs in three American cities, 82% were interested in receiving treatment for HCV infection, but only 27% had been given the opportunity to do so (263). Those who were told they were at risk for cirrhosis or liver cancer were 7 times more likely to be interested in receiving treatment. In Australia, a study of 100 IDUs documented an increase in motivation to be treated from 63% to 93% if they were told there was a 70% chance of the treatment being effective (264). In our centre, 40/50 (80%) expressed an interest in receiving treatment, probably driven by the fact that 76% felt their HCV has negatively impacted their health (265, 266). Of those interested in receiving HCV treatment, 15% had never been approached in this regard, their caregivers citing concerns about unstable drug use (100%), unstable housing (67%) and medical co-morbidities (33%). Of those who had been approached, only 23% had started treatment or were being considered for its initiation, due to lack of follow-up by the patient or physician (26%), non-adherence to pre-treatment appointments (9%), medical co-morbidities (12%), ongoing drug use (56%), unstable housing (21%) and ongoing alcohol use (12%). The majority (65%) had
multiple barriers to treatment. This largely parallels information reported in four separate studies of a total of 673 HCV-infected individuals in various inner city settings. Overall, only 5% or less received treatment and 60-72% (depending on the study) were deemed “ineligible” for treatment for reasons such as lack of follow-up with appointments and issues of medical or psychiatric co-morbidity or ongoing substance abuse (267-270).

Taken as a whole, the current medical literature confirms a very low uptake of HCV treatment in IDUs, despite the fact that the majority of current and past IDUs may be interested in receiving treatment, especially if the issues are discussed in an appropriate context. In surveys of health care providers, the majority of such patients are deemed ineligible for treatment (271), and this is often presented as the justification for why therapy is not even considered as part of the overall plan of care. However, the exclusion criteria may often be barriers that can be overcome if the appropriate structures are in place.

Improved communication between patients and health care providers about the long-term potential risks of chronic HCV infection and the high probability of treatment success in patients infected with viral genotypes that respond more favourably to treatment and the availability of strategies to overcome perceived impediments to a successful therapeutic partnership may be important in improving patient willingness and motivation to receive treatment. The evaluation of each patient individually with all of these factors in mind may be the key to the implementation of optimal practices for the treatment of HCV infection in IDUs.

1.5.3 Treatment of HCV Infection in IDUs: Early Anecdotal Reports

The first reports of patients with a history of substance abuse receiving treatment for HCV infection were published in 1995 (272). Overall, 94% of the 31 previous drug users completed the 6 months of interferon α monotherapy and 28% achieved an SVR, results similar to those reported in contemporary non-IDU populations.

Little was published on this topic over the next 5-6 years, until the work of Backmund in 2001 (256). This was the first study to evaluate treatment for HCV infection in individuals continuing to engage in injection drug use. Patients were examined and treated by specialists in both addiction medicine and hepatology in the setting of an existing opiate detoxification unit. Fifty patients were offered self-administered treatment with interferon α2a (n=34) and interferon α2a
plus weight-based ribavirin (n=16), as it became available. HCV treatment was initiated during the final two weeks of detoxification treatment. In total, 36% of patients achieved an SVR (48% and 26% of patients infected with HCV genotypes 2/3 and genotype 1, respectively). These results were achieved despite the fact that 80% of patients relapsed back to illicit drug use during treatment. Uncontrolled relapse did reduce response rates (24% SVR, vs. 53% SVR in those who subsequently enrolled in a methadone maintenance program). Overall, the factor most associated with success was not drug use per se, but adherence to treatment, in that attendance at greater than two-thirds of clinic visits was significantly associated with improved response rates (45% vs. 6%, p<0.05). In subsequent studies of approximately 100 patients with a history of substance use, SVR rates of 30-40% were reported (273-276).

All of these data are encouraging, but still leave a significant gap in knowledge about the impact of illicit drug use on HCV treatment outcomes. Information is now available from a study by Sylvestre and colleagues in patients enrolled in a methadone maintenance program and receiving HCV treatment in a community-based setting (258, 277). Seventy-six current and former IDUs at two sites in Oakland and New York received self-administered interferon α2b plus ribavirin. At baseline, 59% of patients reported a previous psychiatric diagnosis, 60% were infected with HCV genotype 1, the mean abstinence from illicit drug use was one year (range 0-18 years, 30% < 6 months). An ETR was achieved in 49%, and an SVR in 28% of patients. These results were achieved despite the fact that 59% of patients engaged in illicit drug use during treatment. In this study, the duration of pre-treatment abstinence from illicit drug use was not statistically associated with response rates, nor was intercurrent drug use during therapy, although 0 of 8 individuals with every day/other day drug use responded to treatment. This suggests that occasional drug use does not significantly impact response rates, but an individual threshold effect may be present.

In this context, a study was conducted in a hospital-based setting in Australia in which 12 active IDUs received treatment with either interferon or peginterferon with or without ribavirin (278). In most cases (11/12), drug use occurred at least every week. The ETR and SVR rates were 58% (7/12) and 50% (6/12). In 50 patients enrolled in a methadone maintenance program and receiving HCV treatment, 11 discontinued therapy within the first 8 weeks due to non-adherence (260). Of the remaining 39, 90% then went on to complete treatment with a 54% SVR. This
suggests that we should invest resources in patient support within the first 1-2 months of treatment to maximize the likelihood of success.

Overall, SVR rates of 29% to 50% have been observed among current and former IDUs. From these studies a number of important themes have emerged. First, the treatment of HCV infection in current and former IDUs is both safe and effective when incorporated into an existing infrastructure for the treatment of addiction (256, 258, 260, 279). Second, HCV treatment can be successful even for individuals continuing to engage in illicit drug use, although more frequent use may be associated with poorer outcomes (258, 278). Lastly, HCV treatment does not have a significant impact on drug dependency treatment requirements or lead to increased injection drug use (258-260). It is important to note, however, that the majority of these studies were conducted prior to the availability of peginterferon and some included interferon monotherapy regimens. Further studies investigating the treatment of HCV in current and former drug users with newer combinations of peginterferon are needed.

Moreover, it will be important to identify novel strategies for improving treatment uptake and outcomes in this population. This may include the use of opiate dependence treatments, such as methadone and buprenorphine, as a method of engaging subjects in care for HCV treatment. Several studies have shown encouraging results using these strategies (256, 280). Also, studies investigating novel models for the delivery of HCV treatment are urgently needed in order to enhance adherence and improve outcomes during therapy. Lastly, given the importance of patient support during therapy, research is needed to understand methods for improving the uptake of treatment in IDUs and novel models for improving engagement in care.

Since the first tentative reports a decade ago, there is now a growing confidence that, in certain settings, IDUs can be successfully treated for HCV infection. The key will be to develop systematic programs for the evaluation and follow-up of these individuals to ensure engagement in care before, during and after a decision to initiate treatment has been made.
1.6 Summary

Globally, there continues to be a high prevalence and incidence of HCV infection. The current HCV epidemic in developed countries is almost entirely fueled by IDUs. Following infection, a quarter of individuals will spontaneously clear their infection. However, the majority will develop chronic, persistent infection and be at risk for significant morbidity and mortality. Although some factors associated with viral clearance have been identified, it is not clear whether additional environmental factors among IDUs will impact their ability to resolve infection, including continued exposure to the virus through ongoing injection drug use. Following the development of chronic HCV infection, the progression of liver-disease will occur slowly but inexorably over time. Without treatment, a significant subset of those will develop cirrhosis, which may culminate in the development of end-stage liver disease, hepatocellular carcinoma or death. Although a number of host and viral factors are important in determining how quickly the progression of hepatic fibrosis will occur, poorly understood host-related factors also contribute significantly to disease progression.

HCV is unlike other chronic viral infections such as HIV, in that a cure is possible with currently available regimens of once-weekly peginterferon injections and twice-daily ribavirin pills. Although treatment response depends on the HCV genotype that an individual carries, overall response rates are ~80% in a subset of individuals infected with genotypes 2 and 3. Despite the considerable burden of HCV infection among those that use injection drugs, treatment has often been denied from this group on the basis that a number of barriers to therapy, including a low perceived adherence to therapy, HCV re-infection and a lack of interest in receiving treatment, would yield poor response rates in this population. As such, there has been an extremely low uptake of treatment for HCV infection in this population. There is now a growing body of knowledge which demonstrates that when IDUs are offered treatment for HCV, results similar to large, randomized trials for the treatment of HCV among subjects without addiction can be achieved.
1.7 Key Gaps

Before we embark on public health initiatives focused on expanding access to treatment for HCV infection among IDUs, there are a number of gaps that exist in the body of knowledge surrounding HCV infection in IDUs and several important questions that must be answered. Very little is known about the natural history of HCV in IDUs. Specifically, do IDUs clear HCV infection at the same rate as non-IDUs and what are the factors associated with spontaneous viral clearance? In those that spontaneously clear HCV infection, do IDUs become re-infected with HCV if they continue to be exposed as a result of ongoing injection drug use? There are limited human data in this regard, although chimpanzee studies suggest that protective immunity against HCV may be possible. If this extends to individuals that clear infection following treatment, it would have important implications for the treatment of HCV in IDUs. Further, if we do embark on treatment in this group, will IDUs respond at the same rates that are observed in non-IDUs and what factors are associated with successful response to therapy? There is limited experience with novel formulations of peginterferon and ribavirin in IDUs and a paucity of data on the impact of illicit drug use during therapy for HCV. Importantly, as we refine programs for the treatment of HCV in IDUs, what are the specific components that are required to ensure that higher levels of success can be achieved? Understanding strategies for enhancing engagement in care for HCV and improving adherence during therapy will be essential if treatment is to be successful in IDUs. With this in mind, the focus of this thesis is to characterize spontaneous clearance of HCV, evaluate HCV re-infection following spontaneous clearance and to evaluate novel models for improving uptake and treatment responses among IDUs. Taken together, these findings represent an important contribution to the field and provide important guidance for the development of health policy with respect to HCV infection in IDUs.
1.8 Purpose and Specific Aims

I chose to work towards a better understanding of HCV infection in IDUs through 4 specific aims:

➢ 1) To determine the rate and characteristics of spontaneous clearance of HCV among infected individuals enrolled in a large, community-based cohort in Vancouver.

➢ 2) To determine whether spontaneous clearance of HCV is protective against HCV re-infection.

➢ 3) To evaluate the antiviral efficacy of interferon α-2b or pegylated interferon α-2b in combination with ribavirin among IDUs enrolled in a directly observed therapy program, as measured by sustained virologic response.

➢ 4) To evaluate the uptake and response to treatment among current and former IDUs infected with HCV enrolled in a novel, weekly support group designed to enhance long-term engagement in medical care.
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CHAPTER II
Factors Associated With Spontaneous Clearance of HCV Among Illicit Drug Users

2.1 INTRODUCTION
Illicit drug use is associated with high rates of hepatitis C virus (HCV) transmission in many urban centres. Of the estimated 170 million HCV prevalent cases in the world, greater than 50% occur among injection drug users (IDUs) and over 75% of incident infections occur in this population (1). Acute infection with HCV is characterized by the detection of viremia, subsequent development of HCV-specific antibodies, a high likelihood of persistent viremia and chronic infection (2, 3). Following acute infection, the overall rate of spontaneous viral clearance is estimated to be 25%, but appears to be dependent on the route of transmission and other host and pathogen-related characteristics (4-9). Factors that have been associated with spontaneous clearance include female sex (10-14) and younger age at the time of infection (15, 16). Conversely, black race and co-infection with human immunodeficiency virus (17) (5, 7, 18) have been associated with reduced rates of HCV clearance.

In 1997, studies from the Downtown East Side of Vancouver, home to greater than 5,000 IDUs, reported annual HCV incidence rates remaining above 16 cases per hundred person years between 1996 and 1999 (19-21). The corresponding prevalence of HIV and HCV was 23% and 88%, respectively (20). This neighborhood received international attention in the late 1990s due to increasing visible drug use, a significant rise in overdose deaths and the declaration of a public health emergency due to epidemic rates of HIV and HCV infection. These outbreaks of HIV and HCV infection occurred despite the presence of needle-exchange programs and free access to medical treatment.

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To increase our understanding of the HCV epidemic in this population, identifying the determinants of early clearance of viremia (generally understood to represent a “spontaneous cure” of HCV) is essential. With this in mind, we measured the rate and characteristics of HCV clearance among infected individuals enrolled in a large, community-based cohort in Vancouver.

2.2 PATIENTS AND METHODS

2.2.1 Study Population

The Community Health and Safety Evaluation (CHASE) project is a prospective open cohort study designed to evaluate health service use in the Downtown Eastside of Vancouver. Between January 2003 and June 2004, 3,553 subjects were recruited via community organizations and door-to-door canvassing of a random sample of single occupancy hotels in the community, based on census information. Subjects were eligible for inclusion if they lived, or utilized health services, in the community. Study participants received a CDN$10 stipend to complete a short, interviewer-administered questionnaire to collect information about demographics, health service utilization, HIV testing, HCV testing and recent illicit drug use. Subjects were requested to provide a time limited consent for the researchers to perform linkages with provincial health services databases. This included HCV, HIV and hepatitis B virus (HBV) testing performed at the British Columbia Centre for Disease Control and the University of British Columbia Virology Department. Subjects who received treatment for HCV infection were excluded from this study to eliminate the possibility of treatment induced viral clearance as a confounding factor. Of the CHASE cohort participants, 762 were included in the study based on demonstrating anti-HCV reactivity and having one or more commercial HCV RNA tests performed (Figure 1). The University of British Columbia/Providence Health Care Research Ethics Board approved this study.

2.2.2 Laboratory Testing

Samples from individuals with a confirmed positive test for anti-HCV antibodies were further evaluated for the presence of HCV RNA. HCV persistence was defined by the presence of one or more detectable HCV RNA tests following a positive test for anti-HCV. HCV clearance was defined by the presence of one or more undetectable HCV RNA tests following a positive test for anti-HCV. Individuals were suspected of having acute HCV infection based on a single HCV
RNA positive or negative result within 6 months of their first anti-HCV positive test and were not considered in this analysis because of the potential misclassification of spontaneous viral clearance.

All HCV antibody and RNA testing was performed at two certified provincial laboratories between 1992 and 2005. HCV antibody testing was performed using, second- or third-generation EIA s (May 1992 to September 1993: UBI HCV EIA v2.0 (Organon Teknika, Durham, North Carolina); October 1993 to July 1994: UBI HCV EIA v 2.1 (Organon Teknika, Durham, North Carolina); August 1994 to March 1997: UBI HCV EIA v 4.0 (Organon Teknika, Durham, North Carolina); April 1997 to present: AxSYM HCV v 3.0 (Abbott Diagnostics, Chicago, Illinois). Specimens reactive for anti-HCV antibodies were retested by the second or third generation Recombinant Immunoblot Assay (Chiron, Emeryville, California) until 1999 for confirmation. Between April 1997 and July 1999, AxSYM HCV 3.0 anti-HCV reactive specimens were retested by UBI HCV v4.0 and from August 1999 to present, AxSYM HCV 3.0 reactive samples were retested by Ortho Eci (Ortho Diagnostics, Mississauga, Canada). Only specimens reactive by both manufacturer's tests were considered to be anti-HCV reactive. HCV RNA testing was performed by the qualitative COBAS AMPLICOR HCV Test v2.0 (Roche Diagnostic Systems, Mississauga, Canada) with a limit of detection of 50 IU/mL. HBV and HIV serology test results were abstracted as recorded in the BCCDC virology database by confidential record linkage.

2.2.3 Statistical Analysis
Variables of interest in this analysis included sex, estimated age at infection, ethnicity, housing status, recent treatment with methadone, recent jail time, HCV treatment history, alcohol use, injection drug use, non-injection illicit drug use, previous HBV infection and HIV status. The duration of HCV infection in HCV seroprevalent individuals was calculated using the date of their first recorded positive EIA test for HCV antibodies. In 658 patients that were seroprevalent upon their first test, age at infection was estimated by random sampling from the age distribution of the incident cases. The duration of infection in 104 individuals with HCV seroconversion between 1992 and 2005 was estimated by using the midpoint between the first positive and last negative HCV antibody tests. Aboriginal ethnicity includes all peoples with an indigenous heritage, including Inuit, First Nations, Native Americans, Alaskan Natives and Métis. Exposure to HBV was defined by current or historical anti-hepatitis B core antibody. Active HBV infection was defined by the detection of HBV surface antigen. HIV status was determined by
either serological testing from the British Columbia Centre for Disease Control HIV testing database or by subject self reporting for individuals diagnosed outside the province. Unstable housing was defined as living in a shelter or living on the street/homeless. Injection and non-injection illicit drug use and alcohol use in the past six months was evaluated as “frequent use” (everyday/most days), or “any use” (sub-classified as 2-3 times/week, 2-3 times/month or once/month). Specific drug use evaluations included injection and non-injection cocaine, heroin and crystal methamphetamine use. We then compared characteristics of subjects with and without HCV clearance using two-sample t-test for quantitative variable, a χ² test or Fisher’s Exact Test, as appropriate, for testing differences between proportions. A multiple logistic regression model was then fit comprised of all variables and subsequently reduced using backwards elimination. Statistically significant differences were assessed at a significance level of 0.05 and all reported p-values are two-sided.

2.3 RESULTS
Of the 1,315 HCV antibody positive subjects enrolled in the CHASE cohort, a total of 762 individuals received testing for HCV RNA and were subsequently followed for a median period of 4.4 years. The mean number of HCV RNA tests per individual was 1.6 (range, 1-10). No significant differences were observed in the demographics among HCV antibody positive individuals that did and did not receive HCV RNA testing, including age (P=0.86), male sex (P=0.95), ethnicity (P=0.15), unstable housing (P=0.19), illicit drug use (P=0.42) and HIV infection (P=0.15). However, subjects that did not receive HCV RNA testing were more likely to engage in recent injection drug use (64.3% vs. 56.6%, P=0.006). Overall, 583 (76.5%) subjects had persistent viremia, with 179 (23.5%) determined to have spontaneous clearance of viremia (Figure 1). The demographic and behavioral characteristics of individuals with persistent viremia versus those with spontaneous clearance are shown in Tables 1 and 2. Overall, the mean age was 42.0 and the estimated age at HCV infection was 32.2 years. There were no significant differences in the mean age (41.7 years vs. 42.5 years, P=0.32) or the estimated age at infection (32.4 years vs. 31.5 years, P=0.27) between individuals with persistent viremia versus those with spontaneous clearance.

In the univariate analysis, the ability to develop protective immunity to HCV, evident here by spontaneous clearance of HCV infection, occurred more frequently among individuals of Aboriginal ethnicity [odds ratio (OR), 2.8; 95% confidence interval (CI), 2.0-4.0, P<0.001] and
female gender (OR, 1.8; 95% CI, 1.3-2.6, \(P=0.001\)). Decreased rates of spontaneous HCV clearance were observed in individuals with HIV co-infection (OR, 0.68; 95% CI, 0.46-1.0, \(P=0.06\)). Estimated age at infection, housing status, previous methadone treatment, recent jail time, HBV infection, alcohol use, and illicit non-injection or injection drug use in the preceding six months were not associated with HCV persistence or clearance (Tables 1 and 2).

As shown in Table 3, after adjusting for confounding variables using multiple logistic regression analysis, the factors independently associated with spontaneous clearance of HCV included Aboriginal ethnicity [adjusted odds ratio (AOR), 2.9; 95% CI, 2.0-4.3, \(P<0.001\)] and female sex (AOR, 1.6; 95% CI, 1.10-2.35, \(P=0.01\)). Spontaneous clearance of HCV was inversely associated with the use (versus no use) of any illicit drugs (AOR, 0.54; 95% CI, 0.29-1.0, \(P=0.05\)) and HIV infection (AOR, 0.58; 95% CI, 0.38-0.88, \(P=0.01\)).

In order to identify whether HIV infection impacts HCV clearance or persistence, we identified 51 subjects in whom we could establish the order of HCV and HIV infections based on documented timing of HCV and HIV seroconversion. In total, 48/51 (94%) individuals acquired HCV infection a median of 2.4 (0.2 – 10) years before being diagnosed with HIV.

### 2.4 DISCUSSION

We investigated the rate and characteristics associated with HCV clearance among inner city residents in Vancouver in a large, community-based cohort consisting mainly of illicit drug users. We documented that 23.5% of individuals, in whom testing for HCV antibodies and viremia were available, spontaneously cleared their infection. This is consistent with previously reported clearance rates of 14-46% in non-IDUs (4-8). In our cohort, Aboriginal ethnicity and female sex were associated with an enhanced capacity to clear HCV infection. In contrast, HIV co-infection and illicit drug use were associated with increased persistence of HCV infection.

Our findings with respect to Aboriginal race are consistent with data from other centers in Canada suggesting that spontaneous HCV clearance may be higher in these individuals (22, 23). A similar finding has recently been published in studies of Alaskan Natives (24). Interestingly, other data suggest that African Americans exhibit decreased rates of HCV clearance (5, 7, 18). The basis for this association between race and HCV clearance is not well understood.
We observed that female sex was associated with increased rates of HCV clearance. This is supported by previously published data (10-14) and a recent systematic review of thirty-one longitudinal studies evaluating the correlates of spontaneous HCV clearance (9). In a pooled analysis of 675 subjects with HCV clearance, the investigators determined that males were significantly less likely (OR, 0.43; 95% CI, 0.36-0.53, \( P<0.001 \)) to clear HCV spontaneously (19%) when compared to females (40%). It has been postulated that HCV clearance in females may be facilitated by estrogen (11, 25). However, this difference could also be attributed to genetic or immunologic differences that have not yet been determined.

The association of sex and race with spontaneous HCV clearance speaks to possible roles for host genetics and immunity in viral control. Genetic polymorphisms in a number of immunological proteins involved in the regulation of cellular immune responses (such as IL-10, IL-19, IL-20 and TNF-alpha) as well as in both HLA class I and II molecules are associated with reduced clearance (26-31). Immunologic studies in Aboriginals suggest a lower genetic tendency to produce IL-10 than Caucasians and a reduced susceptibility to HCV protein induced IL-10 immune responses, implicating a role for the immune system in this enhanced protection (32). It has recently been determined that inhibitory NK cells may be important in HCV clearance, and that differing activity of certain genes encoding interactions between HLA class I molecules and NK cells may play an important role in the efficacy of this process (33). However, further research is needed in order to understand the associations between host genetics and the immune system with HCV clearance.

HIV infection was associated with reduced rates of HCV clearance. Similar observations have been found in studies among United States veterans (18), haemophiliacs (16) and IDUs (7). The results from our study suggest that the majority of illicit drug users are infected with HCV a median of 2.4 years prior to HIV infection, which is consistent with reports from other groups (34). Therefore, given that HCV clearance generally occurs within the first 6-12 months of infection, HIV is most often impacting persistence of HCV rather than its initial clearance in this setting. HIV infection may decrease circulating HCV-specific CD4 and CD8 T cells that are generally present in higher levels in individuals that cleared HCV infection (35). This preservation of higher CD4 cell levels, associated with preserved anti-HCV lymphoproliferative responses, may be reduced or eliminated upon HIV infection (35). Our cohort, as currently recruited, does not provide us with the statistical power to evaluate this hypothesis.
In addition, illicit drug use was associated with diminished capacity to resolve HCV infection. Relationships between specific drug use patterns and viral clearance were not detected, though this may reflect sample size. Alternatively, the effect may be of marginal significance, as the overall rate of HCV clearance in our cohort that included a large proportion of IDUs approximated that previously reported in non-IDU populations. The lower level of viral clearance among those who report injecting may also relate to a higher risk of re-infection. It is interesting to note that data from this cohort (36) and others (37) have demonstrated that HCV re-infection after HCV clearance occurs less frequently than de novo HCV infection in IDUs and non-IDUs alike, suggesting little or no effect of this behavior on the virus-host relationship.

This study has a number of limitations, mostly those inherent to observational cohorts. Testing for anti-HCV antibodies and HCV RNA occurred as clinically indicated. In practice, antibody testing would be done periodically in individuals with such high risk of HCV infection, but less symptomatic patients (who may be more likely to resolve infection) may not be tested for HCV RNA and would be missing from our analysis. Moreover, the majority of HCV RNA testing was performed in recent years because of the increased availability of HCV treatment in this population. Viral clearance was, in some cases, confirmed by a single negative test, which may represent fluctuating low levels of viremia rather than true clearance. Also, given the level of detection of the assay used (<50 IU/mL), some individuals defined as spontaneously clearing HCV infection may have low but undetectable viremia. However, the overall rate of HCV clearance (24%) is consistent with other studies and reassures us that our conclusions are valid. Additionally, not all patients received HCV RNA testing, introducing a potential selection bias against individuals who might not have come forward for more comprehensive testing or were likely to receive follow up care. Drug use was only assessed in the 6 months preceding the questionnaire and historical drug use information was not available. However, the similar demographics and HIV status between the two groups suggest a relative comparability of the groups and would indicate similar testing patterns. An additional limitation with this study is that many of the variables such as illicit drug use behaviors were based on patient self-report and may be prone to socially desirable responses.

Given the limited currently available data investigating HCV clearance in IDUs, the results of our study provide novel insights into this issue. Our results suggest that Aboriginal ethnicity and
female sex may promote clearance (perhaps by enhanced immunological control), while HIV co-infection and illicit drug use may reduce the likelihood of clearance, presumably by a similar mechanism. Understanding the mechanisms underlying our observations may be helpful in the management of individuals with acute infection. Moreover, the understanding of factors that promote or hinder the generation of protective immunity may aid in the development of vaccines or improved treatment options for HCV infection. Further studies are required to confirm our observations from a clinical and pathophysiological perspective. This information will be an important step in refining our approach to HCV infection in medical practice.
Table 2.1. Characteristics of participants with persistent HCV versus those with HCV clearance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCV Persistence (Ab+/RNA+) (N=583), n (%)</th>
<th>HCV Clearance (Ab+/RNA-) (N=179), n (%)</th>
<th>OR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>411 (70.5)</td>
<td>102 (57.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>172 (29.5)</td>
<td>77 (43.0)</td>
<td>1.8 (1.3-2.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>389 (66.7)</td>
<td>82 (45.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>145 (24.9)</td>
<td>86 (48.0)</td>
<td>2.8 (2.0-4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>49 (8.4)</td>
<td>11 (6.2)</td>
<td>1.1 (0.53-2.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Estimated Age at Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 years</td>
<td>236 (40.6)</td>
<td>81 (47.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥30 years</td>
<td>345 (59.2)</td>
<td>98 (54.7)</td>
<td>0.83 (0.59-1.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>≤20</td>
<td>41 (7.1)</td>
<td>16 (8.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>195 (33.6)</td>
<td>65 (36.3)</td>
<td>0.85 (0.45-1.6)</td>
<td>0.75</td>
</tr>
<tr>
<td>31-40</td>
<td>208 (35.8)</td>
<td>63 (35.2)</td>
<td>0.78 (0.41-1.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>41-50</td>
<td>111 (19.1)</td>
<td>27 (15.1)</td>
<td>0.62 (0.31-1.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>&gt;50</td>
<td>26 (4.5)</td>
<td>8 (4.5)</td>
<td>0.79 (0.30-2.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Housing Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable</td>
<td>434 (74.4)</td>
<td>124 (69.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stable</td>
<td>149 (25.6)</td>
<td>55 (30.7)</td>
<td>1.3 (0.89-1.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Methadone Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Methadone Treatment</td>
<td>368 (63.1)</td>
<td>125 (69.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methadone Treatment</td>
<td>215 (36.9)</td>
<td>54 (30.2)</td>
<td>0.74 (0.52-1.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Jail time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Jail time</td>
<td>446 (76.5)</td>
<td>138 (77.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jail Time</td>
<td>137 (23.5)</td>
<td>41 (22.9)</td>
<td>0.97 (0.65-1.4)</td>
<td>0.95</td>
</tr>
<tr>
<td>HBV Co-infection**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Active HBV Infection</td>
<td>559 (95.9)</td>
<td>170 (95.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Active HBV Infection</td>
<td>24 (4.1)</td>
<td>9 (5.0)</td>
<td>1.2 (0.56-2.7)</td>
<td>0.67</td>
</tr>
<tr>
<td>HIV-1 Co-infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 negative</td>
<td>406 (69.6)</td>
<td>138 (77.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HIV-1 positive</td>
<td>177 (30.4)</td>
<td>41 (22.9)</td>
<td>0.68 (0.46-1.0)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*As determined by the $\chi^2$ or Fisher’s exact test as appropriate.
Table 2.2. Characteristics of participants with persistent HCV versus those with HCV clearance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCV Persistence (Ab+/RNA+) (N=583), n (%)</th>
<th>HCV Clearance (Ab+/RNA-) (N=179), n (%)</th>
<th>OR (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Use**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>323 (55.4)</td>
<td>94 (52.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any</td>
<td>260 (44.6)</td>
<td>85 (47.5)</td>
<td>1.1 (0.80-1.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Illicit Drug Use**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>42 (7.2)</td>
<td>19 (10.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any</td>
<td>541 (92.8)</td>
<td>160 (89.4)</td>
<td>0.65 (0.37-1.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Injection Drug Use**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>243 (41.7)</td>
<td>88 (49.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any</td>
<td>340 (58.3)</td>
<td>91 (50.8)</td>
<td>0.74 (0.53-1.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Injection Cocaine Use**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>306 (52.5)</td>
<td>106 (59.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any</td>
<td>277 (47.5)</td>
<td>73 (40.8)</td>
<td>0.76 (0.54-1.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Injection Heroin Use**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>388 (66.6)</td>
<td>128 (71.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any</td>
<td>195 (33.4)</td>
<td>51 (28.5)</td>
<td>0.79 (0.55-1.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>Crack Cocaine Use**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>162 (27.8)</td>
<td>56 (31.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any</td>
<td>421 (72.2)</td>
<td>123 (68.7)</td>
<td>0.85 (0.59-1.2)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*As determined by the $\chi^2$ or Fisher’s exact test as appropriate.

**In the past 6 months.
Table 2.3. Multiple logistic regression of factors associated with clearance of HCV infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AOR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboriginal Ethnicity (vs. White)</td>
<td>2.9</td>
<td>2.0-4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.6</td>
<td>1.1-2.4</td>
<td>0.01</td>
</tr>
<tr>
<td>HIV-1 positive</td>
<td>0.58</td>
<td>0.38-0.88</td>
<td>0.01</td>
</tr>
<tr>
<td>Any Illicit Drug Use</td>
<td>0.54</td>
<td>0.29-1.0</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Figure 2.1. Subject Disposition

3,553 Subjects with Questionnaire Data

2,117 Subjects Received HCV Ab

1,315 (63.6%) HCV Ab+ Subjects

48 Subjects Excluded (Received HCV Treatment)

762 (58.0%) Subjects with HCV RNA Testing Available

HCV Persistence (n=583, 76.5%) [Ab+/RNA+]

HCV Clearance (n=179, 23.5%) [Ab+/RNA-]
2.5 REFERENCES


32. Khatkar S AK, Kaita K and Rempel JD. The impact of HCV core and NS3 proteins on Aboriginal and Caucasian PBMC IL-10 production in response to IFN-α. In: 18th Annual Spring meeting of Canadian Society for Immunology; 2005; Whistler, Canada.; 2005.


CHAPTER III
Hepatitis C Virus Re-infection in Injection Drug Users

3.1 INTRODUCTION
Hepatitis C virus (HCV) infection constitutes a major public health burden, affecting more than 170 million individuals throughout the world (1). Injection drug use has emerged as the primary mode of transmission globally, accounting for more than 75% of incident cases (1). The prevalence of HCV infection in injection drug users (IDUs) is 60-90% (2-4), with 80% of these individuals going on to develop persistent, chronic infection (5).

Pharmacologic advances have led to the development of effective treatment regimens leading to a virological “cure” in 50% of HCV infected subjects receiving pegylated interferon in combination with ribavirin (6, 7). Although these outcomes have been replicated in active IDUs (8, 9), there is still concern that the risk of HCV re-infection through recurrent parenteral exposure will negate the benefits of treatment.

In fact, re-infection with HCV after spontaneous clearance has been demonstrated to occur in IDUs with ongoing risk behavior (10, 11), as well as in other groups, including polytransfused children with thalassemia (12) and subjects undergoing liver transplantation (13). Re-infection does occur in chimpanzees rechallenged with HCV after clearance of the original infection (14-17), but the resistance to subsequent HCV infection is relatively greater, which is likely related to immune protection (14, 18). In humans, preliminary data from one cohort suggested that IDUs who successfully clear HCV are less likely to develop viremia following reexposure to HCV than are previously uninfected individuals (19). Given that a greater proportion of IDUs are receiving treatment for HCV, a clearer understanding of this protection from re-infection and its determinants is important. With this in mind, we compared the rate of HCV re-infection among

individuals who had spontaneous HCV clearance with the rate of primary HCV infection among participants in a large observational, community-based cohort.

3.2 PATIENTS AND METHODS

3.2.1 Study Population

The Community Health and Safety Evaluation (CHASE) project is a prospective open cohort study designed to evaluate health service use in the Downtown Eastside of Vancouver. Between January 2003 and June 2004, 3,553 subjects were recruited via community organizations and door-to-door canvassing of a random sample of single occupancy hotels in the community, based on census information. Subjects were eligible for inclusion if they lived or utilized health services in the community. Study participants received a CDN$10 stipend to complete a short, interviewer-administered questionnaire that gathered information on demographics, health service utilization, HIV testing, HCV testing and recent drug use. Subjects were requested to provide time-limited consent for the researchers to link with specific provincial health services databases using subject names and personal health card numbers in order to acquire historical data, including HCV, HIV and hepatitis B virus (HBV) testing performed at the British Columbia Centre for Disease Control and the University of British Columbia Virology Department at St. Paul's Hospital. The University of British Columbia /Providence Health Care Research Ethics Board approved this study.

Individuals were defined as HCV uninfected if the result of their first linked enzyme immunoassay (EIA) test for HCV antibodies (HCV Ab) was negative. Participants were considered HCV infected if the results of their first recorded EIA test for HCV antibodies was positive. HCV clearance was defined as the presence of HCV antibodies followed by one subsequent negative test for HCV RNA (HCV Ab+/HCV RNA-). HCV persistence was defined as a positive test for HCV antibodies followed by at least one HCV RNA positive test with all subsequent tests remaining positive (HCV Ab+/HCV RNA+). Individuals with persistent HCV RNA were excluded from analysis except for the evaluation of demographic characteristics. We then compared the incidence of HCV infection between 1992 and 2005 in individuals with (HCV Ab+/HCV RNA-) and without (HCV Ab-) previous infection in order to evaluate the effect of prior infection on subsequent infection rates.
For the purpose of this study, the index visit by an uninfected subject was considered the date of the first negative HCV antibody test. The incidence of new cases of HCV infection was measured by an HCV antibody negative test and a subsequent positive test during follow-up (HCV Ab-/HCV Ab+), with the date of HCV infection estimated as the midpoint between the last HCV antibody negative test and the first HCV antibody positive test. During the follow-up period, the incidence of HCV re-infection was determined by the detection of HCV RNA following spontaneous clearance of HCV (HCV Ab+/HCV RNA-/HCV RNA+), with the date of HCV re-infection estimated as the midpoint between the last HCV RNA negative test and the first HCV RNA positive test after clearance. Follow-up for individuals developing viremia was defined as the time from the index visit to the date of re-infection or infection. For individuals who remained clear of viremia, this was defined as the time from the index visit to the date of the most recent negative HCV RNA test or HCV antibody test in previously infected and previously uninfected subjects, respectively.

3.2.2 Laboratory Testing

All virology testing was performed at 2 certified provincial laboratories between 1992 and 2005. HCV antibody testing was performed using first-, second- or third-generation enzyme-linked immunosorbent assays (May 1992 to September 1993: UBI HCV EIA v2.0 [Organon Teknika, Durham, NC]; October 1993 to July 1994: UBI HCV EIA v2.1 [Organon Teknika, Durham, NC]; August 1994 to March 1997: UBI HCV EIA v4.0 [Organon Teknika, Durham, NC]; April 1997 to present: AxSYM HCV v3.0 [Abbott Diagnostics, Chicago, IL]). Specimens reactive for anti-HCV antibodies were retested by a second or third generation Recombinant Immunoblot Assay (Chiron, Emeryville, CA) until 1999 to confirm the EIA specificity. Between April 1997 and July 1999, AxSYM HCV v3.0 anti-HCV reactive specimens were retested by UBI HCV v4.0 and from August 1999 to the present time, AxSYM HCV v3.0 reactive samples are retested by Ortho Ecl (Ortho Diagnostics, Mississauga, Canada). Only specimens reactive by both manufacturers' tests were considered to be anti-HCV reactive.

The presence or absence of viremia was detected by HCV RNA testing performed when requested by a physician. Since January 1998, HCV RNA testing has been performed by the qualitative COBAS AMPLICOR HCV Test v2.0 (limit of detection: 50 IU/mL, Roche Diagnostic Systems, Mississauga, Ontario, Canada). To ensure specimen integrity, HCV RNA
testing was performed using dedicated serum samples separated within 4-6 hours of collection or EDTA plasma separated within 3-5 days of collection. HBV and HIV status were determined by confidential record linkage to the British Columbia Centre for Disease Control virology testing database.

3.2.3 Statistical Analysis

Variables of interest in this analysis included age, ethnicity, housing status, alcohol use, injection drug use, non-injection illicit drug use, previous HBV infection and HIV status. The age of a participant was determined as the age on the date the questionnaire was administered. Unstable housing was defined as living in a shelter, rooming house or single occupancy hotel or as living on the street/being homeless. Illicit drug use behavior was defined as the use of injection cocaine, injection heroin, injection crystal methamphetamine, as well as the use of heroin, crack cocaine and crystal methamphetamine though inhalation. Illicit drug use, injection drug use and alcohol use in the past six months was categorized as ‘frequent,’ if used everyday/most days; ‘any,’ if any reported use in the preceding 6 months; or “none,” if no use reported. Exposure to HBV was defined as having had historical positive tests for HBV surface antigen or anti-hepatitis B core total. HIV status was determined by a confidential record linkage to the British Columbia Centre for Disease Control HIV testing database or by subject self-report. We compared characteristics of subjects with and without previous HCV infection using 2-sample t-test for quantitative variables and the $\chi^2$ or Fisher’s Exact Test, as appropriate, for testing differences between two proportions. We also compared the characteristics of subjects with and without incident HCV infection using $\chi^2$ or Fisher’s Exact Test, as appropriate. A multiple logistic regression model comprising potential confounders was used to assess if previous HCV infection was independently associated with reductions in the incidence of HCV infection. Differences were considered statistically significant at $P < .05$ and all reported p-values are 2-sided.

3.3 RESULTS

Of the 3,553 subjects enrolled into the cohort, 2,117 (59.6%) had HCV antibody testing (Fig. 1). Forty-eight subjects reported having previously received treatment for HCV infection and were excluded from further analysis. At baseline, we identified 926 subjects (43.7%) uninfected with HCV, as documented by negative testing for HCV antibodies. The remaining 1,143 individuals
(55.2%) were HCV antibody positive on their first recorded test. HCV RNA testing was available in 658 of these subjects. No significant differences were observed in the demographics between HCV antibody positive individuals that did receive HCV RNA testing and those who did not, including age ($P=0.87$), male sex ($P=0.95$), illicit drug use ($P=0.27$) and HIV infection ($P=0.32$). However, subjects who did not receive HCV RNA testing were more likely to have engaged in recent injection drug use (62.9% vs. 54.4%, $P=0.004$). After identifying 506 individuals with persistent HCV infection on the basis of being HCV RNA positive, we found 152 (23.1%) with spontaneous clearance of viremia.

A comparison between the participants without previous HCV infection and those with HCV clearance is shown in Table 1. The two groups were similar in sex ($P=0.41$) and housing status ($P=0.84$); however, individuals with previous HCV clearance were older (43.7 years vs. 41.2 years, $P<0.001$), more likely to be of Aboriginal ethnicity (50.3% vs. 29.0%, $P<0.001$), more likely to have previous HBV infection (5.9% vs. 1.3%, $P<0.001$) and more likely to be co-infected with HIV (23.5% vs. 7.3%, $P<0.001$) than those previously uninfected with HCV. Although there was no difference in the proportion of subjects who engaged in any illicit drug use ($P=0.50$), individuals previously infected with HCV were more likely to be engaged in frequent illicit drug use (68.0% vs. 55.2%, $P=0.004$) and injection drug use (any; 48.0% vs. 26.0%, $P<0.001$, frequent; 24.8% vs. 13.9%, $P<0.001$). The median follow-up time beyond the index visit for individuals with clearance of viremia ($n=152$) was 5.2 years (IQR, 2.8-7.4) compared to 2.8 years (IQR, 1.4-5.0) for individuals without previous HCV infection (Table 2).

The overall prevalence of HCV infection in this cohort was 63.6% (1315/2069), including in 172 previously uninfected individuals. The occurrence of HCV infection was lower in individuals with previous infection (14/152, 9.2%) than in those without previous infection (172/926, 18.6%). After accounting for duration of follow-up, the incidence of HCV infection was 5 times lower in those previously infected with HCV (1.8 cases/100 person-years; 95% Confidence Interval [CI], 0.9-3.0 cases/100 person-years) than those without previous infection (8.1 cases/100 person-years; 95% CI, 6.9-9.4 cases/100 person-years). This occurred despite those with previous HCV infection being at increased risk for HCV acquisition because of higher rates of HIV co-infection, illicit drug use and injection drug use. The observed difference could not be explained by a lack of follow-up in previously infected individuals, as the median documented time that those in this group were without viremia was 5.4 years (range, 0-13.5 years). In a
logistic regression of individuals with and without incident HCV infection, with previous HCV infection assessed as a covariate along with other potential confounders (age, sex, ethnicity, HIV infection, housing status and illicit and injection drug use), individuals with previous HCV infection and viral clearance were still 4 times less likely to develop incident infection than those infected for the first time [adjusted odds ratio, 0.23; 95% CI, 0.10-0.51, P<0.001].

We also evaluated the occurrence of recurrent HCV viremia in individuals with and without HIV infection and previous viral clearance (Table 3). HCV infection occurred 8 of 117 HIV negative individuals with previous HCV infection (6.8%) as compared to in 6 of 35 HIV co-infected individuals (17.1%). After accounting for follow-up, the incidence of HCV infection in HIV negative individuals with previous HCV clearance (1.4 cases/100 person-years; 95% CI, 0.7-2.9 cases/100 person-years) remained 2 times below that in HIV co-infected individuals (2.8 cases/100 person-years; 95% CI, 1.0-6.1 cases/100 person-years).

Of the 14 subjects with HCV re-infection, 13 had ongoing cocaine use, 9 by injection (Table 4), and 6 were HIV positive. HCV viremia was cleared a second time in 4 subjects (29%), despite ongoing cocaine use by all 4. None of the 4 subjects that cleared HCV a second time were co-infected with HIV at the time they cleared HCV.

3.4 DISCUSSION
In this study of a large community-based cohort of inner-city residents of Vancouver, we have demonstrated that individuals who successfully clear HCV infection have a lower risk of acquiring HCV infection than individuals without previous HCV infection, despite the former group appearing to be at higher risk of exposure. This protection was tracked over a median of 5 years.

The overall rate of clearance of HCV viremia was 23.1%, which is consistent with published data for non-IDUs (20). HCV re-infection with viremia occurred in only 10 of 152 subjects (6.6%), despite 90% of them continuing to engage in illicit drug use, including 50% who reported injection drug use. These findings are not surprising, given that re-infection with HCV after spontaneous clearance is well described in IDUs with ongoing risk behaviors (10, 11).
After adjusting for potential confounding variables, individuals with previous clearance of HCV infection were four times less likely to be re-infected with HCV than were individuals infected for the first time. Therefore, we believe these different rates were not associated with epidemiological differences in the two populations. In fact, these data are consistent with results from another cohort of IDUs in Baltimore, which showed that over a 2 year period IDUs with HCV clearance had an incidence of infection of 6.0 cases/100 person-years in IDUs compared to that of previously uninfected IDUs of 10.5 cases/100 person-years (19). Although our patient population may have differed in important ways from that cohort in race and ethnicity, HIV infection and injection drug use, we observed a similar protection in subjects with previous HCV infection.

HIV infected subjects with previous HCV clearance were 2 times more likely to demonstrate recurrence of HCV viremia (2.8 cases/100 person-years) than those without HIV (1.4 cases/100 person-years). Although it was not possible to definitively establish the order of HIV and HCV infections for some participants in this study, data suggest that 90-95% of HIV infections in IDUs occur after HCV infection (3). As such, this suggests that HIV may be affecting the persistence of HCV rather than its initial clearance. HIV infection may decrease circulating HCV-specific CD4 and CD8 T cells, higher levels of which are generally found in individuals with HCV clearance, leading to either re-infection with HCV or the re-emergence of low-level viremia that may have been undetectable by conventional assays for a period (21).

Our data lend support to the hypothesis that previous exposure to HCV may be protective, possibly on an immunologic basis, despite repeated exposure to HCV. In chimpanzees, re-infection with HCV leads to an attenuated course of infection, with the level and duration of viremia markedly reduced and no evidence of liver disease (15-17). The level of viremia has been linked to the nature of the cellular CD4 and CD8 T-cell responses. The in vivo depletion of memory CD4 T-cells prior to re-infection results in persistent viremia with a failure to resolve HCV infection (22), despite functional memory CD8 T-cell responses in the liver. Similarly, in vivo depletion of CD8 T-cell responses results in prolonged HCV viremia that is not controlled until HCV-specific CD8 T-cells recover in the liver (17). Importantly, it seems that with a rapid, multiantigen T-cell proliferative response, chimpanzees can develop protective immunity that prevents re-infection with both the same and different genotypes of HCV (16, 23). This may also be the case in humans. In one study that considered 3 IDUs with clinical evidence of HCV re-
infection and subsequent clearance, it was demonstrated that clearance was associated with more vigorous CD4+ T-cell responses when compared to patients with acute and chronic HCV infection (24). Further data evaluating viral sequence evolution in IDUs showed that despite ongoing injection drug use during the year of observation, subjects with HCV clearance and HCV persistence demonstrated protection against both re-infection with HCV and superinfection with a different viral genotype, respectively (25).

There are at least two other potential explanations for these results. It has been demonstrated that genetic polymorphisms in some HLA class I and II molecules (26, 27) and genes encoding interactions between HLA class I molecules and NK cells (28) are associated with clearance of HCV infection. Thus, it is possible that those with HCV clearance are a selected group with genetic characteristics protecting against initial HCV infection and subsequent re-infection. Alternatively, given that this study was originally designed to evaluate health utilization, it lacks detailed information on needle sharing, equipment sharing and historical drug use. This is important, as individuals previously exposed to HCV may be more experienced and have safer injection routines and thus may be less likely to share injection equipment with others. Such a behavioral difference (which would protect against HCV re-infection) would not be detected in this study. However, given the higher rate of HIV infection in those with previous clearance, it is more likely that those with HCV clearance remain at higher risk of acquiring HCV infection over time.

This report has a number of limitations inherent to large retrospective studies. Virologic test results were obtained from a historical database that included antibody assays that changed and improved over time. This is particularly relevant to the HCV antibody tests, which may have been less sensitive prior to 1996. In addition, testing was not systematically done, only on physician request, so that subjects who cleared HCV viremia and were later re-infected may have been misclassified as having persistent infection. In some cases, virologic clearance was confirmed by a single negative test, which may have represented fluctuating low level viremia rather than true clearance. This may have overestimated the re-infection rate. Also, some individuals with HCV clearance may have had low-level viremia that was below the limit of detection of the assay (50 IU/mL) and may never have truly cleared their HCV infection. If this were true of some individuals, it would make our analysis a minimum estimate of the difference between the two groups. In addition, not all patients received HCV RNA testing, introducing a
potential selection bias. However, the similar demographics and HIV status between the two
groups would indicate similar testing patterns. Further, the incidence of primary HCV infection
in individuals without previous infection may also be underestimated because of nonsystematic
testing for viremia, once again making our analysis a minimum estimate of the difference
between the two groups. All of the limitations we have raised are best addressed within the
context of a prospective cohort study with systematic laboratory testing for HCV.

Treatment for HCV infection is often withheld from IDUs because of the perceived high risk of
subsequent HCV re-infection after treatment, reducing the impact of treatment on the evolution
of the HCV epidemic. However, our data suggest that spontaneous clearance may confer some
protection against re-infection. If protection against HCV infection extends to those who have
cleared their viremia following antiviral therapy, it could provide a stronger rationale for
expanding treatment programs for IDUs, including those who continue to be at risk for HCV
exposure. Although preliminary data suggest that lower rates of re-infection are observed after
the treatment-induced clearance of HCV infection in IDUs compared to the incidence of HCV
infection in uninfected individuals (29, 30), this must be confirmed in prospective cohorts. Given
that re-infection can occur, it is critical to educate patients about the risk of HCV re-infection
associated with needle and equipment sharing.

In conclusion, further research is required to investigate the mechanism of the effect we have
described in order to define its magnitude and establish how it applies to treated individuals. As
IDUs continue to drive the HCV epidemic in developed countries, it is quite clear that any
efforts at its control must include a comprehensive strategy to address the disease in this target
population. The results of this study provide some assurance that such strategies could be
successfully implemented to limit the impact of HCV in IDUs and in the general population.
Table 3.1. Characteristics of participants without previous infection versus those with HCV clearance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Previously Uninfected</th>
<th>HCV Clearance</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV Ab- (n=926), n (%)</td>
<td>HCV Ab+/ HCV RNA- (n=152), n (%)</td>
<td></td>
</tr>
<tr>
<td>Age (years, mean [SD])</td>
<td>41.2 [11.3]</td>
<td>43.7 [7.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male Sex</td>
<td>628 (67.4)</td>
<td>93 (60.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>541 (58.4)</td>
<td>69 (45.1)</td>
<td>-</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>269 (29.0)</td>
<td>77 (50.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>116 (12.6)</td>
<td>7 (4.6)</td>
<td>0.089</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>68 (7.3)</td>
<td>35 (23.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous HBV infection</td>
<td>12 (1.3)</td>
<td>9 (5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable Housing</td>
<td>646 (69.8)</td>
<td>105 (68.6)</td>
<td>0.84</td>
</tr>
<tr>
<td>Illicit Drug Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>801 (86.5)</td>
<td>135 (88.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Frequent</td>
<td>511 (55.2)</td>
<td>104 (68.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Injection Drug Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>241 (26.0)</td>
<td>73 (48.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequent</td>
<td>129 (13.9)</td>
<td>38 (24.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Student’s Two Sample T-Test for Age, χ² or Fisher’s exact test as appropriate for all other comparisons of associations.
Table 3.2. Occurrence of HCV viremia in all participants without previous infection versus those with HCV clearance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Previously Uninfected</th>
<th>HCV Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV Ab- (n=926), n (%)</td>
<td>HCV Ab+/ HCV RNA- (n=152), n (%)</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>2127</td>
<td>793</td>
</tr>
<tr>
<td>Median Follow-up (years)</td>
<td>2.8</td>
<td>5.2</td>
</tr>
<tr>
<td>Occurrence of Viremia</td>
<td>172/926 (18.6%)</td>
<td>14/152 (9.2%)</td>
</tr>
<tr>
<td>Incidence (/100 person-years, 95% CI)</td>
<td>8.1 (6.9-9.4)</td>
<td>1.8 (0.9-3.0)</td>
</tr>
</tbody>
</table>
Table 3.3. Occurrence of HCV viremia in HIV negative and HIV positive previously infected individuals with HCV clearance (n=152).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCV Clearance</th>
<th>HCV Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV Ab+/ HCV RNA-</td>
<td>HCV Ab+/ HCV RNA-</td>
</tr>
<tr>
<td></td>
<td>HIV negative</td>
<td>HIV positive</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>581</td>
<td>212</td>
</tr>
<tr>
<td>Median Follow-up (years)</td>
<td>5.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Occurrence of Viremia</td>
<td>8/117 (6.8%)</td>
<td>6/35 (17.1%)</td>
</tr>
<tr>
<td>Incidence (/100 person-years, 95% CI)</td>
<td>1.4 (0.7-2.9)</td>
<td>2.8 (1.0-6.1)</td>
</tr>
</tbody>
</table>
Table 3.4. Characteristics of participants with HCV re-infection.

<table>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ab+/RNA-</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>Y</td>
<td>Crack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ab+</td>
<td>RNA-</td>
<td>RNA-/RNA+</td>
<td>RNA-</td>
<td>RNA+</td>
<td>Y</td>
<td>ID Coc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ab+</td>
<td>RNA-</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>N</td>
<td>ID Coc/Crack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ab+</td>
<td>RNA-</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>N</td>
<td>ID Coc/Crack</td>
<td></td>
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<tr>
<td>5</td>
<td>Ab+</td>
<td>RNA-</td>
<td>RNA+/RNA-</td>
<td>RNA+</td>
<td>RNA+</td>
<td>N</td>
<td>ID Coc</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>Ab+</td>
<td>RNA-</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>Y</td>
<td>ID Coc</td>
<td></td>
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<tr>
<td>7</td>
<td>Ab+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>N</td>
<td>ID Coc/Crack</td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>Ab+</td>
<td>RNA+</td>
<td>RNA-/RNA+</td>
<td>RNA-</td>
<td>RNA+</td>
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<tr>
<td>9</td>
<td>Ab+</td>
<td>RNA-</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>Y</td>
<td>Crack</td>
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<td>RNA+</td>
<td>RNA-</td>
<td>RNA-/RNA+</td>
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<td>N</td>
<td>ID Coc</td>
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<td>11</td>
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<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>N</td>
<td>Crack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Ab+</td>
<td>RNA-</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>N</td>
<td>ID Coc</td>
<td></td>
<td></td>
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<tr>
<td>13</td>
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<td>RNA-</td>
<td>RNA+</td>
<td>RNA+</td>
<td>RNA+</td>
<td>Y</td>
<td>ID Coc/Crack</td>
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<td>RNA+</td>
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<td>RNA+</td>
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<td>ID Coc/Crack</td>
<td></td>
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</tbody>
</table>
Figure 3.1. Subject Disposition

*This figure is derived from the same population of individuals discussed in Figure 2.1 (p.65) of Chapter II. The initial cohort of 3,553 subjects, 2,117 of whom received HCV antibody testing and 48 of whom were exclude for having previously received HCV treatment are identical. The 1,143 HCV Ab+ subjects in Table 3.1 are a subset of the 1,315 subjects in Figure 2.1 after having excluded 172 individuals that were initially HCV uninfected (HCV Ab-, n=926) and subsequently became infected during follow-up. The numbers of subjects in the other boxes in this figure were then adjusted as appropriate.
REFERENCES


CHAPTER IV

Directly Observed Therapy for the Treatment of Hepatitis C Virus Infection in Current and Former Injection Drug Users

4.1 INTRODUCTION

Hepatitis C virus (HCV) infection remains a significant global health burden, with over 170 million individuals infected worldwide (1). Only ~25% will spontaneously clear HCV viremia, with the remainder progressing to chronic disease (2). Injection drug use (IDU) remains the primary mode of HCV acquisition, with >50% of prevalent cases and >75% of incident cases associated with this risk behavior (1). The high transmissibility of HCV via needlestick and the presence of a large reservoir of chronic HCV carriers in this population results in HCV prevalence rates ranging between 60 and 90% (1). However, despite this growing epidemic in many urban centres, very few IDUs have received treatment for HCV infection.

Response rates of 50-55% are generally observed in patients receiving pegylated interferon alfa-2a or alfa-2b in combination with twice daily ribavirin for 24-48 weeks (dependant on genotype), a figure is ~80% in a subgroup of individuals carrying HCV genotype 2 or 3 infection (3-6). Current treatment guidelines advocate for treatment of HCV infection in current and former IDUs on an individual basis under specific circumstances (7-9). Despite these recommendations, very few IDUs have actually received treatment to date. This is based on concerns about patient motivation and adherence, medical and psychiatric co-morbidity, re-infection due to recurrent risk behaviors and the lack of infrastructure to ensure access to care during treatment. However, preliminary reports from some centres have confirmed that many IDUs are motivated to receive treatment (10-12), and may be more likely to do so if this is coupled with a comprehensive approach to their medical and psychiatric needs (including a systematic addiction treatment program) within existing infrastructures, perhaps with directly observed therapy (DOT). However, to date, no study has evaluated DOT for the treatment of

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HCV infection. With this in mind, the present study evaluates the safety and efficacy of treatment of HCV infection in current and former IDUs enrolled in a structured DOT program.

4.2 PATIENTS AND METHODS

All patients were HCV-infected IDUs attending one of two multidisciplinary health clinics located in the inner city of Vancouver (the Pender Community Health Centre) or Victoria (the Cool Aid Community Health Centre) in British Columbia, Canada. The clinics offer addiction services such as methadone maintenance therapy, needle exchange, counseling and prevention. In addition to this, other available services included primary care, nursing, addiction counseling, and on-site consultation with infectious diseases specialists.

Men and women >19 years of age, with detectable HCV RNA by polymerase chain reaction (PCR), non-cirrhotic, with alanine aminotransferase (ALT) levels >1.5 times the upper limit of normal (ULN) and in whom there was a reasonable expectation of adherence to therapy were eligible for inclusion in this prospective, observational study. Patients with any cause for chronic liver disease other than HCV, pregnant or breastfeeding women, those with active HBV infection and those with active suicidal ideation, psychosis or mania were excluded from study participation. Patients were also excluded if judged inappropriate for immediate treatment by their primary care physician, based on their medical or psychiatric condition, or their current addiction status. Active (drug abstinence ≤ 6 months) or former (drug abstinence >6 months) injection drug use was not a contraindication for receiving treatment.

Physicians who are addiction specialists at the clinic completed the initial medical evaluation. At baseline, all patients underwent a complete medical history and physical examination. Nursing staff also provides risk behavior education and provides education about the treatment and potential side effects. Patients were required to see an addictions counselor to assess psychiatric status (specifically depression and suicide risk), social stability and current or former illicit drug use behaviors. Once therapy was initiated, patients attended the clinic weekly to be formally evaluated by the nurse and to receive their weekly injections. During these visits, the nurses specifically documented adherence to ribavirin, assessed medication-associated toxicity and ensured appropriate longitudinal monitoring was conducted. Illicit drug use was documented and
blood tests were performed according to the standard of care. Patients maintained frequent contact with physicians for biweekly prescription of methadone and medications needed to address treatment-associated toxicities. Addiction counselors were available on site to provide additional individual support, as required, with particular attention to exacerbation of depression.

For the majority of subjects attending our clinics, HCV medication is provided free of charge through government programs. Patients received combination therapy with ribavirin (RBV, 800-1200 mg/day, based on weight) along with interferon-α2b (IFN-α2b, 3 million international units thrice-weekly) replaced by pegylated interferon-α2b (PEG-IFN-α2b, 1.5 µg/kg once weekly), as it became available. Patients initiating therapy prior to July 2003 received interferon and ribavirin, while those who received therapy after July 2003 received pegylated interferon and ribavirin. Treatment duration was 48 weeks in subjects infected with HCV genotype 1 received and 24 weeks in those infected with HCV genotypes 2/3. Staff administered all IFN (thrice-weekly) and PEG-IFN (weekly) injections under direct observation and ribavirin was self-administered. Subjects experiencing moderate anemia (<10 g/dL) received a ribavirin dose reduction of 200 mg/day, while subjects experiencing more severe anemia (<8.5 g/dL) were discontinued from therapy. Subjects experiencing moderate hematologic toxicity associated with reductions in white blood cells (<1.5 x 10^9/L), neutrophils (0.75 x 10^9/L) or platelets (80 x 10^9/L) received a 50% reduction in interferon dose, while those with more significant reductions in white blood cells (<1.0 x 10^9/L), neutrophils (0.50 x 10^9/L) or platelets (50 x 10^9/L) were discontinued from therapy.

The primary end point for this prospective, observational trial was sustained virologic response (SVR) to interferon-based therapy, defined as an HCV RNA <50 IU/mL at 24 weeks post-treatment (COBAS AMPLICOR HCV Test v2.0, Roche Diagnostic Systems, Mississauga, Canada). Chi-Squared or Fisher's Exact test were used, as appropriate, for all statistical comparisons, which were completed on an intention-to-treat basis. Statistically significant differences were assessed at a significance level of 0.05 and all reported p-values are two-sided. All experimental procedures were followed in accordance with the Helsinki Declaration of 1975. The University of British Columbia Clinical Research Ethics Board approved this study.
4.3 RESULTS

A total of 40 HCV-infected participants were enrolled in the study (of whom 33 were male and 7 were female). Of these, 12 began treatment before July 2003 and received interferon injections thrice weekly, while the remaining 28 were given pegylated interferon once weekly. The demographics and clinical characteristics of subjects enrolled in this study are shown in Table 1. All patients had injection drug use as a risk factor for HCV infection. Fifty three percent of patients were enrolled in a methadone maintenance program, receiving a median dose of 67 mg/day. Overall, 23 patients (58%) self-reported a previous history of depression and 14 (35%) were receiving antidepressants prior to initiating therapy for HCV infection. Eighteen patients (45%) had HCV genotype 1, 6 (15%) had genotype 2 and 16 (40%) had genotype 3. Three patients were co-infected with HIV.

The disposition of the 40 study subjects is shown in Figure 1. In total, 26 subjects completed the full course of therapy. Of the 14 subjects who did not, 5 subjects experienced treatment-limiting adverse events (1 - nausea/vomiting, 1 - tinnitus, 1 - neutropenia, 1 - depression and 1 - anemia). Three subjects infected with genotype 1 were discontinued from therapy due to lack of an early virologic response (EVR), defined as an undetectable viremia or a 2 log_{10} decrease in HCV RNA by week 12. Six subjects were discontinued from treatment due to non-adherence associated with ongoing illicit drug use, four of these reporting concomitant depression. In total, 12/14 (86%) discontinuations occurred within the first four months of therapy (Figure 2).

At the beginning of HCV treatment, 14/40 subjects were on antidepressants, with 4/14 (28%) not completing therapy, 2/3 due to depression and/or illicit drug use and non-adherence. Of the remainder of the population (9/26 reporting a previous history of depression), 4 started on antidepressants during HCV therapy, and 10/26 (38%) did not complete therapy, 4/10 due to depression and/or illicit drug use and non-adherence. In this population, prior use of antidepressants was not predictive of successful treatment completion (p = 0.75).

As shown in Figure 3, at the end of treatment, the proportion of patients responding to HCV therapy was 28 of 40 (70%). However, due to viral relapse in 6 subjects receiving IFN-α2b (3 subjects) and PEG-IFN-α2b (3 subjects), SVR was observed in only 22 of 40 subjects (55%). In total, 8/18 (44%) and 14/22 individuals (64%) infected with HCV genotype 1 and HCV
genotypes 2/3 had an SVR (Figure 4, \(P=0.34\)). Five of twelve individuals (42%) receiving interferon-based therapy achieved an SVR as compared to 17 of 28 (61%) individuals receiving pegylated interferon-based therapy (Figure 4, \(P=0.31\)). Among subjects weighing <75 kg achieved, an SVR was achieved in 60% (9/15) as compared to 52% (13/25) in subjects weighing \(\geq 75\) (\(P=0.75\)). Among patients enrolled in a methadone maintenance program, the SVR rate was 52% (11/21) as compared to 58% (11/19) among subjects not receiving methadone (\(P=0.76\)). In total, 37% (7/19) and 57% (12/21) of subjects receiving and not receiving methadone used illicit drugs during treatment.

The median duration of drug abstinence among all patients was 11.5 months. As shown in Figure 5, there was no difference in SVR among patients that had admitted to drug use in the 6 months preceding therapy (9/14, 64%) and individuals that had not used drugs in the 6 months prior to initiating therapy for HCV infection (13/26, 50%, \(P=0.51\)). Overall, 19/40 patients (48%) used illicit drugs at least once during treatment for HCV infection, with 18 subjects (45%) admitting the use of cocaine or heroin. Of these, 9 used cocaine only, 4 used heroin only and 5 used multiple substances. Of the 19 subjects that used drugs, 10 used them occasionally (monthly/two or fewer times) and 9 used them frequently (everyday/every other day). Four of the nine regular users used injection cocaine, one used injection heroin, one used both injection heroin and cocaine and 2 used crack cocaine. The association between drug use during treatment and sustained virologic response is shown in Figure 5. Overall, there was no difference in response rates between subjects that did (12/21, 57%) and did not (10/19, 53%) use illicit drugs during treatment (\(P=0.99\)). However, the sustained virologic response was 57% in individuals without drug use during treatment, 80% among occasional users and 22% among frequent users. However, these differences did not achieve statistical significance (\(P=0.12\)).

### 4.4 DISCUSSION

This prospective, observational trial is among the first studies evaluating the antiviral efficacy of IFN-\(\alpha\)-2b or PEG-IFN-\(\alpha\)-2b in combination with ribavirin among current and former injection drug users enrolled in a directly observed therapy (DOT) program. Overall, we have demonstrated that 55% of subjects achieved an SVR, despite the fact that many individuals continued to use illicit drugs throughout their course of treatment. These results are comparable to response rates (54-56%) observed to date in large, randomized controlled trials using PEG-IFN-\(\alpha\)-2b in combination with ribavirin for the treatment of HCV infection (3, 5). Our results
were achieved despite the fact that 35% of subjects had used illicit drugs in the 6 months preceding therapy and that 48% of patients used illicit drugs at least once during their course of treatment.

Pretreatment drug abstinence ≤6 months was not associated with poorer outcomes. This is consistent with data from one study of 76 current and former IDUs receiving self-administered IFN α-2b plus ribavirin in a community-based setting (13, 14). They observed that a shorter duration of pre-treatment drug abstinence was not associated with a significant reduction in virologic outcomes (22% vs. 30%, \(P=0.18\)). With this in mind, the decision to initiate treatment for HCV infection in current and former injection drug users should not be arbitrarily based on a pre-defined period of drug abstinence and must be an individualized decision based on the willingness of the patient to initiate treatment, social conditions which may impact the stability of the patient and other medical co-morbidities which may preclude treatment. There are data available to suggest that adherence to pre-treatment appointments may provide a good proxy of adherence to treatment for HCV infection in illicit drug users (15).

Illicit drug use of any kind during treatment for HCV infection was not associated with reduced response rates, unless it exceeds a specific frequency threshold, largely confirming data generated in other evaluations of similar subjects (13, 15-22). In one study of 50 patients offered self-administered treatment with IFN α-2a (n=34) and IFN α-2a plus weight-based ribavirin (n=16), 36% of patients achieved an SVR, despite the fact that 80% of patients relapsed to illicit drug use during treatment (15). Of the 76 subjects receiving IFN α-2b plus ribavirin in a study by Sylvestre et al., 28% of subjects achieved a sustained virologic response, despite the fact that 59% used illicit drugs during treatment (13). Intercurrent drug use was not associated with poorer outcomes (\(P=0.09\)). However, 0/8 individuals with drug use every 1-2 days responded to treatment. Data from 12 active IDUs receiving treatment with either IFN or PEG-IFN with or without RBV in a hospital-based setting in Australia demonstrated SVR rates of 50% (16). In most cases (11/12), drug use occurred at least every week. Based on these data, historical or ongoing illicit drug use should not necessarily be considered a contraindication for HCV therapy. However, further prospective studies appropriately powered to address the impact of both illicit drug use prior to and during treatment are needed.
There were several limitations to this study. First, this study is a prospective, observational trial. Although a randomized trial comparing DOT to self-administered therapy would be ideal, this was not possible in this setting given that DOT is the standard of care at these sites. Second, it would have been useful to have a comparison group of subjects that did not initiate treatment to understand the factors that are associated with the uptake of HCV treatment in this population. Such a study is currently ongoing in our centre. Lastly, the sample size was relatively small with only 40 patients having initiated treatment. However, these results provide important data supporting the proof-of-concept of DOT HCV treatment, providing the foundation for future prospective trials with the appropriate comparison groups. At our centres, a study is underway comparing response rates, costs and patient quality of life after treatment for HCV infection among current and former IDUs receiving care within either a high or low multidisciplinary program.

Given the paucity of data evaluating the treatment of HCV infection in current and former injection drug users, the results from this study provide further evidence to suggest that the treatment of HCV infection in this group can be successful, even despite ongoing substance use during therapy. Our model utilizes the pre-existing infrastructure for the treatment of primary care and addiction within an inner city community health clinic to provide treatment for HCV. Important components of this model include a comprehensive multidisciplinary team and directly observed therapy (DOT). This includes the integration of administrative staff, nurses, counselors, physicians and researchers (providing the necessary expertise to evaluate the program in an objective manner). Nursing support is an absolutely essential component of the program. Nurses provide patient education prior to and during treatment, assess medication-associated toxicity, and ensure appropriate longitudinal monitoring is conducted as they administer weekly interferon injections. Directly observed monitoring of interferon injections may provide an important means of engaging subjects and maintaining a continuity of care during treatment. This also allows the multidisciplinary team to immediately address any side effects, ongoing illicit drug use, psychiatric issues and adherence issues which may arise.

Some have suggested that the use of antidepressants as a prophylactic measure at the time of initiation of HCV treatment may help reduce the occurrence of drug-associated depression and reduce the rate of premature treatment discontinuation. In our observational cohort, the patients that started therapy on antidepressants were no more likely to complete it. A number of small
studies suggest that prophylactic treatment with antidepressants may be effective in reducing discontinuations associated with IFN-mediated depression (23, 24). However, this issue may be best resolved in a single prospective, randomized controlled study of adequate power. Such a study is already underway in Canada, CTN 194.

Given that the future burden of HCV infection will be largely among IDUs, programs for the treatment of HCV in this population must be expanded. Successful pilot programs have been described in a number of centres in North America (13, 21, 25, 26), Europe (15, 17, 19, 20, 22) and Australia (16). Our data add to this body of knowledge, in an era where more convenient formulations of interferon are available, allowing for more cost-effective DOT programs (requiring a single injection every week) to be set up. However, there still exists a considerable knowledge gap in this area. There are no data to recommend the best treatment program for IDUs, including the type and cost of infrastructure that must be put in place. Strategies for managing the neuropsychiatric side effects of interferon are also needed. Data evaluating HCV re-infection is also sparse. Although there are some data suggesting that prior spontaneous clearance of HCV infection is protective with respect to HCV re-infection (27, 28), it is not clear whether protection against HCV infection extends to those who have cleared their viremia following antiviral therapy. Preliminary data suggests that lower rates of re-infection are observed after the treatment-induced clearance of HCV infection in IDUs when compared to the incidence of HCV infection in uninfected individuals (17, 29), however, this must be confirmed in prospective cohorts. Moreover, given that re-infection will still occur (although perhaps at a lower rate), it is critical to educate patients about the potential risks for HCV re-infection associated with needle and equipment sharing.

As IDUs continue to drive the HCV epidemic throughout the world, it is obvious that any attempt at its control must include systematic programs for the treatment of HCV infection in this population. Ultimately, the components of an effective program may be best evaluated in prospective trials, to allow for the identification of the essential elements of a successful program. Information derived from such trials will lead to the design of guidelines for the approach to HCV-infected IDUs in any situation in which they may be encountered.
Table 4.1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age – years (SD)</td>
<td>42.7 (8.6)</td>
</tr>
<tr>
<td>Male sex – n (%)</td>
<td>33 (82.5)</td>
</tr>
<tr>
<td>Body weight – kg</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>82.8 (16.8)</td>
</tr>
<tr>
<td>≥75 kg – n (%)</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Mean Estimated Duration of Infection – years (SD)</td>
<td>13.2 (10.0)</td>
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<tr>
<td>Drug Abstinence</td>
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<tr>
<td>&lt; 6 months – n (%)</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td>Median Time – months (IQR)</td>
<td>11.5 (4.8-30.0)</td>
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<tr>
<td>On Methadone Maintenance Therapy – n (%)</td>
<td>21 (52.5)</td>
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<tr>
<td>Median Methadone Dose – milligrams/day (SD)</td>
<td>67 (36)</td>
</tr>
<tr>
<td>History of Depression – n (%)</td>
<td>23 (58.0)</td>
</tr>
<tr>
<td>Pre-treatment with antidepressants – n (%)</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td>HCV Genotype – n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18 (45.0)</td>
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<tr>
<td>2</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>3</td>
<td>16 (40.0)</td>
</tr>
<tr>
<td>Alanine aminotransferase – U/liter</td>
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</tr>
<tr>
<td>Median (IQR)</td>
<td>139 (87-216)</td>
</tr>
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<td>Median Alanine aminotransferase Quotient (IQR)</td>
<td>2.53 (1.58-3.93)</td>
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<tr>
<td>Median AST – U/liter (IQR)</td>
<td>93 (60-144)</td>
</tr>
<tr>
<td>HIV infection – n (%)</td>
<td>3 (7.5)</td>
</tr>
</tbody>
</table>

*SD, Standard Deviation; IQR, Interquartile range; U/liter, Units/liter.
Figure 4.1. Subject Disposition. AEs, Adverse Events; EVR, early virologic response

40 patients initiated treatment

IFN α-2b + RBV (n=12)
- 0 discontinued due to AEs
- 1 discontinued due to drug relapse
- 2 non-responder (Genotype 1 inadequate EVR)

Completed Treatment (n=9)

PEG-IFN α-2b + RBV (n=28)
- 5 discontinued due to AEs
- 5 discontinued due to drug relapse
- 1 non-responder (Genotype 1 inadequate EVR)

Completed Treatment (n=17)
Figure 4.2. Number of patients discontinuing interferon-based therapy early.
Figure 4.3. Virological response to treatment in all patients as measured by HCV RNA. EOT, End of treatment; SVR, sustained virologic response.
Figure 4.4. Virological response to treatment according to genotype and regimen received as measured by SVR, sustained virologic response.
Figure 4.5. Virological response to treatment according to duration of drug abstinence and intercurrent drug use as measured by SVR, sustained virologic response.
4.5 REFERENCES


CHAPTER V

Treatment Uptake and Outcomes Among Current and Former Injection Drug Users Receiving Directly Observed Therapy Within a Multidisciplinary Group Model for the Treatment of Hepatitis C Virus Infection¹

5.1 INTRODUCTION

Hepatitis C virus (HCV) is a significant global health burden, with over 170 million people infected worldwide (1). Injection drug use (IDU) remains the primary mode of HCV acquisition in the developed world (1). However, HCV treatment programs for illicit drug users have not been part of the response to this explosive epidemic. Reports from Australia and Canada demonstrated that in 2003 and 2004, respectively, only 3-4% of these individuals had received treatment for HCV infection (2, 3). This low uptake of HCV treatment is associated with barriers including lack of follow-up with appointments, issues of medical or psychiatric comorbidity and ongoing substance abuse (4-7).

Response rates of ~55% are observed in patients receiving pegylated interferon and ribavirin, a figure that exceeds 80% in individuals carrying HCV genotype 2 or 3 infection (8-11). In the past, guidelines had excluded illicit drug users from being considered for therapy unless they had abstained from risk behaviors for HCV transmission for at least 6 months. However, data from our centre (12) and others (13-22) suggest that illicit drug users can be successfully treated for HCV infection. Programs with the highest success rates tend to use an existing infrastructure for the treatment of addiction into which HCV therapy can be integrated. The key is to ensure engagement in care before, during and after a decision to initiate treatment has been made. However, there are very little data investigating the specific components of various programs that are important for successful treatment of HCV infection in illicit drug users.

One potential strategy for improving outcomes is the development and implementation of support groups for patients leading up to treatment for HCV infection. This provides a mechanism for regularly scheduled follow-up, patient education and peer support that may even be continued during the course of HCV therapy. With this in mind, we sought to evaluate the uptake and response to treatment among current and former IDUs infected with HCV enrolled in a weekly support group designed to enhance long-term engagement in medical care.

5.2 PATIENTS AND METHODS
All patients were HCV-infected illicit drug users attending an inner city multidisciplinary health clinic (the Pender Community Health Centre, PCHC) located in Vancouver, Canada. The PCHC has a mandate to provide primary care for residents of this area and offers addiction services including methadone maintenance therapy, needle exchange, and counseling. There are up to seven physicians, four registered nurses, six drug and alcohol counselors and on-site consultation with infectious diseases specialists.

For this study, we sought to evaluate the rate of HCV treatment initiation and outcomes among individuals attending a weekly support group for HCV infection. Starting in March 2005, subjects with detectable HCV RNA and an interest in receiving HCV treatment were referred by clinic physicians and addiction counselors to the group. The model for support was based on the O.A.S.I.S model developed in Oakland, CA (13). Attendance to the once-weekly group was not mandatory, but was recorded from the first day that the patient attended the group and monitored at subsequent weekly meetings. Addictions counselors moderated the group, with nurses and research staff supporting its conduct. This group provided an opportunity for treatment candidates to interact directly with those that were receiving or had completed treatment and to gain insight into the evaluation of liver disease and what to expect during treatment. Patients who qualified for HCV treatment on medical grounds would then be seen by clinic physicians for HCV evaluation and to plan for the initiation of therapy.

Funding for HCV treatment in British Columbia is provided through government programs and is either partially or fully reimbursed (based on patient income level). The clinical criteria for government reimbursement are: documented viremia, along with either elevated alanine aminotransferase (ALT) enzyme levels (1.5 times the upper limit of normal on 2 occasions at least 3 months apart) or liver biopsy demonstrating at least Knodell stage 2 fibrosis with no
evidence of decompensated cirrhosis. Men and women >19 years of age who fulfilled
government criteria for subsidized treatment and in whom there was a reasonable expectation of
adherence to therapy were eligible to receive it. Patients with any cause of chronic liver disease
other than HCV, pregnant or breastfeeding women, those with active suicidal ideation, psychosis
or mania or those judged inappropriate for treatment by their physician, based on their medical
or psychiatric condition, or their current addiction status (daily injection drug use in the setting
of unstable housing) were not offered treatment for HCV infection.

Once a patient was judged to be a candidate for treatment (based on attendance to pre-treatment
medical evaluations, social stability and absence of medical or psychiatric co-morbidities), a
clinic physician completed a medical history and physical examination. Patients underwent
testing for HIV, HCV and hepatitis B virus as well as baseline hematology and biochemistry
testing. Nursing staff provided education about treatment and side effects. Patients were required
to see an addiction counselor to assess psychiatric status (depression and suicide risk), social
stability and illicit drug use, with an emphasis on ongoing risk for HCV transmission. Once
therapy was initiated, patients attended the clinic weekly to be evaluated by a nurse and to
receive PEG-IFN injections administered by clinic staff (RBV was self-administered). During
these visits, the nurse specifically documented adherence, illicit drug use, side effects and
ensured appropriate longitudinal monitoring was conducted. Interferon adherence was assessed
by direct observation and ribavirin adherence was self-reported weekly. Addiction counselors
provided additional individual support, with particular attention to symptoms of depression.

Subjects initiating therapy were entered into a prospective, observational efficacy trial. Patients
received combination therapy with ribavirin (800-1200 mg/day) along with either pegylated
interferon-α2b (PEG-IFN-α2b, 1.5 µg/kg once-weekly) or pegylated interferon-α2a (PEG-IFN-
α2a, 180 µg once-weekly). Treatment duration was 48 weeks (HCV genotype 1) or 24 weeks
(HCV genotypes 2/3). Staff administered all PEG-IFN injections under direct observation and
RBV was self-administered. The primary end point for this trial was end of treatment response
(ETR), defined as having HCV RNA <50 IU/mL at the end of treatment (COBAS AMPLICOR
HCV Test v2.0, Roche Diagnostic Systems, Mississauga, Canada). The Mann-Whitney test was
used to assess differences in median attendance between groups of patients, while Fisher's exact
test was used to assess differences in proportions. All two-sided p-values<0.05 were considered
statistically significant. All experimental procedures were implemented in accordance with the Helsinki Declaration of 1975. The University of British Columbia Clinical Research Ethics Board approved this study.

5.3 RESULTS

Overall, 80 subjects were referred to the group over a period of 80 weeks, with the mean attendance being 12 subjects per week (range 3-20). The disposition of the 80 subjects referred into the program is shown in Figure 1. Among the 8 (10%) in whom it was decided that treatment would not be initiated, 6 did not require treatment, while 2 had contraindications for immediate treatment (1 – diabetes/malnutrition/depression, 1 – severe depression). In total, 23 (29%) were lost to follow-up. Ten percent (8/80) of subjects had completed or initiated treatment for HCV infection prior to attending the group. Twenty-five percent of subjects (20/80) were currently under evaluation for treatment of HCV and 26% (21/80) had initiated or completed treatment for HCV infection. In a comparison of subjects that had initiated or completed treatment for HCV infection (21/80) and those lost to follow up (23/80), those having received treatment for HCV infection had a higher median attendance [22.7 meetings (Interquartile range, IQR = 13-32) vs. 3.4 meetings (IQR=1-5, P<0.001)] and were more likely to attend >3 clinic visits (100% vs. 35%, P<0.001) than those lost to follow up.

Of the 21 subjects who initiated treatment for HCV infection, 18 received care at this site and were enrolled into a prospective observational study of HCV therapy. The other three received treatment elsewhere. Subjects received either PEG-IFN-α-2a (n=14) or PEG-IFN-α-2b (n=4) in combination with RBV. The demographics and clinical characteristics of the 18 subjects enrolled in this study to date are shown in Tables 1 and 2. All patients had IDU as a risk factor for HCV infection. The mean attendance to the weekly group prior to initiating therapy was 79%, while the mean time to treatment initiation after presenting to the group was 9.5 weeks. Of the 18 subjects treated at PCHC, 56% (n=10) had reported illicit drug use in 6 months preceding therapy, while the median time of drug abstinence was 4 months. Seven subjects (39%) were actively using illicit drugs at the time of therapy initiation. A high proportion of treated subjects were infected with HCV genotype 2 (22%) and genotype 3 (56%). Eight subjects (44%) were receiving methadone maintenance therapy.
The disposition of the 18 study subjects is shown in Figure 1. Treatment is still ongoing in 6 patients, while 12 have completed or discontinued therapy. Of the 12 that have completed treatment, early discontinuation was required in 8/12 (67%) of subjects, with 5 experiencing treatment-limiting adverse events (4 - depression and 1 - anemia). Two of the four subjects who discontinued due to depression chose not to receive antidepressants prior to or during treatment for HCV. One subject remained viremic after 24 weeks of therapy (HIV co-infected). Two subjects were discontinued from treatment due to non-adherence associated with ongoing illicit drug use.

In total, 12 patients completed or discontinued treatment. At baseline, 9/12 subjects were receiving prophylactic treatment with antidepressants (7 - citalopram, 1 - venlafaxine, 1 - amitriptyline), while no patient started antidepressants during treatment. The median duration of non-injection and injection drug abstinence among all 12 patients completing therapy was 5 and 8 months, respectively. Nine subjects (75%) used illicit drugs and four subjects (33%) used injection drugs at least once during treatment (all four injectors used heroin). Of these, 1 used cocaine alone (non-injection), 3 used cocaine (non-injection) and heroin (injection), 2 used heroin alone (1 - non-injection and injection, 1 - injection) and 1 used methamphetamine alone (non-injection). Five of the nine subjects also used marijuana during treatment (with 3 also having used heroin, cocaine or methamphetamine). The mean number of days of drug use during treatment was 2, 3, 11 and 54 per individual for cocaine, heroin, methamphetamine and marijuana respectively. As shown in Figure 2, the proportion of patients responding to HCV therapy in those having completed or discontinued treatment was 8/12 (67%). In total, 2/3 (67%) and 6/9 individuals (67%) infected with HCV genotype 1 and HCV genotypes 2/3 had an ETR.

In all patients having completed or discontinued therapy for HCV infection (n=12), 57.8% of medication doses were administered over a median of 14 (genotypes 2/3) or 28 (genotype 1) weeks. The on-treatment mean directly observed adherence to interferon was 99.1%, while the mean self-reported adherence to ribavirin was 97.7%. Adverse events were mild to moderate in severity and typical of treatment with pegylated interferon and ribavirin. The most commonly reported adverse events were fatigue (100%), nausea (92%), anorexia (83%), headache (67%) and depression (67%). Only 2 patients required dose-reductions in RBV, while no patient required a dose-reduction of PEG-IFN.
5.4 DISCUSSION

Historically, the uptake of HCV treatment has been low among IDUs, despite this group being at highest risk for HCV (1). A number of studies have demonstrated that IDUs can be successfully treated for HCV infection (13-21). However, there are little data evaluating programs for successfully engaging these individuals in HCV care and the specific programmatic components that are important for success. One potential strategy for improving patient engagement in care would be increased reliance on peer-support as a tool, coupled with directly observed therapy for the delivery of the medications in those requiring treatment.

Overall, we observed a high uptake of HCV treatment among IDUs attending a weekly HCV peer support group. Among attendees, we were first able to identify a proportion of infected subjects that did not require treatment for HCV infection based on disease severity and develop a plan for continued follow-up, which is enhanced by their participation in the group. Only 29% were lost to follow-up. Individuals lost to follow-up tended to exhibit a lower weekly attendance and were less likely to attend >3 clinic visits when compared to subjects initiating treatment for HCV. This suggests that initial attendance provides a strong indication of future attendance and that individualized approaches need to be developed to better engage some individuals in care. However, for the vast majority of HCV-infected IDUs in our clinic, the group provides an important means of identifying individuals with a demonstrated interest in addressing their HCV infection. We observed a high uptake of HCV treatment among attendees, with 51% either receiving or about to receive therapy. This figure is impressive considering the numerous barriers associated with treatment in this population, speaking to the success of our model.

Our preliminary results are quite encouraging, given that 67% of subjects receiving directly observed therapy with PEG-IFN and RBV achieved an ETR. This response to treatment is no doubt increased by the fact that there was a selection bias of individuals with HCV genotypes 2/3 (78%), which is higher than the prevalence of these genotypes reported in IDUs in Vancouver (41%) (23). This being said, our results are comparable to those reported in large, randomized controlled trials of PEG-IFN and RBV for the treatment of HCV infection (8-10) and were achieved despite the fact that 56% of subjects had used illicit drugs in the 6 months preceding therapy and that 75% of patients used illicit drugs at least once during their course of treatment. This is similar to results from a previous study at our centre among 40 current and former drug
users. Overall, 55% achieved a sustained virologic response (SVR), despite the fact that many individuals continued to use illicit drugs during treatment (12).

As we move forward, it will be important to further document SVR rates, as the ultimate measure of treatment efficacy. This will be particularly relevant as data now suggest that shorter durations of HCV treatment (such as those received by a number of our subjects) may be efficacious in subjects infected with HCV genotypes 2/3 (24, 25). With this in mind, there is confidence that a large majority will go on to achieve SVR, especially given that the on-treatment adherence to pegylated-interferon and ribavirin was extremely high in this study (95-100%). It is also important to understand that 75% of subjects required early treatment discontinuation and only 58% received a full course of treatment according to published therapeutic guidelines. Discontinuations were often related to depression, and we need to develop specific strategies for addressing this question.

Given that three-quarters of new cases of HCV infection occur in IDUs, it is clear that any comprehensive approach to control this epidemic must include a systematic strategy to address this group. Our study demonstrates that relatively simple programs can be established to engage IDUs in care. At our center, this is accomplished by incorporating an HCV peer-support group into our established multidisciplinary model addressing addiction and other medical conditions simultaneously and includes directly observed therapy for the delivery of medication. Although the specific components required for a successful approach will vary in other centres, appropriate patient selection within a multi-disciplinary model for the delivery of care to this inner city will be required. Such programs will be a valuable approach in the war against HCV infection in the risk group in which it is most prevalent.
Figure 5.1. Patient Disposition

Referred to HCV Rx Group (n=80)

- Treatment not medically indicated (n=8, 10%)
- Completed/Initiated treatment prior to group (n=8, 10%)
- Received/Receiving treatment (n=21, 26%)
- Lost to follow-up (n=23, 29%)
- Under evaluation for HCV treatment (n=20, 25%)

- Received care at another centre (n=3)

Initiated treatment with PEG-IFN + RBV (n=18)

- 5 discontinued due to AEs (4 - depression, 1 - anemia)
- 1 non-responder (Genotype 1 inadequate EVR)

- 2 discontinued due to relapse
- Treatment is ongoing in 6 subjects

- 4 completed the full treatment duration
Table 5.1. Baseline characteristics among the 18 subjects in whom treatment for HCV infection was initiated.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age – years (SD)</td>
<td>42.8 (6.6)</td>
</tr>
<tr>
<td>Male sex – n (%)</td>
<td>17 (94%)</td>
</tr>
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<td>Body weight – kg</td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>80.3 (10.9)</td>
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<tr>
<td>≥75 kg – n (%)</td>
<td>12 (67%)</td>
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<tr>
<td>Mean Estimated Duration of Infection – years (SD)</td>
<td>17.1 (6.6)</td>
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<tr>
<td>Drug Abstinence</td>
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<tr>
<td>&lt; 6 months – n (%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Median Time – months (IQR)</td>
<td>4 (0-60)</td>
</tr>
<tr>
<td>On Methadone Maintenance Therapy – n (%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Median Methadone Dose – milligrams/day (IQR)</td>
<td>123 (75-143)</td>
</tr>
<tr>
<td>Mean Beck Depression Index (SD)</td>
<td>9.8 (1-23)</td>
</tr>
<tr>
<td>Pre-treatment with antidepressants – n (%)</td>
<td>14 (78%)</td>
</tr>
<tr>
<td>HCV Genotype – n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>3</td>
<td>11 (61%)</td>
</tr>
<tr>
<td>Median ALT – U/liter (IQR)</td>
<td>141 (85-256)</td>
</tr>
<tr>
<td>Median AST – U/liter (IQR)</td>
<td>91 (61-139)</td>
</tr>
<tr>
<td>HIV infection – n (%)</td>
<td>4 (22%)</td>
</tr>
</tbody>
</table>

*SD, standard deviation; IQR, Interquartile range
Table 5.2. Treatment for hepatitis C virus (HCV) infection among the 18 current and former injection drug users initiating therapy at the Pender Community Health Centre in Vancouver, Canada.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years/sex</th>
<th>HIV Status</th>
<th>HCV Genotype</th>
<th>Drug Abstinence Prior to Treatment (months)</th>
<th>Major Drug(s) Used</th>
<th>Frequency at Time of Last Use</th>
<th>Treatment for Drug Dependence (planned duration)</th>
<th>Type of PEG-IFN + RBV</th>
<th>Status</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39/M</td>
<td>Negative</td>
<td>3a</td>
<td>8</td>
<td>Heroin/Cocaine</td>
<td>Daily</td>
<td>No</td>
<td>a2a (24 wks)</td>
<td>Completed</td>
<td>SVR</td>
</tr>
<tr>
<td>2</td>
<td>41/M</td>
<td>Negative</td>
<td>2b</td>
<td>0</td>
<td>Heroin</td>
<td>Daily</td>
<td>Methadone</td>
<td>a2a (24 wks)</td>
<td>Ceased week 15</td>
<td>SVR</td>
</tr>
<tr>
<td>3</td>
<td>37/M</td>
<td>Negative</td>
<td>3a</td>
<td>3</td>
<td>Heroin</td>
<td>Monthly</td>
<td>Methadone</td>
<td>a2a (24 wks)</td>
<td>Completed</td>
<td>SVR</td>
</tr>
<tr>
<td>4</td>
<td>36/M</td>
<td>Negative</td>
<td>1a</td>
<td>7</td>
<td>Heroin/Cocaine</td>
<td>Daily</td>
<td>No</td>
<td>a2a (48 wks)</td>
<td>Ceased week 22</td>
<td>SVR</td>
</tr>
<tr>
<td>5</td>
<td>37/M</td>
<td>Positive</td>
<td>lutsf</td>
<td>0</td>
<td>Methamphetamine</td>
<td>Daily</td>
<td>Methadone</td>
<td>a2a (48 wks)</td>
<td>Ceased week 27</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>46/M</td>
<td>Negative</td>
<td>1utsf</td>
<td>0</td>
<td>Marijuana</td>
<td>Daily</td>
<td>No</td>
<td>a2a (48 wks)</td>
<td>Completed</td>
<td>ETR</td>
</tr>
<tr>
<td>7</td>
<td>46/M</td>
<td>Negative</td>
<td>3a</td>
<td>5</td>
<td>Heroin/Crack</td>
<td>Daily</td>
<td>No</td>
<td>a2a (24 wks)</td>
<td>Ceased week 14</td>
<td>ETR</td>
</tr>
<tr>
<td>8</td>
<td>43/M</td>
<td>Positive</td>
<td>3a</td>
<td>20</td>
<td>Heroin</td>
<td>Weekly</td>
<td>Methadone</td>
<td>a2b (24 wks)</td>
<td>Ceased week 4</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>40/M</td>
<td>Negative</td>
<td>lutsf</td>
<td>8</td>
<td>Cocaine</td>
<td>Other day</td>
<td>No</td>
<td>a2b (24 wks)</td>
<td>Completed</td>
<td>ETR</td>
</tr>
<tr>
<td>10</td>
<td>48/F</td>
<td>Positive</td>
<td>3a</td>
<td>12</td>
<td>Heroin</td>
<td>Daily</td>
<td>Methadone</td>
<td>a2b (24 wks)</td>
<td>Ceased week 5</td>
<td>NR</td>
</tr>
<tr>
<td>11</td>
<td>42/M</td>
<td>Negative</td>
<td>2b</td>
<td>60</td>
<td>Heroin</td>
<td>Daily</td>
<td>Methadone</td>
<td>a2b (24 wks)</td>
<td>Ceased week 5</td>
<td>ETR</td>
</tr>
<tr>
<td>12</td>
<td>48/M</td>
<td>Negative</td>
<td>1b</td>
<td>0</td>
<td>Cocaine/Crack</td>
<td>Daily</td>
<td>No</td>
<td>a2a (48 wks)</td>
<td>Ongoing week 22</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>38/M</td>
<td>Negative</td>
<td>3a</td>
<td>0</td>
<td>Heroin/Crack</td>
<td>Other day</td>
<td>No</td>
<td>a2a (24 wks)</td>
<td>Ongoing week 3</td>
<td>NR</td>
</tr>
<tr>
<td>14</td>
<td>45/M</td>
<td>Negative</td>
<td>3a</td>
<td>0</td>
<td>Cocaine</td>
<td>Daily</td>
<td>No</td>
<td>a2a (24 wks)</td>
<td>Ongoing week 12</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>48/M</td>
<td>Positive</td>
<td>3a</td>
<td>3</td>
<td>Cocaine</td>
<td>Daily</td>
<td>Methadone</td>
<td>a2a (24 wks)</td>
<td>Ongoing week 15</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>52/M</td>
<td>Negative</td>
<td>2utsf</td>
<td>0</td>
<td>Cocaine</td>
<td>Monthly</td>
<td>No</td>
<td>a2a (24 wks)</td>
<td>Ongoing week 14</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>28/M</td>
<td>Negative</td>
<td>3a</td>
<td>12</td>
<td>Heroin</td>
<td>Daily</td>
<td>Methadone</td>
<td>a2a (24 wks)</td>
<td>Ongoing week 16</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>56/M</td>
<td>Negative</td>
<td>3a</td>
<td>6</td>
<td>Heroin</td>
<td>Daily</td>
<td>No</td>
<td>a2a (24 wks)</td>
<td>Ongoing week 19</td>
<td>-</td>
</tr>
</tbody>
</table>

*utsf, unable to subtype further, ETR, end of treatment response; SVR, sustained virological response.
Figure 5.2. Virological response to treatment according to genotype in the 12 patients having completed therapy as measured by HCV RNA at the end of treatment; ETR.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>% ETR</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>67%</td>
<td>8/12</td>
</tr>
<tr>
<td>Geno 1</td>
<td>67%</td>
<td>2/3</td>
</tr>
<tr>
<td>Geno 2</td>
<td>100%</td>
<td>2/2</td>
</tr>
<tr>
<td>Geno 3</td>
<td>57%</td>
<td>4/7</td>
</tr>
</tbody>
</table>
5.5 REFERENCES


5. Fishbein DA, Lo Y, Reinus JF, Gourevitch MN, Klein RS. Factors associated with successful referral for clinical care of drug users with chronic hepatitis C who have or are at risk for HIV infection. J Acquir Immune Defic Syndr 2004;37:1367-1375.


CHAPTER VI

General Conclusions & Recommendations for Future Work

Injection drug users (IDUs) represent the core of the HCV epidemic. Although clearance of HCV will occur in a minority of infected subjects, most will develop chronic infection. Without antiviral therapy, chronic HCV infection will lead to long-term liver-associated morbidity and mortality. However, it is not clear whether treatment can be effective among current and former IDUs, given a number of barriers to therapy. Understanding the natural history of HCV infection among IDUs and how they respond to effective treatment in a controlled setting will be absolutely essential in reducing the future global burden of HCV disease, given that this group represents the majority of infected individuals. This thesis focuses on understanding components of the natural history and treatment of HCV infection in IDUs. Specifically, it focuses on identifying factors associated with spontaneous clearance of HCV infection in this population and understanding whether spontaneous clearance of HCV provides protection against re-infection. This thesis also evaluates novel models for improving uptake and response rates for treatment of HCV among current and former IDUs with chronic HCV infection. Taken together, these data add significantly to the body of knowledge of HCV infection in IDUs.

6.1 General Conclusions

6.1.1 Natural History of HCV in IDUs

First, within a large community-based cohort of illicit drug users, we have demonstrated that Aboriginal ethnicity and female sex were associated with an enhanced likelihood of clearing HCV infection spontaneously, while HIV co-infection and illicit drug use were associated with increased persistence of HCV infection. Our findings with respect to the impact of Aboriginal ethnicity on clearance of HCV confirm preliminary data from other centres suggesting a higher rate of clearance in this group (1-3) and add to the body of knowledge demonstrating that ethnicity impacts clearance of HCV (4-6). Similarly, the finding that females demonstrated higher rates of clearance also confirm a number of reports in the literature in IDU and non-IDU populations (7) (8-12). A number of potential mechanisms explaining the impact of gender and ethnicity on spontaneous HCV clearance have been proposed (9, 13-21). An emerging common theme implicates a central role of host genetics. Specifically, it is postulated that certain
genetically encoded proteins are important in the innate and adaptive immune responses against HCV infection.

Also consistent with previous findings, we demonstrated that HIV infection was associated with decreased clearance of HCV infection. However, given that the order of HIV and HCV infections are often not known in IDUs, it is not certain whether HIV is impacting clearance or persistence of HCV. We demonstrated that HCV infections generally arose several years before HIV infections did. Given that spontaneous clearance of HCV generally occurs within the first year of infection, this provides evidence to suggest that HIV is impacting the persistence of HCV rather than its initial clearance. HIV infection may decrease circulating HCV-specific CD4 and CD8 T cells that are generally present in higher levels in individuals with HCV clearance leading to either re-infection with HCV or the re-emergence of low-level viremia that may have been undetectable by conventional assays for a period of time (22).

We also demonstrated that illicit drug use was associated with increased persistence of HCV. This may be related to an increased susceptibility towards re-infection with HCV. However, one study demonstrated that HCV re-infection after HCV clearance occurs less frequently than in individuals with primary infection (23). This suggests that HCV clearance may be protective with respect to HCV re-infection and that IDUs may actually be getting re-infected prior to clearance having had a chance to occur, making it appear as if they are more susceptible to viral persistence.

The observation that illicit drug use had a marginal impact on clearance of HCV led to the hypothesis that previous HCV clearance is protective against HCV re-infection. We investigated this by comparing the rate of HCV re-infection among individuals who had spontaneous HCV clearance with the rate of primary HCV infection among participants enrolled in the same cohort as we evaluated in the previous study. After adjusting for potential confounding variables, we observed that individuals with successful clearance of HCV were four times less susceptible to HCV re-infection when compared to individuals becoming infected for the first time. This represents the largest study of HCV re-infection to date and confirms previous findings demonstrating a lower rate of HCV re-infection among individuals with documented virologic clearance (23). In addition, individuals with HIV/HCV co-infection were two times more likely to demonstrate recurrence of HCV viremia than those with HCV alone. Whether this is a result
of an increased risk of becoming re-infected with HCV or the recrudescence of low-level HCV viremia after the acquisition of HIV infection remains to be determined.

Overall, the absence of chronic re-infection over a long duration of follow-up (5.2 years) in this large study indicates that some IDUs may be protected from HCV re-infection either through reduced risk behaviours for its acquisition, host factors responsible for the resolution of primary viremia or a partial protective immunity leading to enhanced clearance after re-infection. In chimpanzees re-infected with HCV, there is rapid control of viral replication, short-lived viremia and universal spontaneous resolution of secondary infection (24). Additionally, in humans and chimpanzees, re-infection generally leads to an attenuated course of infection, with the level and duration of viremia being markedly reduced (25-28). If a similar protection against HCV re-infection can be demonstrated among IDUs having cleared HCV successfully following treatment, it could have significant implications for the expansion of programs for the therapy of HCV infected IDUs.

6.1.2 Treatment of HCV in IDUs

To date, no study has investigated directly observed therapy (DOT) for the treatment of HCV infection in IDUs. With this in mind, we sought to evaluate the efficacy of treatment of HCV infection in current and former IDUs enrolled in a prospective, multidisciplinary, directly observed therapy (DOT) program. The overall response rates observed in this study parallels results from large, randomized controlled trials using peginterferon and ribavirin, which have generally excluded subjects with ongoing illicit drug use behaviours. In this study, this response was achieved despite the fact that many individuals continued to use illicit drugs during treatment. Although some guidelines exclude subjects with illicit drug use in the six months preceding therapy for HCV, similar response rates were achieved in subjects with ≤6 or >6 months of drug abstinence. Illicit drug use of any kind during treatment for HCV infection was not associated with reduced response rates, unless it exceeded a specific threshold. These results confirm data from other groups among current and former IDUs for the treatment of HCV (29-38). This suggests that the decision to treat HCV in current and former IDUs must be individualized based on medical indications and contra-indications to treatment, the willingness of the patient to initiate therapy and our ability to deliver treatment in a setting to maximize the likelihood of success. In particular, the decision to treat should not be based solely on a pre-
defined period of drug abstinence. Taken together, these data demonstrate that IDUs can be safely and successfully treated for HCV infection within a multidisciplinary program integrating HCV, addiction and primary care. However, it is important to note that the responses achieved in this study may exceed those observed among a less selected population of HCV-infected IDUs. As we move forward, it will be important to develop novel strategies for engaging IDUs in care for HCV and otherwise creating the winning conditions to maximize response rates.

Although uptake of HCV treatment has been low among IDUs, one strategy for improving engagement in HCV care may include the development and implementation of support groups for subjects considering treatment. We evaluated the uptake and response to therapy among current and former IDUs infected with HCV attending a weekly support group developed to enhance long-term engagement in medical care for HCV. Among current and former IDUs referred to this group, the overall uptake of HCV treatment was high, with one half of the patients either receiving or about to receive therapy for HCV. Although almost a quarter of subjects were subsequently lost to follow-up and these individuals could be identified by a lower weekly attendance and lower likelihood to attend >3 clinic visits. Similar to the data presented in chapter IV, we observed high response rates to therapy, which may have been associated with the higher proportion of subjects with genotype 2 and 3 enrolled in this study. However, individuals enrolled in this study may have also been a higher risk group of patients, given that over half of subjects had used illicit drugs in the six months preceding therapy and almost three-quarters engaged in illicit drug use at least once during treatment for HCV. Regardless, these data demonstrate that a novel model integrating an HCV support group, multidisciplinary care and DOT can lead to high rates of uptake and response to HCV treatment among current and former IDUs.

6.2 Limitations

There are a number of additional limitations that should be addressed from the study evaluating HCV re-infection in IDUs. First, the demographic and behavioural characteristics differ among those with HCV clearance and those previously uninfected with HCV. Individuals with clearance are often older and may have reduced risk behaviour following a diagnosis of HCV infection. However, although older, they were using illicit drugs more often than subjects previously uninfected with HCV suggesting that the risk of HCV acquisition actually remained
high, making any demonstration of reduced rates of infection even more significant. This being said, longitudinal reporting of injection drug use behaviour was not available and it was not possible to delineate the specific nature of risks associated with drug use (including injection equipment sharing) that would more accurately define HCV transmission risks. However, the extent of the protection we observed makes us confident that there was a protective effect, although measuring the magnitude of this effect would require more reliable risk behaviour data and more systematic HCV RNA testing. Lastly, given that the HCV RNA testing is heterogeneous and broad, it is possible that cases of transient HCV re-infection were missed among those with clearance who resolved a secondary case of re-infection. Irrespective of these limitations, the absence of chronic re-infection over a long duration of follow-up among those with spontaneous clearance of HCV indicates that some IDUs are protected against re-infection with HCV.

There are also limitations associated with our work evaluating the treatment of HCV infection among IDUs. First, it is likely that there is a significant selection bias associated with the studies of treatment and participation in support groups. It is likely that a selection bias may have resulted in the treatment of more stable patients with a higher likelihood of success. Similarly, individuals with a demonstrated interest in receiving treatment for HCV infection may have been more likely referred to the HCV support group, resulting in a referral bias. Thus, these results may not be generalizable to the overall population of HCV-infected IDUs. It would be useful to have a comparison group of those not having received treatment to understand the factors associated with HCV treatment uptake in this setting. Both observational studies are also limited by their small sample sizes, making it difficult to identify statistically significant factors associated with treatment outcome. However, these results provide important data supporting the proof-of-concept of DOT for HCV treatment, providing the foundation for future randomized controlled trials with the appropriate comparison groups to overcome the limitations of our observational work.

6.3 Overall Significance of Results and Future Directions

The research presented in this thesis has significant implications for the field of HCV infection. Little is known about the natural history of HCV in IDUs, including factors associated with HCV clearance and the risk of HCV re-infection following successful clearance. The findings that
Aboriginal ethnicity is associated with increased HCV clearance and that HIV infection is associated with increased HCV persistence are important. These data provide the basis for the design and development of the appropriate studies to prospectively evaluate the impact of Aboriginal ethnicity and HIV on HCV clearance and persistence, incorporating the investigation of the appropriate genetic and immunologic parameters that may explain the mechanisms behind these observations. Further trans-disciplinary studies evaluating the epidemiology, genetics and immunology of HCV clearance in Aboriginals and those infected with HIV are needed. This may uncover important aspects of HCV-specific immunity that could aid in the development of novel vaccines and treatments for HCV infection.

The finding that previous clearance of HCV is protective against HCV re-infection also has important implications for the field. Although data in chimpanzees suggest that protective immunity can be achieved among individuals with HCV clearance, there have been little human data in this regard. Our study provides convincing evidence that some IDUs may be protected from HCV re-infection after successful clearance. Also, it is apparent that HIV infection may lead to increased persistence of HCV. For the field of HCV, further investigation into this observation may provide insight into how the immune system controls HCV infection. Also, if a similar protection is observed among individuals clearing HCV infection as a result of treatment for HCV, it would provide a stronger rationale for the development of treatment programs for HCV-infected IDUs. However, given the limitations of our retrospective study, we are not able to determine whether this protection occurs through reduced risk behaviours for acquisition, host factors responsible for the resolution of primary viremia, a partial protective immunity leading to enhanced clearance after re-infection or a combination of the above factors. These issues will be addressed within a prospective study planned in our centre.

Future prospective, interdisciplinary studies integrating epidemiology and basic science are needed to evaluate the natural history of HCV re-infection in IDUs (including the impact of HIV infection on persistence of HCV) and should include a detailed assessment of risk behaviours and more frequent and systematic HCV RNA testing. Also, as a greater number of IDUs are treated for HCV infection, it will be important to document risk behaviours following successful clearance and evaluate whether a similar protection against re-infection is observed in the setting of treatment-induced clearance. This type of information is necessary to better understand the
immunopathogenesis and natural history of HCV in IDUs, thereby helping to define public health HCV control measures and treatment recommendations.

Lastly, we have demonstrated that the treatment of HCV is both safe and effective when incorporated into a multidisciplinary model including directly observed (DOT) therapy. The virologic response rates we have documented are similar to those observed in non-IDU populations. This provides further impetus to support the expansion of HCV treatment within models which incorporate the treatment of addiction and HCV infection. Directly observed therapy and peer-group support represent two important strategies that may enhance the engagement of IDUs into treatment for HCV and improve adherence during therapy.

However, there are still gaps in understanding the specific programmatic components that are required for the successful engagement of IDUs in care for HCV and improving outcomes while receiving therapy. Among active users, there needs to be further research into novel methods of using drug dependence treatment for engaging IDUs in treatment for HCV, including investigations into the impact of various drug dependency treatments (i.e. methadone, buprenorphine) on response to treatment. Young IDUs constitute the majority of new infections and research is urgently needed to understand their acceptance and response to treatment. Given that acute HCV infection can be cured in 85-95% of subjects, the identification, prevention and treatment of young IDUs could have enormous public health impact. Lastly, further randomized, controlled trials evaluating various strategies for the treatment of HCV in IDUs are urgently needed. This will require the development of international collaborative projects to ensure that recruitment of these studies is possible and that the results are more widely generalizable. Given that IDUs are at the core of the current and future HCV epidemic, future research investigating strategies for addressing HCV infection in IDUs will have important implications for the reduction of the global burden of HCV.

6.4 Closing Remarks
Health care practitioners have often avoided caring for IDUs, citing concerns that certain approaches or programs are actually contraindicated on medical grounds. This is often a convenient means of rationalizing a lack of comfort in dealing with such a population, not to mention a perception of addiction as a personal choice rather than a disease. It has been my
observation that if the right structure is put in place, many IDUs will seek to engage in care in a productive manner. In the work I have presented in this thesis, I have demonstrated that, at least for HCV infection, the response to complex treatment may be as good as reported in a population of rigorously selected clinical trial participants.

A society is evaluated based on how it treats its less fortunate. Western society in particular will be evaluated on how it deals with its inner city populations, including many IDUs. As part of these interventions, a systematic approach to HCV infection will be required, as many of the inhabitants of these inner cities are already living with this chronic disease. Insomuch as I have generated rigorous data to help inform the development of such an approach, I have not only contributed to the advancement of science, but also to the advancement of society as a whole. For having been afforded this opportunity, I am eternally grateful.
6.5 References


APPENDIX
Certificate of Research Ethics Board Approval
Amendment

<table>
<thead>
<tr>
<th>Principal Investigator:</th>
<th>Department:</th>
<th>Reference Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Mark Tyndall</td>
<td>Infectious Diseases</td>
<td>P02-0263</td>
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Institution(s) Where Research Will be Carried Out:
Community Based Organizations in the Vancouver Downtown Eastside, Single Room Occupancy Units, VCHA Community Health Clinics

Co-investigators:
T. Kerr, C. Lai

Sponsoring Agencies:
Vancouver Coastal Health Authority

Project Title:
Community Health and Safety Evaluation (CHASE) Project

Date of Initial Approval: December 9, 2002
Term of Initial Approval: 1 Year
Amendment Approved: JUN 1 5 2006

Documents Included in this Approval:
Consent Form Version 1.2 (dated May 2006); Survey

The Chair/Associate Chair of the UBC/PHC REB has reviewed the amendment(s) for the above-named project and the accompanying documentation was found to be acceptable on ethical grounds for research involving human subjects.

The REB approval period for this amendment expires on the one-year anniversary date of the REB approval for the entire study.

CERTIFICATION
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards as defined in part C Division 5 of the Food and Drug Regulations.
2. This Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices and
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial, which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

Approval of the Clinical Research Ethics Board by one of:
Dr. I. Fedoroff, Chair
Dr. A. McLeod, Associate Chair

Date: JUN 1 5 2006